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S-001 - THE EFFECT OF METAL CHELATORS ON BREAST CANCER STEM CELLS

Özer Ufuk¹,²

¹Moleküler Biyoloji ve Genetik Bölümü, Fen Fakültesi, Dicle Üniversitesi, Diyarbakır, Türkiye
²Center For Colon Cancer Research, University Of South Carolina, Columbia, Sc, USA

Background and Aim: Neoplastic cells need essential metals such as iron and copper for cellular functions and rapid growth. In breast cancer cells, human epidermal growth factor receptor 2 (HER2) is overexpressed around 30% with poor prognosis and this results in elevated the proportion of cancer stem cells (CSCs) that are in charge of cancer recurrence. Metal chelation and changing their redox cycle in favor of oxidative stress may be a critical to make these cells vulnerable to cell death. Investigating whether metal chelation alters HER2-induced CSC population may provide a new tools for breast cancer therapy.

Material and Methods: MCF7-HER2, overexpressing HER2, and MCF7-vec control cells were used to evaluate the effect of HER2. Also, we have used other breast cancer cell lines; HCC1954, MDA-MB-435 and Hs578T in order to substantiate our results. DFO and Dp44mT were used as metal chelators. ROS production, iron levels and CSC survival in response to chelators were detected by flow cytometry and cell viability was measured by MTT assay.

Results: MCF7-HER2 cells require iron more than their vector counterparts and HER2-increased CSCs are vulnerable to iron chelation. Additionally, this sensitivity of CSCs to iron reduction is obviously indicated in other breast cancer cell lines. Finally, the concept is also shown in neoplastically transformed breast cancer cell line, HMLER. ROS levels were relatively increased by Dp44mT in the cells and this was reversed by combination of iron while copper combination further induced ROS. Parallel changes were observed in the inhibition of cell growth by Dp44mT and this was partially rescued by NAC supplement.

Discussion and Conclusion: Altogether, this study demonstrates that iron depletion causes toxicity for CSCs. Dp44mT depletes iron and binds copper to form redox active complex that leads to oxidative stress. This dual cytotoxic cases are significant for survival of cancer cells.

Keywords: Breast cancer, Cancer stem cells, DFO, Dp44mT, HER2

Effects of iron and iron chelators on the proportion of CSCs

Cells were grown ± 20 µM FeCl3 and its combinations with 2 nM Dp44mT for 3 days, and 10 µM DFO for 5 days. They are stained with CD44-FITC and CD24-PE antibodies and then flow cytometry assay was done. Results represent 3 separately repeated experiments
Effects of paclitaxel and DFO on CSC population in HMLE and HMLER cells.

A. HMLE cells were treated with paclitaxel (0.5, 1 and 2 nM) and DFO (5, 10 and 20 µM) for 4 days and recovered with fresh media for another 4 days. HMLER cells were treated with DFO (1, 5, 10 and 20 µM) as the same way and then flow cytometry assay was done. Results represents 3 separately repeated experiments. B. Basal iron levels were measured with C-AM and RPA staining followed flow cytometry assay. Bars represent fold increase of the mean fluorescence ± SEM from 3 experiments.

S-002 - MATERNAL MICROCHIMERIC CELLS TURN INTO CANCER STEM CELLS?

Demirhan Osman1, Taştemir Deniz2, Yalav Orçun3, Bakan Ergin Melek4, Çetinel Nesrin1

1Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University, Balcali-Adana/Turkey.
2the Department of General Surgery, Faculty of Medicine, Çukurova University, Balcali-Adana/Turkey.
3Department of Pathology, Faculty of Medicine, Çukurova University, Balcali-Adana/Turkey.
4Vocational School of Health Services, Adıyaman University, Adıyaman, Turkey.

Background: We are only beginning to understand the role that fetal-maternal microchimeric cells (F-MMcCs) play in cancer. Although their function is not yet fully known, it would be really cool to understand functionally what the F-MMcCs may be doing in a normal healthy pregnancy and postpartum or in the offspring. Whether, F-MMcCs have a beneficial or detrimental effect partially depends on what kind of cells it develops into, but more so on how the mother’s children responds to having those extra cells around. The phenomenon of feta-maternal microchimerism inspires numerous questions. We aimed to evaluate the possible roles of MMcCs in sarcoma cancer by FISH.

Materials and Methods: We report a case of UPS in a 73-year-old male, with STS, enlarging mass in the left breast with a history of one year. There was a firm and rounded edge mass, about 7x7 cm diameter, behind the nipple areola complex in the left breast. Right breast and right axillary were completely normal. Breast ultrasound revealed solid hypoechoic mass including central necrosis in left breast, bilateral axilla are reported as normal and computer tomography indicated 5x8 cm mass with high peripheral vascular and apperriance of hypodense necrotic at the center. A small piece of the tumor sample and the peripheral blood sample were obtained for genetic studies. The FISH and standard cytogenetic techniques were used for the cancer tissue and blood tissue to detect the MMCs, respectively.

Results: We found the MMcCs in 18% of sarcoma tissue-cells and in 0.2% of the blood tissue-cells. There was a significant difference in the frequencies of McCs between the tumoral tissue and the blood tissue (p<0.0001).

Conclusion: The available informations suggests that there is two basic possibilities,
S-003 - THE IN VITRO EFFECT OF SANGUINARINE DIFFERS ON NEUROBLASTOMA STEM CELLS BASED ON THE SERUM

Erçetin Özdemir Ayşe Pınar¹, Aktaş Safiye¹, Yavuz Busra², Ozturk Tuğba², Kaman Damla², Sulu Melik², Altun Zekiye¹, Cecen Emre¹, Olgun Nur³

¹Basic Oncology Department, Institute of Oncology, Dokuz Eylül University, Izmir, Turkey
²Biology Department, Faculty of Science, Ege University, Izmir, Turkey
³Pediatric Oncology Department, Adnan Menderes University, Aydın, Turkey
⁴Pediatric Oncology Department, Institute of Oncology, Dokuz Eylül University, Izmir, Turkey

Neuroblastoma (NB) is the most common extracranial solid cancer in childhood. Cancer stem cells (CSCs) are thought to be associated with micrometastasis, cause of cancer, drug resistance and recurrences. Recent studies showed that sanguinarine (Sng) could be used as an anti-cancer due to its apoptosis inducing mechanism. FBS is used as a common supplement in most of the in vitro studies however there are other factors interacting with tumor cells and CSCs in in vivo conditions. Thus, the aim of this study was to evaluate the effect of Sng on NB CSCs in different culture conditions.

CD133+ cancer stem cells were isolated from Kelly(N-myc+) NB cells with magnetic beads. Normal serum (NS) was obtained from peripheral blood sample of a healthy donor. CSCs were incubated in four different subgroups such as; RPMI+FBS, RPMI+NS, RPMI+NS+Sng and RPMI+FBS+Sng. After 24 hours Annexin V staining was performed to evaluate apoptosis and CD133 positivity was analyzed by flow cytometry to evaluate CSCs differentiation.

Late apoptotic CSCs were more in FBS+Sng medium than in medium containing NS. Also, in medium containing NS has lower CD133 positivity. In other words, medium containing NS cells were more differentiated in comparison with other conditions. According to our results, the type of serum used in in vitro experiments affect apoptosis and differentiation of CSCs induced by Sng. In addition, our study showed that Sng induces apoptosis in NB CSCs. We suggest that different serum conditions should be included in studies evaluating the effect of an anti-cancer agent.

Keywords: Neuroblastoma, Cancer Stem Cells, Sanguinarine, Serum
S-004 - CYTOTOXIC SYNERGY BETWEEN TINGENIN B AND PACLITAXEL AGAINST BREAST CANCER STEM CELLS: INDUCTION OF MITOCHONDRIA DEPENDENT APOPTOSIS

Yılmaztepe Oral Arzu1, Çevatemre Buse2, Karakas Didem2, Aztopal Nazlihan2, Ulukaya Engin1

1Department of Clinical Biochemistry, Faculty of Medicine, Uludag University, Bursa, Turkey
2Department of Biology, Faculty of Arts and Sciences, Uludag University, Bursa, Turkey

Introduction: Despite the advances in chemotherapy regimens, the outcome of patients with breast cancer is not satisfactory. In recent years, this failure attributed to cancer stem cells (CSCs) as they show and/or gain resistance to therapies. Thus, compounds that target CSCs are urgently needed. The aim of this study is to investigate the cytotoxic activity of tingenin b (or 22β-hydroxytingenone, a quinone-methide triterpenoid structurally related to tingenone) in combination with paclitaxel against breast CSCs.

Material&Methods: The anti-growth activity was investigated by the ATP assay. Mode of cell death was evaluated using fluorescence microscopy (Hoechst 33342+Propidium iodide staining), western blotting (apoptosis related markers) and flow cytometry (annexin v staining, determination of caspase 3/7 activity, mitochondrial membrane potential, BCL-2 and PI3K expressions).

Results: It has been found that combination of tingenin b and paclitaxel enhanced the cytotoxic activity and apoptotic cell death at 72 h, compared to single use of each agent in MCF-7s (cancer stem cell enriched population). Apoptosis was evident by the presence of pyknotic nuclei, annexin v staining positivity, increased caspase 3/7 activity, Bcl-2 inactivation, cleavage of PARP and increased expression of Bax. The PI3K/AKT pathway was also found to be inhibited by this combinatorial treatment. In addition, the stemness factor, Oct4, was also found to be decreased.

Discussion: The combination of tingenin b and paclitaxel exerted a promising cytotoxic and apoptotic effect on cancer stem cells of breast cancer. Therefore, the application of this combination may be regarded as a novel and effective approach for due to its cytotoxic activity and apoptosis inducing effect against breast CSCs even in vivo experiments are required for the proof-of-concept.

Keywords: Cytotoxic, Synergy, Between

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S-005 - THE PLANT-DERIVED TRITERPENOID PRISTIMERIN IS A POTENT ANTICANCER AGENT DUE TO ITS CYTOTOXIC ACTIVITY ON BREAST CANCER IN VITRO AND IN VIVO

Çevatemre Buse1, Ėrkısa Merve1, Aztopal Nazlihan1, Karakaş Didem1, Alper Pınar1, Tsimplouli Chrisienda2, Sereti Evangelia2, Dimas Konstantinos2, Ikizimur Armutuk E11, Gürel Gurevin Ebru1, Uvey Ayca1, Mori Mattia1, Berardozzi Simone6, Ingallina Cinzia6, Botta Bruno6, Ulukaya Engin7

1Uludag University, Faculty of Arts and Sciences, Department of Biology, Bursa, Turkey
2Department of Pharmacology, Faculty of Medicine, University of Thessaly, Larissa, Greece
3Department of Histology and Embryology, Faculty of Veterinary Medicine, Istanbul University, 34320, Istanbul-Turkey
4Department of Biology, Faculty of Science, Istanbul University, 34134, Istanbul-Turkey
5Center for Life Nano Science@Sapienza, Istituto Italiano di Tecnologia, viale Regina Elena 291, 00161 Roma, Italy
6Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza University of Roma, piazzale Aldo Moro 5, 00185 Roma, Italy
7Uludag University, Faculty of Medicine, Department of Medical Biochemistry, Bursa, Turkey

Introduction: Several natural products have been suggested as effective agents for breast cancer and given the important role of CSCs (Cancer Stem Cells) in breast tumorigenesis and progression, it is worth investigating the effects of pristimerin on CSCs (MCF-7s) and their parental cell line MCF-7 and also MDA-MB-231.

Material and Methods: The anti-growth activity of pristimerin against MCF-7 and MCF-7s (cancer stem cell enriched population) cells was investigated by the ATP assay and XCELLigence System. Mode of cell death was evaluated using TEM and fluorescence microscopy (Hoechst 33342+Propidium iodide staining), western blotting (autophagy, apoptosis and ER-stress related markers) and flow cytometry (annexin v staining, caspase 3/7 activity, BCL-2 and PI3K expression).

Results: Pristimerin decreased the cell viability in a dose dependent manner in breast cancer cells. In addition, as expected, MCF-7s cells were less sensitive to paclitaxel.
pristimerin (IC50 values were found to be 0.75 µM, 1.75 µM and 0.38 µM for MCF-7, MCF-7s and MDA-MB-231 respectively). Pristimerin also inhibited sphere formation at lower doses (<1.56 µM). Apoptosis was induced in MCF-7 and MCF-7s cells which was evidenced by pyknotic nuclei, annexin V staining, caspase 3/7 activation, BCL-2 dephosphorylation and cleavage of PARP. In addition, regarding the extensive cytoplasmic vacuolation in both cells, we suggest that these cells may be dying via autophagy. However, analysis of the expressions of autophagy related proteins (p62 and LC3-II) revealed a process in which autophagic flux was blocked rather than being stimulated. Furthermore, apoptotic cell death was found to harbor endoplasmic reticulum stress and unfolded protein response (UPR) in breast cancer cells. Lastly, pristimerin inhibited the growth of MCF-7 and MDA-MB-231 xenografts. In these tumors, Pristimerin reduced the expression of Akt and PCNA. Besides, the cleavage of PARP, and levels of PTEN, active caspase 3 and/or 7, LC3B, TUNEL stainings were found to be increased.

Discussion: Collectively, pristimerin exerted both in vitro and in vivo cytotoxic and anti-growth effects on breast cancer cells. Our observations identified a mechanism by which pristimerin functions as an anticancer agent.

Keywords: Plant, Derived, Triterpenoid

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S-006 - AKT/PKB-MEDIATED PHOSPHORYLATION OF TWIST1 IS ESSENTIAL FOR TUMOR GROWTH AND METASTASIS

Pehlivanoglu Suray1, Gorgisen Gokhan2, Kahraman Dirice Sevim3, Ozes Osman Nidai4

1Necmettin Erbakan University, Faculty of Science, Department of Molecular Biology and Genetics, Konya, Turkey.
2Yuzuncu Yil University, Faculty of Medicine, Department of Medical Biology, Van, Turkey.
3Harvard Medical School, Joslin Diabetes Center, Section on Islet Cell and Regenerative Biology, Boston, United States.
4Akdeniz University, Faculty of Medicine, Department of Medical Biology and Genetics, Antalya, Turkey.

Introduction: Cancer cells show epithelial-mesenchymal transition (EMT) during cell migration, and invasion. Within this period it has been shown that the conserved basic helix-loop-helix transcription factor Twist1 plays pivotal role during EMT. The molecular mechanism responsible for Twist1 function is not fully understood. In this context, we aimed to clarify the activation mechanism of Twist1.

Material and Methods: In our study, we have made use of 293T and MDA-MB-231 cell lines. Twist1 cDNA was cloned into the pcDNA3.1 expression vector. Site-directed mutagenesis is used to generate A and E mutations in S42,T121, and S123 residues of Twist1. The interaction between AKT/PKB and Twist1 was shown by IP and in vitro kinase assays. DNA binding properties of the Twist1 was analyzed by using EMSA method. The EMT marker expression levels, the proliferation, and the migration rates of 293T cells that expressed wild type, A, and E mutants of Twist1 were determined.

Results: Here we show that Twist1 binds to and phosphorylated by AKT/PKB at S42,T121 and S123. While conversion of S42,T121 and S123 to phosphorylation-mimicking glutamic acids created active Twist1, Alanin mutants of the same sites diminished the DNA-binding and transactivating functions of Twist1. In line with this, Glutamic Acids mutants suppressed the expression of E-Cadherin, whose expression is negatively regulated by active Twist1. Alanin mutants induced the expression of E-Cadherin. Similarly, we tested the impact of above mentioned mutants on cell migration and proliferation. Our results demonstrated that while Glutamic acid mutants accelerated, Alanin mutants suppressed the migration and...
proliferation of 293T cells.

**Discussion:** According to our results, S42,T121, and S123 amino acids are important for the activation of Twist1. Thus, Twist1 and PI3K-AKT/PKB pathway plays an important role in induction of EMT-mediated metastasis. In this context, Twist1 could be evaluated as a new therapeutic molecule in cancer therapy.

**Keywords:** Twist1, AKT, Metastasis

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**S-007 - NOVEL FUNCTION OF ELF3: A POTENTIAL REGULATOR OF MET**

*Sengez Burcu, Aygün İlkin, Alotaibi Hani*

*Izmir International Biomedicine and Genome Institute, Dokuz Eylul University, Izmir, TURKEY*

**Introduction and Aim:** To date, there is a substantial amount of data in the literature analyzing the epithelial to mesenchymal transition (EMT) program both in development and during tumorigenesis, but a similar understanding of the mesenchymal to epithelial (MET) program is still lagging. Similar to the requirement of EMT in tumor progression, MET is also essential for metastasis. Thus, a better understanding of how MET is regulated is of utmost importance for better management of metastatic disease.

Recently, we have identified a feed forward loop composed of the transcription factors Grhl3 and Hnf4α which are essential for the progression of MET (Figure 1). In particular, we became interested in the Ets transcription factor Elf3 as a potential regulator of Grhl3.

**Results:** Despite the strong association of Elf3 with an epithelial phenotype, the expression levels of Elf3 remained stable during EMT-MET. We also found that silencing of Elf3 resulted in a failure to initiate MET in NMuMG cells. In addition, the levels of Grhl3, Ehf, Cebpa and Hnf4α were significantly downregulated in the absence of Elf3, Cdh1 expression was unaffected. To our surprise, E-cadherin was not localized to the plasma membrane, instead, it localized in the cytoplasm, which explains the failure of MET. We also identified that Elf3 could activate the promoter of Grhl3.

**Conclusions:** Our unpublished data suggest an active role of Elf3 in controlling MET. First, we found that Elf3 is a potential regulator of Grhl3, in several epithelial cell lines as well as during the MET induction in NMuMG cells. Second, our preliminary findings presented here suggest a function of Elf3 in regulating the relocation of E-cadherin to the plasma membrane. We hypothesize that Elf3 accomplishes this function by regulating either members of the post-translational modification pathways, or members of the trafficking pathways to the plasma membrane.

**Keywords:** Mesenchymal to epithelial transition, Grhl3, Elf3
Figure 1

During EMT activators of E-cad expression are downregulated and transcription at the Cdh1 locus is blocked by at least one of the EMT inducers Zeb1, Zeb2, Snail, Slug and Twist by binding to E-boxes at the promoter. Upon MET induction Grhl3 is binding to sites at Cdh1 and Hnf4a. Subsequent expression of Hnf4a leads to recruitment of Grhl3 and Hnf4a to intronic enhancers that induces DNA looping by interaction of the two factors and at the TSS that involves PolII (grey) and p300 (yellow) (enhancer cooperativity). The assembly and stabilization of the core transcription machinery leads to induction of E-cad expression. Up- and downregulation is indicated by vertical green and red arrows, respectively.

S-008 - TARGETING OF Na\textsubscript{1.5} CHANNEL IN METASTATIC BREAST CANCER MODELS IN VITRO AND IN VIVO MICE AS A NOVEL THERAPY

Erdogan Mumin Alper\textsuperscript{1}, Ozpolat Bulent\textsuperscript{2}

\textsuperscript{1}Department of Physiology, School of Medicine, Ege University, Izmir, Turkey; Department of Experimental Therapeutics, UT MD Anderson Cancer Center, Houston, TX, USA

\textsuperscript{2}Department of Experimental Therapeutics, UT MD Anderson Cancer Center, Houston, TX, USA

Introduction and Aim: Breast cancer (BCa) is the most common cancer among women worldwide. The major reason for patient death is due to metastasis and resistance to current therapies. Thus, the novel targeted therapeutic strategies is urgently needed. Voltage-gated ion channels (VGSC) are a group of ion channels that has been correlated with BCa. Importantly, VGSC activity contributes to many cellular behaviors integral to metastasis. In a recent study, authors determined upregulation of the sodium channel Na\textsubscript{1.5} and its neonatal spliced form (nNa\textsubscript{1.5}) in metastatic BCa cells and breast tumors from patients who had a recurrence. The aim of the current study was to reveal molecular mechanisms underlying the effects of Na\textsubscript{1.5} and nNa\textsubscript{1.5} down-regulation on BCa \textit{in vitro} and \textit{in vivo}.

Material and Methods: As \textit{in vitro} experiments, cell proliferation, invasion, apoptosis, cell cycle, western blot, RT-PCR etc. analysis were performed after siRNA treatments in BCa cells. Effects of Na\textsubscript{1.5} siRNA treatments (nanoliposomal) on both tumor growth and metastasis of breast cancer were evaluated by performing xenograft orthotopic breast cancer and lung metastasis models \textit{in vivo}.

Results: Our results showed that expression of Na\textsubscript{1.5} and nNa\textsubscript{1.5} mRNAs are higher in metastatic BCa cells. Specific Na\textsubscript{1.5} siRNA treatments caused a significant reduction in cell proliferation/colony formation/drug resistance/invasion/migration/wound-healing capacity in metastatic BCa cells (p<0.0001), but didn’t effect normal MCF10A cell proliferation. These siRNAs also increased the level of apoptosis and caused G1-cell cycle arrest in MDA-MB-231 cells (p<0.0001). Targeting of these channels inhibited tumor growth, tumor weight and lung metastasis \textit{in vivo} (p<0.0001). Additionally, we found that these channels may enhance tumorigenesis and metastasis through the upregulation of pro-tumorigenic and metastatic proteins in BCa.

Conclusion: In conclusion, it was revealed that these channels have an important
role in the metastasis and progression of BCa and targeting Naᵥ1.5s by siRNA may be beneficial to BCa patients.

**Keywords:** Breast Cancer, Metastasis, Nanoliposom, Naᵥ1.5, siRNA

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**S-009 - TGF-β RECEPTOR I/II SIGNALING AT PRIMARY CILIA MEMBRANE IS REGULATED BY CERAMIDE TO MODULATE CELL MIGRATION**

Gencer Salih¹, Öğretmen Besim²

¹Department of Molecular Biology and Genetics, Uskudar University, Istanbul, Turkey
²Department of Biochemistry and Molecular Biology, Medical University of South Carolina, Charleston, USA

Mechanisms that regulate TGF-beta receptor I/II (TβRI/II) trafficking to primary cilia membrane for mediating signal transduction remain unknown. Here, we show that ceramide synthase 4 (CerS4) generated ceramide, bioactive sphingolipid, stabilized Smad7-TβRI association, which then inhibited the trafficking of TβRI/II to primary cilia membrane. Expression of a mutant TβRI, which is resistant to Smad7 binding/inhibition, restored receptor signaling to increase migration in response to CerS4/ceramide induction. Genetic or molecular alterations of CerS4 abundance prevented Smad7-TβRI inhibitory complex, and increased association between Arl6 transporter and TβRI via novel cilia targeting signal (31-ATALQ-35). Mutation of the cilia targeting signal abolished the trafficking of the receptor to the cilia membrane in response to CerS4 knockdown in various cell types. Localization of TβRI/II to primary cilia activated sonic hedgehog (Shh) receptor smoothened (Smo), inducing migration/invasion and liver metastasis both in wild type and CerS4/−/− knockout mice in response to endogenous CerS4/ceramide knockdown in 4T1 mammary cancer cells, injected in the mammary pads. Smad7 overexpression or primary cilia inhibition by shRNA-mediated knockdown of intraflagella transport protein 88 (IFT88) prevented TβRI-Smo crosstalk and attenuated liver metastasis of mammary cancer cells stably transfected with shRNA against CerS4/ceramide. Overall, these data define a key mechanism for the regulation of TβRI/II targeting selectively at the primary cilia membrane by CerS4/ceramide-Smad7 inhibitory complex to control Shh-mediated cell migration and invasion without affecting canonical TGF-β signaling.

**Keywords:** Metastasis, Primary cilia, TGF-beta, Sonic Hedgehog, Ceramide
S-010 - IN SILICO IDENTIFICATION OF COMPOUNDS WITH SELECTIVE ACTION ON EPITHELIAL OR MESENCHYMAL TUMOR CELLS

Demirkol Seçil, Güre Ali Osmay

Molecular Biology and Genetics, Bilkent University, Ankara, TURKEY

Aim: Although epithelial to mesenchymal transition (EMT) is a biological event applicable to all tumor types studied so far, published gene signatures defining the epithelial or mesenchymal status of cancer cells or tissues have been mostly tissue specific. Recent studies showed that EMT status can be determined with certain gene lists independent of tissue-type. In this study, we aimed to identify drugs with differential effects on mesenchymal, and epithelial groups regardless of the tissue type.

Methods: We used one gene list determining EMT status of cancer cell lines (1), as well as one we generated ourselves to analyze in silico several cell line panels (2,3), and defined the compounds which can selectively inhibit the growth of epithelial and mesenchymal cells.

Results: We thus identified compounds that caused growth inhibition of either epithelial or mesenchymal cells, and observed groups of drugs behaving in a similar pattern. Proteomic analysis of cell lines within each group identified pathways related to sensitivity of drug subgroups. Our analysis revealed that the EMT based classification was also related to the stemness status of cancer cell lines.

Conclusion: Our study demonstrates a novel use for online databases and might help us understand the major mechanisms that should be targeted for both types of cancer cells.

Keywords: Epithelial, Mesenchymal, Transition, Tumor Heterogeneity, Chemotherapy

S-011 - THE EXPRESSION LEVEL OF NF-KB/P65 INCREASES IN BORTEZOMIB-RESISTANT MULTIPLE MYELOMA CELL LINES

Tarhan Mehtap, Öztürk Kamile

Aksaray University, Science and Letter Faculty, Molecular Biology Department, 68011, Aksaray

Background: Multiple myeloma (MM) is a hematologic malignancy characterized by the accumulation of clonal plasma cells in the bone marrow. MM cells often show constitutive expression of nuclear factor kappa B (NF-kB) transcription factors. Bortezomib, the first therapeutic proteasome inhibitor, was approved for the treatment of MM. The primary action of bortezomib is explained by blocking the NF-kB activation pathway. Treatment of MM with bortezomib has greatly improved survival for patients, however relapse due to bortezomib-resistance is inevitable and the disease remains incurable. Although, NF-kB activation is involved in MM pathogenesis, its role in bortezomib-resistance is controversial.

Methods: In this study, we aimed to investigate the effects of NF-kB/p65 and p50 subunits in bortezomib-resistance mechanism of MM cells. We utilized bortezomib-sensitive KMS-28 and bortezomib-resistant KMS-20 human MM cell lines. These cells were treated with different concentration of bortezomib for 12, 24 and 48h. The effects on cell viability of bortezomib were determined using the MTT assay. The expression levels of NF-kB/p65 and p50 subunits were determined by real time RT-PCR method.

Results: Bortezomib time and dose dependently reduced cell viability in MM cells. In bortezomib-sensitive KMS-28 cell line, IC50 values were 11.83, 5.30, 3.67 nM at 12, 24 and 48h, respectively. In bortezomib-resistant KMS-20 cell line, IC50 values were 32.06, 15.62, 6.05 nM at 12, 24 and 48h, respectively. In KMS-28 cell line, the expression levels of p65 and p50 did not show any change with dose and time dependent. Moreover, the expression levels of NF-kB/p65 were observed increased in a dose dependent manner in bortezomib resistant KMS-20 cells, whereas no changes were observed in the NF-kB/p50 levels.

Conclusion: Bortezomib-resistance in MM cells can be associated with increasing of NF-kB/p65 expression levels in the high bortezomib concentrations

Keywords: Bortezomib Resistance, Multiple Myeloma, NF-kB Signaling
S-012 - INVESTIGATION OF ANTI CANCER PROPERTIES OF NEW SULPHONAMIDE DERIVATIVE SHOWED CARBONIC ANHYDRASE-IX ENZYME INHIBITOR FEATURE

Koyuncu Ismail1, Yüksekdağ Özgür2, Koçyiğit Abdürrahim3, Güler Eray Metin4, Durgun Mustafa3, Kırım Adnan1, Gönel Ataman1

1Harran University, Faculty of Medicine, Department of Medical Biochemistry, Sanlıurfa, Turkey  
2Harran University, Faculty of Arts and Sciences, Department of Biology, Sanlıurfa, Turkey  
3Harran University, Faculty of Arts and Sciences, Department of Chemistry, Sanlıurfa, Turkey  
4Bezmialem Vakif University, Faculty of Medicine, Department of Medical Biochemistry, Istanbul, Turkey

Introduction: Membrane-associated carbonic anhydrase CA-IX is one of the most important enzymes, which is related to tumour metabolism. Especially, CA-IX is an attractive target for cancer therapy. For, while it is over-expressed in a wide variety of solid tumours, CA-IX is expressed in a limited way in normal tissues. Pharmacologic interference of CA-IX catalytic activity has showed that by consequently disrupting pH regulation by cancer cells, CAIX-specific small molecule inhibitors impairs primary tumour growth and metastasis. Recently, CA-IX inhibitors have been proposed as a potential new class of anti-tumour agents.

The aim of this study is to evaluate the anti-tumour activity of CA inhibitors, two newly synthesized aromatic sulphonamides with high affinity for CAIX, 4-(2-(5-bromo-2-hydroxybenzylidene) amino)ethylbenzenesulfonamide (H2) and 4-(2-(5-chloro-2-hydroxybenzylidene)amino)ethyl benzenesulfonamide) (H4) and against human tumour cells.

Materials and Methods: The effects of H2 and H4 on cell cyto-toxicity have been evaluated by using CA-IX positive HELA, HT-29 cells and CA IX negative MDA-MB-231 cells. As a normal cell PNT-1A, HEK-293 is used. The effect of sulphonamides on cell viability is determined through WST-1 assay and then IC50 value of each compound is assessed. Apoptosis induction is determined by flow cytometry annexin V analyse, Anti proliferative effects of compounds are determined by using BrdU elisa assay. Intra-cellular accumulation of ROS is determined using the fluorescent probes.

Findings: H2 and H4 could reduce cell cyto-toxicity, proliferation and induce apoptosis in HELA cells. Moreover, all two inhibitors could increase intra-cellular ROS production in the same cells. The two inhibitors do not show any anti-tumour activity in normal PNT-1 cells.

Conclusion: CA inhibition can decrease cell proliferation and induce apoptosis in human tumour cells. The ability of CA inhibitors to increase ROS might trigger cell apoptosis. Activation of this apoptotic cascade is probably mediated by inhibition of the CA IX isoform.

Keywords: Sulphonamide erivatives, Anti-cancer, Apoptosis, Carbonic anhydrase-IX

The molecule structures of sulphonamide compounds

H2: 4-(2-(5-bromo-2-hydroxybenzylidene) amino)ethylbenzenesulfonamide and H4: 4-(2-(5-chloro-2-hydroxybenzylidene)amino)ethyl. benzenesulfonamide).

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S-013 - THE EFFECT OF THE ROSMARinus OFFICINALIS ON TEMOZOLomIDE RESISTANT GliOBLASTOMA (U87 MG) CELLS

Özdemir Damla Meryem1, Göktürk Dilek2
1Adana Science and Technology University, Graduate School of Natural and Applied Sciences, Department of Nanotechnology & Engineering Sciences, ADANA, Turkey
2Adana Science and Technology University, Faculty of Engineering and Natural Sciences, Department of Bioengineering, ADANA, Turkey

Introduction: Glioblastoma multiforme (GBM) is the most common and aggressive type of the primary brain cancer. Temozolomide is the primary medicine of GBM. But sometimes GBM can gain resistance to temozolomide. In this case some other chemotherapeutics can be used but they have serious side reactions. To avoid this we aimed to investigate the effect of Rosmarinus Officinalis (rosemary), an aromatic plant that posses phenolic diterpenes such as carnosol, carnosic acid, rosmarinic acid and effective for various cancer types.

Methods: Studies were carried out with the Glioblastoma (GBM) cell line (U87 MG) and Mouse Embryonic Fibroblast (MEF) cell line. Cells were seeded into 24 well plate and cultured. Rosemary was prepared as tea and was given to cells at various doses (1/1000, 1/100 and 1/75 (v/v)). Cells were incubated for 1 day and cell viability was measured by neutral red assay. Then with optimum dose of rosemary only GBM cells were cultured for 3 and 5 days and cell viability assays were applied.

Results: According to neutral red assay, at increasing concentrations of rosemary, MEF cells proliferated whereas GBM cells couldn’t survive. Even 1/1000 (v/v) rosemary increased the viability of healthy cells about 8% and reduced the viability of tumor cells about 23%. The 1/75 (v/v) rosemary concentration which is determined as optimum, increased the viability of healthy MEF cells by nearly 9.5% and reduced the viability of GBM cells by nearly 42%. Also 1/75 (v/v) rosemary concentration reduced the viability of GBM cells in 3 days by nearly 57% and in 5 days by nearly 44%.

Conclusion: The results show that, while rosemary helps to proliferation of healthy cells, it eliminates the tumor cells. It can be said that rosemary has a potential to be cure for temozolomide resistant GBM without damaging the healthy cells.

Keywords: Glioblastoma multiforme, MEF, Neutral Red, Rosmarinus Officinalis, Temozolomide

S-014 - SYNTHESIS, CHARACTERIZATION AND DNA INTERATION OF NOVEL PLATINUM(II) COMPLEXES CONTAINING SUBSTITUTEDBENZIMIDAZOLE LIGANDS

Utku Semra1, Nzeiyama Abdoul1, Açık Leyla2, Çelevi Keskin Ayten1
1Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Mersin University, Mersin, Turkey
2Department of Biology, Faculty of Science, Gazi University, Ankara, Turkey
3Department of Bioengineering, Faculty of Engineering, Kırıkkale University, Kırıkkale, Turkey

Objectives: The fortuitous discovery of cisplatin in 1965, and by the 1978, it had been approved by FDA for treatment of the different types of cancer such as testicular, ovarian, head and neck, colon, bladder, gastric, and lung cancer. However, there are two considerable problems associated with clinical cisplatin usage: intrinsic or acquired resistance and side effects including nephrotoxicity, ototoxicity, nausea and emetogenicity. These have led to the development of cisplatin analogs that would be clinically effective without and/or less toxicity. From this context, we report on the synthesis and spectral characterization of eight new platinum(II) complexes of the type [Pt(L1-L4)2Cl2] C1-C4 and [Pt(L1-L4)2I2] C5-C8 (L1=5(6)-chlorobenzimidazole, L2=5(6)-methylbenzimidazole, L3=5(6)-chloro-2-methylbenzimidazole, L4=5(6)-methyl-2-methylbenzimidazole). The interactions with pBR322 plasmid DNA and inhibition of the BamHl and HindIII restriction enzyme activity through the synthesized complexes were also studied.

Methods: C1-C4 or C5-C8 were prepared by the reaction of the corresponding ligand and K2PtCl4 or K2PtI4 in ethanol/water solution. The plasmid DNA interactions and restriction enzyme activities of them were also investigated using Agarose Gel Electrophoresis method.

Results: An attempts of synthesizing new potent anticancer drugs were done by combining Pt(II) chlorido and iodido compounds with benzimidazole derivatives ligands L1-L4. The description of compounds after the synthesis was assumed by using spectroscopic characterization, pBr322 plasmid DNA interaction and then BamHI and HindIII restriction enzymes. Therefore, looking after plasmid DNA interacting outcomes, synthesized complexes modified the tertiary structure of pBR322 plasmid DNA, and the results showed that the complex C2 was highly active compound regarding to all synthesized complexes.
Conclusion: It was profound that the labile ligands containing chlorido (C1-C4) are more active than those containing iodido (C5-C8). Promising biological activity from synthesized complexes provides useful information for further cytotoxic evaluation including cisplatin resistant cell lines and future platinum-drug design strategies.

Keywords: benzimidazole, platinum complexes, synthesis, gel electrophoresis, cisplatin

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S-015 - ANTICANCER EFFECTS ON HUMAN LEUKEMIA HL-60 CELL LINE AND MOLECULAR DOCKING STUDIES OF NOVEL 2,5-DISUBSTITUTED-BENZOazoLE DERIVATIVES

Oksuzoglu Emine1, Ertan Boğazi Tugba2, Tarhan Mehtap1, Ozturk Kamile1, Yıldız İlkyay2

1Molecular Biology Division, Department of Biology, Faculty of Science and Letters, Akşaray University, 068100, Akşaray, Turkey
2Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Tandogan, 06100, Ankara, Turkey

Introduction and Aim: Cancer is a disease that leads mortality in the worldwide. Recently, many efforts have been made to develop more effective ways of treating cancers and to search for novel chemotherapeutic agents with minimal side effects. Benzoxazoles, which are an important class of heterocyclic compounds that exhibit substantial biological and pharmacological activities. We previously synthesized some novel 2,5-disubstituted benzoxazole derivatives¹.². In this study, synthesized derivatives were evaluated from anticancer perspective by using various assays.

Materials and Methods: These compounds were investigated for their antitumor activities against human leukemia HL-60 cell line by using the MTT cell proliferation assay and IC50 values of the compounds were determined. Moreover, molecular docking into active site of the DNA Topo II enzyme was performed on 3QX3.PDB file in order to find out possible mechanism of antitumor effect.

Results: The results showed that some of the 2,5-disubstituted benzoxazoles were found to be more potent antitumor activity against human leukemia HL-60 cells than the well-known anticancer drug etoposide. Moreover, molecular docking studies revealed that active benzoxazoles interacted into an active site of DNA Topo II enzyme with a low binding energies.

Discussion and Conclusions: According to all obtained results showed that active 2,5-disubstituted-benzoxazole derivatives could be potential drug candidates as new antitumor agents and are worthy to carry on the anticancer studies.

Keywords: Anticancer drugs, Antitumor effect, Benzoxazoles, Human leukemia HL-60 cell line, Molecular docking
S-016 - EFFECTS OF EMBELIN ON BREAST CANCER CELL PROLIFERATION AND APOPTOSIS; COMPARING WITH DOCATAXEL AND TAMOXIFEN

Tekin Gülsüm1, Koçak Fatma Emel2, Koçak Cengiz3, Öztürk Bahadır1

1Department of Medical Biochemistry, Faculty of Medicine, Selcuk University, Konya, Turkey
2Department of Medical Biochemistry, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey
3Department of Medical Pathology, Faculty of Medicine, Dumlupinar University, Kutahya, Turkey

Introduction: Embelin is a X-linked inhibitor of apoptosis protein (XIAP) which obtained from Embele ribes plant and shown to exhibit chemopreventive, anti-inflammatory, NF-κB down-regulative and apoptotic activities through an unknown mechanism. In this study, the effect of different concentrations and durations of embelin to cell proliferation was investigated in MCF–7 (ER+, PR+, HER-2-) and MDA MB-231 (ER-, PR-, HER-2-) breast cancer cell lines by comparing with Tamoxifen and Docetaxel.

Material and Method: A real-time cell analyzer (xCELLigence, Roche Diagnostics GmbH, Penzbeerg, Germany) was used to evaluate the effects of different doses of Embelin (12.5-100µM), Tamoxifen (12.5-100µM) and Docetaxel (12.5-100nM) on the proliferation of both cell lines and determined IC50 for each drug. Cell blocks were prepared from cultured cells treated with drugs and formalin-fixed paraffin-embedded breast cancer cells were examined histopathologically using Haematoxylin&Eosin staining method. In addition, the expressions of Ki-67, Bcl-2, BAX, and cyclin-D1 were assessed immunohistochemically. Statistical analysis was performed GraphPad Prism version 6.05 (GraphPad Software, Inc., CA, USA).

Results: Embelin inhibits the proliferation in both cell lines time and dose dependent manner. IC50 for Embelin, Tamoxifen and Docetaxel in MDA MB-231 and MCF-7 cells were 64µM at 40h and 63µM at 66h; 50 µM at 45h and 40 µM at 41h; 32 nM at 60h and 43nM at 40h, respectively. As a results of histopathologic and immunohistochemical analysis, Embelin decreases Ki-67, cyclin-D1 and increases BAX/Bcl-2 ratio in both breast cancer cells. Tamoxifen and Docetaxel effects have been compared with Embelin.

Conclusions: According to results, Embelin is more effective in both cell lines compared with Docetaxel and it also has more potent for MDA MB-231 compared with MCF–7. This knowledge could be beneficial in the development Embelin-based therapies for treating breast cancer.

Keywords: Docetaxel, Embelin, MCF-7, MDA MB-231, Tamoxifen
S-017 - 3,4-BIS(3'-INDOLYL)-1,2,5-OXADIAZOLES, ANALOGUES OF MARINE ALKALOID NORTOPSENTIN: SYNTHESIS AND ANTIPROLIFERATIVE ACTIVITY

Sevgi Fatih¹, Tekin Gülsüm², Ünlü Ali²

¹Vocational School of Health Services, Medical Laboratory Program, Selcuk University, Konya, TURKEY
²Department of Biochemistry, Selcuk University Faculty of Medicine, Konya, TURKEY

Introduction: Nortopsentsins A-C, having a characteristic 2,4-bis(3’indolyl) imidazole skeleton, were isolated from marine sponge spongesorites ruetzleri, exhibited invitro cytotoxicity against P388 cells (IC50,4,5-20.7µM). Due to their interesting biological activities, various bis(indolyl) derivatives in which the imidazole moiety of nortopsentin was replaced by thiazole,pyrazole, furan,thiophene, etc. rings were designed and synthesized.Our aim is synthesis of new analogues of nortopsentin in which the central imidazole ring is replaced by 1,2,5-oxadiazole (furazan), in order to study how these structural modifications influence biological activity.

Methods: We have developed a new strategy for the synthesis Bisindolyl furazans. Initially indoles react with dichloroglyoxime from electron-rich carbon atom (C3), and thus C-C bound α-dioximes are obtained.Conversion of α-dioximes to the bioactive furazanes achieved by microwave assisted dehydration of dioximes. This method, which was carried out using the closed vessel microwave system, was a technique that was used for the first time in furazan synthesis. A real-time cell analyzer (xCELLigence, Roche Diagnostics) was used to evaluate the effects of different doses of the synthesized compounds on the proliferation of MCF–7 breast cancer cell line.Changes in the number of cells in special cell culture flasks that containing micro-electrodes was observed continuously for every 15 minutes during the 54 hours.

Results: In the present work we have synthesized three novel 3,4-Bis(3’indolyl) furazans from parent novel vic-dioximes. All of newly synthesized compounds characterized in terms of various techniques, such as 1H-NMR, 13C-NMR, FT-IR, LC-MS, and elemental analyses. The analogue with 2-methylindole substituent showed the best antiproliferative activity with IC50 23,7 µM for MCF–7 breast cancer cell line.

Conclusion: We have developed a highly efficient synthesis of 3,4-Bis(3’-indolyl)-1,2,5-oxadiazole, which are analogues of marine bis(indole)alkaloid of nortopsentins. The compounds exhibited mild to good cytotoxic activities against MCF–7 breast cancer cell line. Extensive exploration of structure–activity relationship of this novel 1,2,5-oxadiazole scaffold and its biological target studies are underway.

Keywords: Bisindole, Furazan, Microwave Synthesis, Nortopsentin, Oxadiazoles
**S-018 - BIOASSAY-GUIDED ISOLATION AND CYTOTOXIC EFFECTS OF EXTRACT AND CHEMICAL CONSTITUENTS OF CHRYSOPHTHALMUM MONTANUM (DC.) BOISS. OF TURKISH ORIGIN**

Fatma Ayaz1, Nurgun Kucukboyaci1, Nezhun Goren2, Ihsan Calis1, Seyma Aydinlik1, Engin Ulukaya1, Hayri Duman6, Sammer Yousus7, Muhammad Iqbal Choudhary7

1Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, Ankara, Turkey
2Department of Molecular Biology and Genetics, Faculty of Science and Arts, Yildiz Technical University, Istanbul, Turkey; H. E. J. Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Karachi, Pakistan
3Department of Pharmacognosy, Faculty of Pharmacy, Near East University, Nicosia, Turkish Republic of Northern Cyprus
4Department of Biology, Faculty of Science, Uludag University, Bursa, Turkey
5Department of Clinical Biochemistry, Faculty of Medicine, Uludag University, Bursa, Turkey
6Department of Biology, Faculty of Science, Gazi University, Ankara, Turkey
7H. E. J. Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Karachi, Pakistan

**Introduction:** Asteraceae family is known to have ethnomedicinal uses in cancer related diseases, and mainly investigated on cytotoxic activity. The genus *Chrysophthalmum* Schultz Bip., Asteraceae, comprises three species in Turkey. *C. montanum* (DC.) Boiss., also known “tutça”, “nezle otu”, is used on injured part of the body, against flu and sinusitis. The aim of the present study was to isolate and identify the active natural constituents from the aerial parts of *C. montanum* through bioactivity-guided fractionation.

**Material and Methods:** Aerial parts of *C. montanum* were extracted with methanol (80%). The methanolic extract was successively partitioned with n-hexane, chloroform, n-butanol, and water. The chloroform extract was subjected to separation and purification by using various chromatographic techniques. The structures of the isolated four compounds were identified by means of spectral methods, such as UV, IR, NMR, X-ray crystallography as well as EI- and HREI-MS. Beside that various cancer cells (MCF-7 and MDA-MB-231 breast; LNCaP and PC3 prostate; A549 and PC3 lung, and HT-29 colon cancer cell lines) were treated with 20 µg/ml (1), (2), (3) and (4) guaianolides. Sulforhodamine B (SRB) assay was performed to determine cytotoxicity after 48h treatment.

**Results:** The active chloroform fraction yield four guaianolides (1), (2), (3), and (4). Our data showed that (1), (3) and (4) strongly decreased cell viability compared to (2). On the other hand, our finding led us to consider (2) has a specific and selective effect on LNCAP cells.

**Conclusion:** This is the first report on the cytotoxic activity of phytochemical constituents of *C. montanum*. Based on these results, (1), (3) and (4) can be regarded as an effective approach for the treatment of cancer cells mentioned above. Therefore, these compounds deserve further attention for the proof of concept in the treatment of various cancer cells.

**Keywords:** Bioassay-guided, cytotoxic activity, *Chrysophthalmum montanum*, Asteraceae

(1) 6α-acetoxy-4α-hydroxy-9β,10β-epoxy-1βH-guaia-11(13)-en-12.8α-olide
S-019 - ANKAFERD BLOOD STOPPER INDUCES DNA DAMAGE, APOPTOSIS AND CYTOTOXIC ACTIVITY BY GENERATING REACTIVE OXYGEN SPECIES IN MELANOMA CELLS IN VITRO

Kocyigit Abdurrahim, Güler Eray Metin
Bezmialem Vakif University School of Medicine Department of Medical Biochemistry

Introduction: Although, Ankaferd Blood Stopper (ABS) could be utilized successfully as hemostatic agent for the management of clinical hemorrhages, studies demonstrated that it has cytotoxic and apoptotic effects on cells. However, the mechanism(s) of these effect has not been elucidated yet. In this study, cytotoxic, genotoxic, apoptotic and reactive oxygen generating (ROS) activities of ABS were investigated in melanoma cancer and normal cells.

Material and Methods: The cells were incubated with different concentrations of ABS (0.125 to 2 %) for 24 h. The cell viability was assessed based on ATP cell viability assay. Intracellular accumulation of reactive oxygen species (ROS) was determined using the fluorescent probes 2’,7’-dichloro-dihydrofluoresceindiacetate (DCFH-DA). DNA damage was evaluated by alkaline single cell gel electrophoresis assay (Comet Assay) and, apoptosis induction was detected by acridine orange (AO) staining method.

Results: Our results demonstrated that ABS increases DNA damage, apoptosis and ROS levels in both melanoma and normal cells in a dose dependent manner, and all of these activities were significantly higher in melanoma cells than in normal cells. There was a statistically significant positive correlation between DNA damage, apoptosis and ROS levels in ABS treated melanoma and normal cells.

Conclusion: Our results revealed that although ABS commonly used as hemostatic agent, it causes DNA damage and apoptosis by generating ROS activity in a dose dependent manner. Further studies are needed to better understand the anticancer potential of this novel hemostatic agent. These results could also contribute to the development of new treatment for cancer.

Keywords: Ankaferd, Apoptosis, Cytotoxicity, DNA Damage, Reactive Oxygen Species
S-020 - EVALUATING THE CANCER THERAPEUTIC POTENTIAL OF SUPRAMOLECULAR CALIX[4]AREN NANOFIBERS

Uyar Arpacı Pembegül¹, Özcan Fatih², Ertul Şerif³

¹Department of Biotechnology, Science Faculty, Selçuk University, Konya, Turkey
²Department of Chemistry, Science Faculty, Selçuk University, Konya, Turkey

Introduction: The search for new potent anticancer drugs that can only target cancer cells, rather than affecting normal tissues is very much commendable. Supramolecular approaches have been applied to drug delivery systems and have attracted much attention. Calixarenes are a family of bowl or cone shaped synthetic supramolecular macrocycles, composed of phenol units linked by methylene bridges through an aldehyde. The search for new potent anticancer drugs that can only target cancer cells, rather than affecting normal tissues is very much commendable. Calixarene is a highly promising candidate in this regard, and could be modified to fabricate nanofibers by electrospinning and appropriately used for targeted chemotherapy.

Methods: Non-polymeric calixarenes nanofibers were obtained from the newly synthesized organic 5,11,17,23-Tetra-tert-buty1-25,27-bis(4-aminomethyl-pyridineamido)-26,28-dihydroxyx calendar[4]arene(4-AMP) by electrospinning. FT-IR, 1H-NMR and 13C-NMR [3] and SEM analysis were done to characterize newly synthesized 4-AMP. As cancer and healthy in-vitro models, Caco-2 and L-929 cells (2x10⁵) were cultured on nanofibers, respectively. After 48 h incubation, cell growth/ proliferation analysis were done by XTT assay and to evaluate cell morphology and adhesion to nanofiber SEM measurement were done.

Results: A series of experiments were performed for optimizing electrospinning parameters used to fabricate the calixarenes nanofibers. It could be observed that the proliferation rate on nanofibers of L-929 were higher than Caco-2 cells with XTT results. % cell viability of Caco-2 cells for 48 h was less than 10, however L-929 proliferated well (almost 100 %). There were low cell adhesion of Caco-2 when compare to L-929 on calixarenes nanofibers viewed by SEM/EDS.

Discussion and Conclusions: In this work,non-polymeric calixarenes nanofibers was fabricated through using electrospinning techniques and characterized to colon cancer cells. The results reported in this study demonstrated that tumor-preferential in-vitro cytotoxicity of calix[4]aren nanofibers against Caco-2 over L-929 cells present a promising approach for efficient and safe cancer therapy.

Keywords: Calixarenes Nanofibers, Electrospinning, Tumor-Preferential Cytotoxicity

S-021 - EVALUATION OF THE EFFECTS OF THYMOQUINONE TO DYNAMIC THIOL-DISULFIDE HOMEOSTASIS DURING TOTAL BODY IRRADIATION IN RATS

Deniz Cigdem Damla¹, Aktan Meryem², Erel Ozcan³, Gurbilek Mehmet¹, Koc Mehmet²

¹Department of Medical Biochemistry, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey
²Department of Radiation Oncology, Meram School of Medicine, Necmettin Erbakan University, Konya, Turkey
³Department of Biochemistry, Faculty of Medicine, Yildirim Beyazit University, Ankara, Turkey

Purpose and Objective(s): Ionizing radiation-induced free radicals causes functional and structural harmful effects. Thiol, an important antioxidant, plays an major role in the eradication of reactive oxygen molecules. Thiol/disulfide homeostasis is a marker for oxidative stress. The objective of this study was to assess the potential effects of Thymoquinone (TQ) to dynamic thiol/disulfide homeostasis of rats received total body irradiation.

Materials and Methods: Twenty-two adult Sprague-Dawley rats were divided into 3 groups. Sham control group (n=6) did not receive thymoquinone or irradiation. Irradiation (IR) group (n=8) received only total body IR of 6 Gy. TQ+IR group (n=8) received IR plus TQ (10 mg/kg, i.p, 30 min before IR). One and a half hour following IR, blood samples were taken. Thiol/ disulfide homeostasis parameters in blood were analysed by a newly established method that measures the exact thiol/disulphide status in the body. Data analyses were performed using SAS 9.4. The statistical comparison of results has been performed by using Welch’s Analysis of variance (ANOVA) and Tukey test.

Results: Native Thiol was highest in Sham-Control group. Native Thiol levels of IR group was significantly lower than Sham-Control group when compared (p=0.03). Total Thiol and Disulfide levels were not found different among groups (p<0.05). Disulfide/Native Thiol Ratio was least in Sham-Control group and Only Disulfide/Native Thiol Ratio of IR group was significantly higher than Sham-Control group (p=0.027). Disulfide/Total Thiol and Native Thiol/Total Thiol Ratios were found significantly different between Sham-Control group and IR group (p=0.007 and p<0.007, respectively).
**Conclusion:** In TQ+IR group; Disulfide, Native thiol, Total thiol, Disulfide/Native Thiol Ratio, Disulfide/Total Thiol Ratio and Native Thiol/Total Thiol Ratio means were not found significantly different when compared with Sham-Control group. Consequently, the use of TQ before radiation treatment, helps to protect the rats from oxidant side effects of radiation.

**Keywords:** Disulfide, Irradiation, Thiol, Thymoquinone

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**S-022 - A RELATIONSHIP BETWEEN MOLECULAR STRUCTURE AND ANTICANCER ACTIVITY/CYTOTOXICITY FOR POLY(MALEIC ANHYDRIDE-CO-VINYL ACETATE)/DRUGS CONJUGATES WITH GEMCITABINE, CYTERABIN AND METHOTREXATE DRUGS**

Karakuş Gülderen

*Cumhuriyet University, Faculty of Pharmacy, Pharmaceutical Chemistry, 58140, Sivas, Turkey*

**Introduction:** Anticancer drugs such as Gemcitabine, Methotrexate and Cyterabin, which are commonly used for treatment of breast cancer, has a limited use due to their short half-life and also they have too many side effects depending on their cytotoxic effects on tissues. The objectives of this study to conjugated the anticancer agents, Gemcitabine Methotrexate, and Cyterabin, to drug carrier poly(maleic anhydride-co-vinyl acetate) (MAVA) copolymer for improve their water solubility; decrease toxic effects; and increase antitumor activity compared to crude drug.

**Material and Methods:** Structural characterization of the conjugates, MAVA/Gemcitabine, MAVA/Methotrexate and MAVA/Cyterabin, were performed by Fourier Transform Infrared Spectroscopy (FTIR) and Proton Nuclear Magnetic Resonance Spectroscopy (1H-NMR). Anticancer activity of conjugates on MCF-7 cells was determined by XTT assay in comparison with pure drugs, while their toxic effects on L929 cells were determined by XTT assay again in comparison with the pure drug. The results were also analyzed statistically with the Mann-Whitney-U Test.

**Results:** The synthesized conjugates structurally characterized with successful amidation mechanism and they exhibited good solubility in water. Killing effects for the highest concentration of Gemcitabine, Methotrexate, and Cyterabin on MCF-7 cells as follows: Cyterabin (70.17%) > MAVA/Methotrexate (65.19%) > MAVA/Cyterabin (60.64%) > Methotrexate (58.43%) > MAVA/Gemcitabine (54.84%) > Gemcitabine (39.45%) (p<0.05).

Toxic effects for the highest concentration of Gemcitabine, Methotrexate, and Cyterabin on L929 cell lines (as a function of vitality rate) as follows: MAVA/Cyterabin (100%) > Cyterabin (89.86%) > MAVA/Methotrexate (77.10%) > Methotrexate (75.45%) > MAVA/Gemcitabine (73.03%) > Gemcitabine (62.11%) (p<0.05).

**Conclusion:** Water-soluble MAVA/Gemcitabine, MAVA/Methotrexate, and
MAVA/Cyterabin conjugates observed that current anticancer activity was increased as the result of the formation of conjugates, and that also their toxic effect was decreased, compared to the its crude drug. Furthermore conjugates of Cyterabine and Gemcitabine are almost the same anticancer activity because they have very similar molecular structure.

**Keywords:** Anticancer Activity, Cytotoxicity, Gemcitabine, Metotharexate, Cyterabin

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**S-023 - THE ROLE OF REL PROTO-ONCOGENE IN FOLLICULAR LYMPHOMA DEVELOPMENT**

Baytak Esra¹, Hu Xiaozhou², Li Jinnan³, Okay Kaan², Hu Genfu⁴, Scuto Anna⁵, Zhang Wenyan³, Küçük Can¹

¹İzmir International Biomedicine and Genome Institute (iBG-İzmir), Dokuz Eylül University, İzmir, Turkey; Department of Medical Biology, Faculty of Medicine, Dokuz Eylül University, İzmir, Turkey

²İzmir International Biomedicine and Genome Institute (iBG-İzmir), Dokuz Eylül University, İzmir, Turkey

³Department of Pathology, West China Hospital of Sichuan University, Chengdu, Guangxi, China

⁴İzmir International Biomedicine and Genome Institute (iBG-İzmir), Dokuz Eylül University, İzmir, Turkey; Department of Clinical Medicine, Guilin Medical University, Guangxi, China

⁵Department of Pathology, City of Hope Medical Center, Duarte, California

Follicular lymphoma (FL) is the second most frequent lymphoma with limited knowledge regarding its etiology. REL, a proto-oncogene located on frequently amplified 2p16.1-p15 locus, has been known to promote tumorigenesis in many cancer types through deregulation of the NF-κB pathway; however, its role in FL pathogenesis has not been addressed.

In this study, we evaluated REL copy number status with q-PCR in FFPE FL tumors. Using the same tumor samples we determined REL mRNA expression with q-RT-PCR and then investigated whether there is any association between REL amplification and mRNA expression, which did not show a notable correlation. REL conserved coding sequence analysis with PCR-Sanger did not reveal any oncogenic mutation in FL tumors. However, REL amplification correlated with B symptoms and high grade disease. Next we ectopically expressed c-REL in a FL cell line, and observed moderate level of positive selection under limiting serum concentrations in support of an oncogenic role.

To sum up, REL may have a marginal role in FL pathobiology, and other genes in 2p16.1-p15 locus may have a more pivotal role.

**Keywords:** Amplification, FL, NF-κB, Oncogene, REL
**S-024 - ACHIEVEMENT OF BETULINIC ACID ON EGFR INITIATED SIGNALLING**

Gul Huseyin, Demiroğlu Zergeroğlu Asuman
Gebze Technical University, Department of Molecular Biology & Genetics, Gebze/Kocaeli

**Introduction:** It is recognized that unrestrained activation of Epidermal Growth Factor Receptor (EGFR) signalling contributes the progression of cancers including Malignant Mesotheliomas. Betulinic acid (BA) is a plant derived compound, which has an anti-carcinogenic activity mostly associated with apoptosis. The aim of this work is to investigate the effect of BA on EGF induced signal pathways in Malignant Mesothelioma (MM) cells.

**Material Methods:** MeT-5A (Mesothelial) and SPC212 (MM) cell lines were used as models for treatments. Cell viability was measured by MTS assay; protein phosphorylations and gene expressions were assessed by western blot and RT-qPCR.

**Results:** BA reduced viability of MM cells in a concentration and time dependent manner. The viability of mesothelial cells were also decreased, but only at high concentrations and late time periods. BA inhibited phosphorylation of EGFR, MAPK/ERK, PI3K/AKT and STAT proteins but induced JNK and p38 proteins in MM cells. qRT-PCR analysis revealed that STAT3 and STAT5 mRNA levels were down regulated in BA treated cells.

**Discussion and Conclusion:** The effect of BA on the viability of MM cells is more potent than that of mesothelial cells. This suggests that BA reduces cell viability and it is more cytotoxic to malignant cells than normal cells. Our results corroborate with current reports indicating that BA shows selective cytotoxicity to some tumour cells, but not to normal cells in vitro. In addition BA is able to inhibit EGF induced cancer proliferative and survival pathways in MM cells. Thus, according to our results, we propose that BA can be thought of a promising chemotherapeutic agent with potential future use in the treatment of MMs with uncontrolled EGFR signalling.

**Keywords:** Betulinic acid, EGFR, ERK1/2, AKT, STAT

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**S-025 - CHARACTERIZATION OF PROTEIN-PROTEIN INTERACTIONS BETWEEN OF THE MO25α AND CCM3 SCAFFOLD SIGNAL TRANSDUCERS AND THE STK25 PROTEIN KINASE**

Ağca Can Ali1, Hergovich Alexander2

1Department of Molecular Biology and Genetics, Faculty of Arts and Sciences, Bingöl University, Bingöl, Turkey; UCL Cancer Institute, University College London, WC1E 6BT, London, United Kingdom.
2UCL Cancer Institute, University College London, WC1E 6BT, London, United Kingdom.

**Background:** The Ste20 (sterile 20) proteins are a large family of serine/treonine kinases, which are involved in a number of biological functions such as the regulation of cell proliferation, programmed cell death (apoptosis) and cell differentiation. In this study, we aimed to expand the horizon of our current understanding of the regulation of the serine/threonine kinase 25 (STK25), a member of the Ste20-like kinase family, by the disease-associated scaffold proteins CCM3 and MO25α.

**Material and Methods:** To characterize the interactions of STK25 wild-type (wt) and mutant variants with the signal transducers CCM3 or MO25α, human embryonic kidney HEK293 cells were transfected with myc-tagged STK25 versions and HA-tagged CCM3 or MO25α, and their interactions analysed by a series of co-immunoprecipitation experiments.

**Results:** Our results suggest that STK25 carrying mutations at L386D/A389D/V409D/V409D, L408D/V409D, or A389D display impaired interactions with CCM3. In contrast, the L386D/A389D/L408D/V409D variant of STK25, like STK25(I67A), interacted normally with MO25α, while the STK25(E54A) mutant did not bind to MO25α.

**Conclusion:** Our findings collectively suggest that two residues of STK25 are essential for the interactions of STK25 with CCM3 and MO25α, respectively. Ala389 of STK25 is required for complex formation with CCM3, while Glu54 of STK25 is central for the association of STK25 with MO25α. Thus, we describe here the identification and characterisation of STK25 mutants that allow the dissection of the importance of protein-protein interactions between STK25 and CCM3 and MO25α, respectively.

**Keywords:** MO25α, CCM3, STK25, co-immunoprecipitation
S-026 - THE ROLE OF YAP1 IN PROSTATE CANCER TUMORIGENESIS

Kisaayak Collak Filiz¹, Demir Ummuhan¹, Sagır Fatma¹, Ozkanli Seyma², Engin Zerk Pınar², Kurum Esra³

¹Istanbul Medeniyet University, Faculty of Engineering and Natural Sciences, Molecular Biology and Genetics Department
²Istanbul Medeniyet University, Faculty of Medicine, Pathology Department
³Yale School of Public Health

Introduction: YAP is a transcriptional co-activator negatively regulated by Hippo Tumor Suppressor Pathway. The pathway inactivates YAP by phosphorylating and increasing its cytoplasmic localization through binding with the 14-3-3 proteins. Deregulation of the pathway has been shown to have a role in tumorigenesis and metastasis including prostate cancer (PCa).

Methods: Immunohistochemical staining of YAP1 and phosphorylated YAP1 (pYAP1) at S127 protein was used to assess the expression of proteins in prostate tumor tissues. The Kruskal Wallis H-test and postdoc pairwise comparison test were used to determine the statistical significance of the data. siRNA oligonucleotides were used to knockdown the expression of YAP1 and their effects on prostate cancer cells were investigated using cell viability, proliferation, migration, invasion, clonogenic and anchorage-independent growth assays.

Results: IHC in PCa tissues revealed YAP1 staining intensities were moderate to weak in the nucleus and cytoplasm of the tumor cells, whereas the adjacent normal epithelial showed strong staining. pYAP1 staining was not observed in the nucleus of tumor and normal cells. There was a significant association between YAP1 staining intensity and extraprostatic extension (EPE). In cultured cells, YAP1 expression increased in the whole cell lysates of AR negative (PC3 and DU145) compared to AR positive (LNCaP) cell lines and primary prostate epithelial cells. Treatment of LNCaP and PC3 with YAP1-targeting siRNA oligonucleotides (YAP1 siRNA) significantly reduced their proliferation in vitro. Furthermore, treatment with YAP1 siRNA diminished the clonogenicity and anchorage-independent growth on soft agar and migration and invasion of PC3 cells, suggesting a role of YAP1 in PCa tumorigenesis.

Conclusions: Loss of function experiments in LNCaP and PC3 revealed that YAP1
potentially plays an important role in migration and invasion. Importantly, in vitro results were supported by data from human tumors; clinically high expression of YAP in prostate tumors is correlated with EPE.

**Keywords:** Hippo Pathway, YAP1, Prostate Cancer, Migration, Invasion

**S-027 - NEGATIVE EFFECTS OF MYELOMA CELLS ON SENESCENT MESENCHYMAL STROMAL CELLS ANTI-TUMOUR PARACRINE ACTIVITY**

Özcan Servet

Erciyes University Faculty of Science, Biology Department & Genome and Stem Cell Center - GENKÖK

Mesenchymal stromal cells can be found in many organismal tissues and plays an important role in tissue growth and repair. Cellular senescence is a process that results from a variety of stresses that lead to a state of irreversible growth arrest. This encounter is adamant by secreted specific factors that is called senescence associated secretory phenotype (SASP). These secreted factors effect neighboring cells that are sensitive to senescence and prevent them from entering the neoplastic process. SASP factors alert the normal tissue cells to stop supporting neoplastic cells. These factors have positive effects as well as negative effects. It was observed that SASP has a negative effect that accelerates the tumor growth in the late stage of tumorigenesis. Cancer cells are able to misuse SASP elements to survive and grow.

In this study, we cultivated cancer cells in the presence of naive senescent MSC conditioned media (CM) and evaluated their proliferation, DNA damage, apoptosis and senescence. Our findings indicated that senescent secretomes induced apoptosis or senescence on cancer cells. However, this anti-tumor activity became impaired when senescent cells had previous contact (primed) with cancer cells. Conditional media was collected from each group and the secreted proteins were isolated. The isolated proteins were identified by using LC-MS/MS and the data analysis was performed by using PANTHER, DAVID and Ingeniuty Pathway Analysis (IPA).

According to our findings, cancer cells can misuse SASP factors as they induce a change in protein production by interacting with senescent cells. Priming with myeloma cells induced the production of 55 proteins and repressed the expression or secretion of 102 proteins.

Repressed proteins generally belong to networks associated with senescence, apoptosis, catabolic or anabolic processes while expressed ones belong to ECM networks and the promotion of metastasis.

**Keywords:** Secretome, Proteome, Stem Cell, Senescence
S-028 - DOES MW RADIATION AFFECT GENE EXPRESSION, APOPTOTIC LEVEL AND CELL CYCLE PROGRESSION OF HUMAN SH-SY5Y NEUROBLASTOMA CELLS?
Kayhan Handan1, Esmekaya Meric Arda2, Yar Saglam Atiye Seda3, Canseven Ayse Gulnihal2, Yagci Munci1, Seyhan Nesrin1

1Gazi University Faculty of Medicine Department of Adult Hematology, Ankara, Turkey
2Gazi University Faculty of Medicine Department of Biophysics, Ankara, Turkey
3Gazi University Faculty of Medicine Department of Medical Biology, Ankara, Turkey

Neuroblastoma (NB) is a cancer that occurs in sympathetic nervous system arising from neuroblasts and nerve tissue of the adrenal gland, neck, chest, or spinal cord. It is an embryonal malignancy and affects infants and children. In this study, we investigated the effects of Microwave (MW) radiation on apoptotic activity, cell viability and cell cycle progression in human SH-SY5Y NB cells which can give information about MW radiation effects on neural cells covering the period from the embryonic stages to infants.

SH-SY5Y NB cells were exposed to 2.1 GHz W-CDMA modulated MW radiation for 24 hours (h) at a Specific Absorption Rate (SAR) of 0.491 W/kg. Control samples were in the same conditions with MW exposed samples but they were not exposed to MW radiation. The apoptotic activity of cells was measured by Annexin-V-FITC and propidium Iodide (PI) staining. Moreover, mRNA levels of proliferative and cell cycle proteins were determined by real time RT-PCR. The change in cell cycle progression was observed by using CycleTest-Plus DNA reagent. No significant change was observed in apoptotic activity of MW exposed cells compared to control cells. The mRNA levels of c-myc and cyclin D1 were significantly reduced in MW group (p<0.05). The percentage of MW exposed cells in G1 phase was significantly higher than the percentage of control cells in G1 phase. MW radiation caused cell cycle arrest in G1 phase. These results showed that 2.1 GHz W-CDMA modulated MW radiation did not cause apoptotic cell death but changed cell cycle progression.

**Keywords:** Microwave radiation, Neuroblastoma, SH-SY5Y, c-myc, cyclin D1
S-029 - INVESTIGATE THE ANTITUMOR EFFECTS OF ÇEMEN EXTRACT

Çinar Serife¹, Bozkurt Özlem², Yılmaz Seher³, Ertekin Tolga⁴, Nisari Mehtap⁵, Şeker Karatoprak Gökçe⁶, Ülger Harun⁴

¹KTO Karatay University, Faculty of Medicine, Department of Anatomy, Konya
²Hacı Bektaş Veli Nevşehir University, Semra and Vefa Kucuk Health College, Nevşehir
³Bozok University, Faculty of Medicine, Department of Anatomy, Yozgat
⁴Erciyes University, Faculty of Medicine, Department of Anatomy, Kayseri
⁵Erciyes University, Faculty of Pharmacy, Department of Pharmacognosy, Kayseri

Background and Aim: Currently cancer was identified of one of the leading causes of death. Therefore studies on cancer is increasing day by day. Cemen that was made by mixture of fenugreek, red pepper, garlic, cumin, black pepper, clove, coriander, cinnamon, ginger and pimento. In this study, we investigated to antitumor effect of extract that derived from çemen on Ehrlich ascites tumor carrying Balb/C mice.

Materials and Methods: Cemen extract concentration determined 200-400mg/kg; 250-500 and 1000µg/ml respectively in vivo and in vitro studies. In vitro study, while at the end of 3 and 24 hours cell culture, cells counted, in vivo study tracking weight were performed in animal experiments. In the end of experiment, acid fluid volume and cell number of intraperitoneal fluid were calculated. Metastasis of EAT cells were evaluated histologically on abdominal organs.

Results: Our founding that çemen extract delaying the weight gain due to proliferation of EAT cells. The number of cells in the asiss fluid were statistically lower (p=0.041) in the group that given 400mg/kg cemen extract (47.28x10⁶) than control group (67.60x10⁶). After 3 hours culture period, there were no significant difference between groups in the number of viable cells. After 24 hours cell cultures, the viable cells number were significantly decrease in the treatment groups (5.7±0.2, 5.7±0.2and5.6±0.1) when compared to control group (5.9±0.2) (p=0.013). Tissues that taken from abdominal organs on control and treatment groups were evaluated histopathologically. While there was intensive EAT cells adhesion on the tissues that taken from control group, there was reduciton in the treatment groups.

Discussion and Conclusion: As a result, the cemen extract shows antitumor effect on EAT cells. We believe that our studies will be guiding for new studies about çemen and çemen could be advised as a food because of its anticancer effect.

Keywords: Allium sativum L., Capsicum annuum L., Çemen, Ehrlich ascites tumor, Trigonella foenumgraecum L.

S-030 - THE REAL TIME MONITORIZATION OF THE CYTOTOXIC EFFECTS OF VANADIUM PENTAOKSIDE ON DIFFERENT CANCER CELL LINES.

Yerer Aycan Mükerrem Betül, Arslan Aysçe Kübra, Öztürk Ebru, Dokumacı Alim Hüseyin

University of Erciyes, Faculty of Pharmacy, Dept. of Pharmacology, 38039, Kayseri

Introduction: Conventional cancer treatment’s relapse rate is often high and since mortality of the patients are high, new anticancer drugs are being sought day by day. Vanadium compounds have various pharmacological effects and the recent evidences reveal that it might be one of the new generation promising metal drugs of the future. In this study, the cytotoxicity of the vanadium compound V205 has been investigated on A549, Colo205 and MCF7 cell lines in a real time manner via Real Time Cell Analyzer.

Materials and Methods: To examine the cytotoxic effects of the compound vanadium pentoxide, on A549, Colo205 and MCF7 cell lines were seeded to plates as 12.500cells/well., and healthy fibroblast cells as 3000cells/well. 6 different doses of vanadium pentoxide (250µM, 200µM, 150µM, 100µM, 50µM, 25µM) were applied to examine the effects to the cell lines and Cell indexes were profiled to evaluate the cytotoxic effect and the IC50 levels were calculated.

Results: IC50 levels were calculated for each cell at 12th and 24th h. For MCF7 The IC50 level for 12th h was 64.14uM, where as it was 118.58uM and 136.9UM for Colo205 and A549cell lines respectively. Our studies revealed that the vanadium compound containing vanadium pentoxide element has been found to reduce cell viability in a dose dependent manner and this is the known first study profiling the real time effects of the compound on cell lines used.

Conclusion: Vanadium pentoxide, coming from a new generation metal based drugs with various pharmacological effect is promising to be one of the promising medicine. These results are further mechanism of action studies can be studied to outline the effectiveness of the compounds on these cell lines. The combination of conventional anticaner drugs can be used to increase the effectiveness and reduce the side effects of these drugs.

Keywords: Vanadium pentaoxide, A549, MCF7, Colo 205, Xcelligence
S-031 - THE DETECTION OF CURCUMINS’ ANTITUMORAL EFFECTS VIA ARGYROPHILIC NUCLEOLAR ORGANIZING REGION–ASSOCIATED PROTEIN SYNTHESIS IN MICE WITH EHRILICH’S ASCITIC CARCINOMA

Nisari Mehtap¹, Yılmaz Seher², Eröz Recep³, Ertekin Tolga¹, Bircan Duygu³, Ülger Harun¹

¹Department of Anatomy, Erciyes University School of Medicine, Kayseri, Turkey
²Department of Anatomy, Bozok University School of Medicine, Yozgat, Turkey
³Department of Medical Genetics, Düzce University School of Medicine, Düzce, Turkey

Background: Curcumin is a polyphenol compound that has antioxidant, anticancer, anti-inflammatory, anti-hyperlipidemic and antimicrobial effects. Nucleolar-organizing regions are the sites of the gene on chromosomes. The present study was aimed to show the antitumoral effect of curcumin via AgNOR protein synthesis in Ehrlich’s ascitic carcinoma (EAC) bearing mice.

Methods: Twenty three mice with EAC were randomly divided to 3 groups as positive control (n=7), group 2 (n=8) and 3(n=8) treated intraperitoneally with curcumin (25 mg/kg) and (50 mg/kg), respectively. The animals were sacrificed on 16 d, the solid tumors were removed out. Then, total AgNOR area/nuclear area (TAA/NA) and mean AgNOR number were estimated for each mice.

Results: Statistically significant differences were determined among whole groups for TAA/NA ratio (p<0.000), conversly mean AgNOR number (p=0.361). In comparison of two groups; while no difference was determined between control and curcumin (25 mg/kg) groups (p=0.061), the significant differences were detected between control and curcumin (50 mg/kg) groups (p=0.000) and between curcumin (25 mg/kg) and curcumin (50 mg/kg) groups (p=0.000) for TAA/NA ratio. However there was no significant difference for mean AgNOR number in double comparison of the groups.

Conclusion: The current study showed that curcumin has a crucial function against cancer development. Also both AgNOR values may be used as biomarkers for detection of most reliable therapeutic dose selection of cancer treatment.

Keywords: AgNORs, Cancer Treatments, Curcumin, NOR, rDNA

S-032 - THE USING OF AGNOR PARAMETERS FOR DISCRIMINATION OF BENIGN AND MALIGN BREAST LESION

Köksal Mehmet¹, Doğan Serap¹, Eröz Recep², Öztürk Figen¹, Öztürk Ahmet¹, Cücer Nurhan¹

¹Erciyes Üniversitesi Kayseri
²Düzce Üniversitesi Düzce

Introduction: In the worldwide, the most common type of cancer in women is breast cancer. Therefore the development of early diagnostic tests for breast cancer is very important. Total amount of AgNOR proteins is related to the cell proliferation rate. Thus, we evaluated the potential of the AgNOR parameters for being a useful tool for the diagnostic and prognostic purposes in distinguishing malignant and benign breast lesions.

Materials and Methods: For the comparision of the benign and malignant breast lesions using with AgNOR staining technique, three groups consist of control (n=14), benign (n=18) and malignant (n=28) were included in the study. The AgNOR staining technique was performed for slides of each individual and both mean AgNOR number and total AgNOR area/Nuclear Area (TAA / NA) ratio were evaluated via a special computer program. Fifty nuclei for each individuals were evaluated and mean AgNOR number and TAA/NA were counted and measured.

Results: The mean AgNOR number and TAA/NA were detected as 1.09 ± 0.54 and 2.51 ± 0.11 for control group, respectively. These values were 2.29 ± 1.13 and 4.21 ± 1.07 for benign and 3.03±1.86 and 6.55±2.73 for malign, respectively. According to the data, the differences were statistically significant for TAA/NA values for all comparison combinations between the three groups (p <0.001). A statistically significant difference was detected among control and both benign and malignant group for mean AgNOR area/Nuclear Area (p <0.001). But the difference between benign and malignant group was not significant for mean AgNOR number (p>0.05).

Conclusion: As a result, we thought that the evaluation of TAA/NA rate, when compared with the AgNOR number, to be a more sensitive and useful tool for distinguishing benign and the malignant breast lesions from each other.

Keywords: AgNOR, Brast Cancer, FNAB

Bu çalışma Erciyes Üniversitesi BAP birimi tarafından TDK-2013-4723 koduyla desteklenmiştir, üniversite etk kurulu tarafından 2013/193 karar numarası ile onaylanmıştır.
S-033 - IN VITRO ANTIOXIDANT PROPERTIES AND THE EVALUATION OF ANTIPROLIFERATIVE AND APOPTOTIC ACTIVITIES ON HELA, MCF-7, OE-33 AND HEPG2 CELL LINES OF THE EXTRACTS FROM MEDICINAL PLANT GENISTA LYDIA VAR. LYDIA (FABACEAE)

Tarhan Leman¹, Tongul Burcu², Kavakçaoğlu Berına³

¹Dokuz Eylül Üniversitesi, Fen Fakültesi, Kimya Bölümü, İzmir
²Dokuz Eylül Üniversitesi, Fen Bilimleri Enstitüsü Kimya Anabilim Dalı, İzmir

Background and Aim: Genista lydia has been used to treat menopausal symptoms, estrogen related diseases as prostate and breast cancers, osteoporosis and cardiovascular diseases in traditional medicine because of its known phytoestrogen content. It was aimed to investigate the antioxidant capacities and also cytotoxic and apoptotic effects of G. lydia extracts on HeLa, MCF-7, OE-33 and HepG2 cell lines.

Materials and Methods: The antioxidant properties were evaluated by measuring OH• and DPPH radical scavenging activity, total phenolic-flavonoid content, reducing power and metal chelating capacity. While colorimetric assay was used to evaluate cytotoxic activity, fluorometric assays were performed to assess the apoptotic activity of the extracts.

Results: The highest OH• and DPPH scavenging activities were found in EA and EA, extracts with the IC50 value of 9.75 and 250.00 μg/ml, respectively. While the highest total phenolic content was found in the ChlF extract as 152.36 mg gallic acid/g, the highest total flavonoid content was observed in WL with 96.92 mg catechin/g. Met/WL extract was found as the most effective in terms of its reducing power with the EC50 value of 1.51 mg/mL and metal chelating activity with 8.65%. While the most effective extract on HeLa proliferation was Met/WL, Met/WL F was the most effective one on MCF-7 and OE-33 independent from caspase-3 and -9 activities. Although impressive apoptosis induction could not be observed in MCF-7, the percentage of apoptotic cell death increased from 12.9 to 72.9% in OE-33 treated with Met/WL F but caspase-3 and -9 independently.

Discussion and Conclusion: G. lydia extracts showed apoptotic activities on HeLa and OE-33 independent from caspase-3 and -9 activities.

Keywords: Genista Lydia Var. Lydia (Fabaceae), Antioxidant Activity, Cytotoxicity, Antiproliferative Effect, Apoptosis

S-034 - CHARACTERIZATION OF NOVEL WNT/β-CATENIN PATHWAY TARGETS

Akiva Izzet, Birgül Iyison Necla

Boğaziçi University, Molecular Biology and Genetics department, İstanbul

Introduction and Purpose: Wnt/β-catenin signaling pathway is an evolutionary conserved pathway which has important functions in vertebrate development, axis formation, cellular proliferation and morphogenesis. Apart from its roles in various cellular processes, Wnt/β-catenin signaling pathway is also one of the most important intracellular pathways for cancer progression. Previous studies confirmed BRI3 gene to be one of the transcriptional target genes of this pathway and MGAT1 gene was determined to be among the putative target genes. The main purpose of this study is further characterization of these candidate molecules in order to elucidate their biological roles and eventual implications in cancer.

Material and Methods: Yeast-two-Hybrid Assay, Coimmunoprecipitation, Confocal Microscopy, Overexpression studies in Huh7-Hepatocellular Carcinoma cells, Luciferase Reporter Assay, Western Blotting, Quantitative Real-Time-PCR Analysis, Cell Proliferation and Cell Migration Assay, Xenograft Assay in NUDE/SCID mice, RNA-Sequencing.

Results: Functional characterization of novel Wnt/β-catenin pathway targets has been carried out by using various approaches. Among these; cell proliferation and migration assays showed that, Huh7 cells stably expressing each of the BRI3 and MGAT1 genes have greater proliferative and invasive capabilities compared to control Huh7 cells. Furthermore, in vivo xenograft experiments were performed and it was determined that the stable overexpression of both of these genes in Huh7 cell lines lead to tumorigenesis in NUDE/SCID mice.

Discussion and Conclusion: As a result of xenograft assays, BRI3 and MGAT1 are determined to have tumorigenic effect when overexpressed in stable cell lines. RNA-Sequencing is used in order to determine the possible interacting pathways in their cancer initiation process. IFITM3 and MGAT1 proteins were confirmed as novel binding partners for BRI3 by Y2H and Co-IP techniques. BRI3 is upregulated in response to TNF-α treatment and overexpression of BRI3 leads to an increase in NFkB promoter activity. MGAT1 is a putative novel target of Wnt/β-catenin signaling pathway and is upregulated in response to β-catenin activation.

Keywords: Wnt/β-catenin pathway, BRI3, MGAT1, Xenograft, RNA-Sequencing
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S-035 - THE EFFECTS OF ACEYTL-L CARNITINE ON CISPLATIN AND RADIATION INDUCED APOPTOSIS TREATMENT ON MEDULLOBLASTOMA CELLS

Pamukoğlu Kaynar Ayça1, Altun Zekiye1, Ercetin Özdemir Ayse Pınar1, Olgun Yuksel2, Cetinkaya Oguz2, Aktas Safiye1, Olgun Nur4

1Basic Oncology Department, Institute of Oncology, Dokuz Eylül University, Izmir, Turkey
2Otorhinolaryngology Department, Dokuz Eylül University, Izmir, Turkey
3Radiation Oncology Department, Dokuz Eylül University, Izmir, Turkey
4Pediatric Oncology Department, Institute of Oncology, Dokuz Eylül University, Izmir, Turkey

Aim: Cisplatin and radiotherapy are commonly used regimens in the treatment of pediatric malignant tumors such as medulloblastoma. Acetyl-L-carnitine (ALC) is a natural compound and it has protective effects against CDDP induced toxicities. The effects of ALC on apoptotic cell death mechanism of CDDP and if radiotherapy (RT) added with cisplatin therapy on medulloblastoma cells whether they will change cell death mechanism were aimed.

Methods: HTB-186 medulloblastoma cells were maintained in DMEM containing 5% FBS at 37°C. Cells were incubated with CDDP, RT, ALC and combinations by 24 hours. Cell viability was measured with using WST-1 test. The LD50 doses of 75uM CDDP, 5Gy RT, 25uM ALC and combinations were detected by viability assay. The apoptotic cell death evaluated with Annexin-PI analyzed with Flow Cytometry. Mann-Whitney U test used for statistical evaluation and p<0.05 was accepted as a significant level.

Results: Apoptotic cell death was apoptosis 16% in the control group, 77,9% in the 75uM CDDP and 28,95% 5Gy RT group. Apoptotic cell death was apoptosis 15,8% in the 25uM ALC, 48,1% 25uM ALC+75uM CDDP and 35,3% 50uM ALC+5Gy RT group. Apoptotic cell death was apoptosis 86,3% in the 75uM CDDP+5Gy RT and 49 % in the 25uM ALC+75uM CDDP+5Gy RT group.

Conclusion: CDDP and RT apoptotic cell death were increased compared to that in the control group. ALC+CDDP and ALC+RT apoptotic cell death were decreased compared to that in the CDDP and RT group. ALC decreased the apoptotic cell death of cells with CDDP and RT treatment affected in medulloblastoma cells.

Keywords: Medulloblastoma, Cisplatin, Radiotherapy, Acetyl-L-Carnitine, Apoptosis
S-036 - ANTIPROLIFERATIVE AND APOPTOTIC EFFECTS OF THYMOL (THYME VULGARIS), A NOVEL MONOTERPENE PHENOL, IN THE PC-3 AND DU-145 HUMAN PROSTATE CANCER CELL LINES

Elbe Hulya1, Yigitturk Gurkan2

1Mugla Sıtkı Kocman University, Faculty of Medicine, Department of Histology and Embryology, Mugla
2Ege University, Faculty of Medicine, Department of Histology and Embryology, Izmir

Background: Prostate cancer is one of the most common malignant tumors and the leading cause of cancer related death in men. Many anticancer drugs currently used clinically have been isolated from plant species or are based on such substances. Accumulating data has revealed anticancer activity in plant-derived monoterpenes. Conventional treatment of prostate cancer has been proven to be effective but there are still many highly undesirable side effects. Thus, an alternative chemotherapy agent is needed that has similar efficacy of conventional chemotherapy with minimal side effects. Thymol (5-methyl-2-isopropylphenol) is an oxygenated aromatic compound from monoterpenes group. It is the main constituent of thyme essential oil and shows antioxidant, antiseptic and antiproliferative properties. The aim of this study is to determine the antiproliferative activity and apoptotic effect of thymol on PC-3 and Du-145 human prostate cancer cells.

Methods: PC-3 and DU-145 cell lines were treated with different concentrations of thymol (100, 200, 400, 600, 800 µM) at 24 h, 48h and 72h. The cell viability was investigated by MTT assay and analysis of apoptosis with annexin V assay was determined by the Muse® Cell Analyzer.

Results: The study clearly showed the dose and time-dependent cytotoxic effect of thymol in PC-3 and DU-145 cell lines. The half maximal inhibitory concentration (IC50) values of thymol at 24h, 48h and 72h were 799, 721, 448 µM and 711, 601, 552 µM, respectively. Thymol significantly induced apoptosis in all groups as dose-dependent. Statistical analysis showed significant difference between thymol treated cell lines compared to control (p<0.001).

Conclusion: The data in the present study clearly demonstrated that thymol has apoptotic and antiproliferative properties towards PC-3 and DU-145 prostate cancer cell lines. Thymol could have a potential therapeutic significance in treating cancer.

Keywords: Thymol, Prostate Cancer, Apoptosis, Antiproliferative

S-037 - DYNAMIC ASSESSMENT OF ANTIPROLIFERATIVE AND ANTIMIGRATORY ACTIVITIES OF THE NATURAL SMALL-MOLECULE ALECTORONIC ACID BY USING REAL TIME CELL ANALYZERS (RTCA)

Varol Mehmet1, Dikmen Miriş2

1Department of Molecular Biology and Genetics, Faculty of Science, Mugla Sıtki Kocman University, Kotecli Campus, 48000, Mugla, TURKEY.
2Department of Pharmacology, Faculty of Pharmacy, Anadolu University, Yunusemre Campus, 26470, Eskişehir, TURKEY.

Introduction: Many drugs originate from the natural sources, and lichens have a great potential to produce unique compounds which have been found pharmacologically active against many biological targets due to their unique structures as a result of the collective metabolism within their complex symbiotic structures composed by heterotrophic mycobionts and autotrophic photobionts [1].

Material and Methods: The natural small-molecule named “alectoronic acid” was isolated from the Tephromela atra (Fée) and chemical characterization was realized by using 1H-NMR, IR and melting point analyses. The anti-proliferative activity was determined on human endothelial cells (HUVEC), breast carcinoma cell line (T-47D) and cisplatin-resistant breast adenocarcinoma cell line (HCC1428) by using xCELLigence RTCA MP. The antimigratory activity of alectoronic acid, it was previously established as anti-angiogenic compound by using endothelial tube formation assay, was evaluated on HUVECs by performing RTCA DP system.

Results: The obtained results showed that alectoronic acid blocks the proliferation of all of the three cell lines by depending on its increasing concentration and application time, and the proliferation of T-47D cells were more effected than HCC1428. Interestingly, alectoronic acid showed no significant anti-proliferative activity on healthy endothelial cells except the high concentrations such as 200 and 400 µM. The antimigratory activity study by using the non-toxic 25, 50 and 100 µM concentrations indicated that alectoronic acid dramatically inhibits endothelial cell migration in a correlation with angiogenesis study.

Conclusion: Consequently, alectoronic acid might be potential anti-cancer drug ingredient among the anti-angiogenic, anti-migratory and tumor suppressor activities for the prolong tumor control as some of the other lichen substances [1-2].

Keywords: Alectoronic Acid, Angiogenesis, Lichen, Migration, Proliferation.
S-038 - ANTI-CANCER EFFECT OF URFA PISTACHIO (PISTACIA VERA) GREEN HULL EXTRACT ON COLON ADENOCARCINOMA CELLS

Koyuncu İsmail¹, Koçyiğit Abdurrahim², Yüksekdağ Özgür², Gürler Eray Metin³, Gönen Ataman¹, Kirmit Adnan¹

¹Harran University, Faculty of Medicine, Department of Medical Biochemistry, Sanlıurfa, Turkey
²Harran University, Faculty of Arts and Sciences, Department of Biology, Sanlıurfa, Turkey
³Bezmialem Vakif University, Faculty of Medicine, Department of Medical Biochemistry, Istanbul, Turkey

Introduction: Pistacia vera L. is among the top fifty nutrition products that have the highest antioxidant potential due to its rich phenolic compound content and therefore is regarded to be a unique food. Also, it contains bioactive polyphenols such as isoflavones and trans-resveratrols that have anti-cancer potential. In the present study, we have investigated cytotoxic and apoptotic effect of P. vera green hull extract on cancer cells.

Materials and Methods: P. vera green hull (skin) were extracted in different solvents, sequentially. The obtained five extracts were analysed for their in vitro anti-cancer properties, using the MTT assay, on five human carcinomas: colon (HT-29, DLD-1), breast (MCF-7, MDA-MB-231), prostate (PC-3), endometrium (ECC-1) and cervix (HeLa) cancer and normal PNT-1A cell lines. The cells were incubated with different doses of extracts (5 to 500 μg/ml) for 24 hours. The cell viability was assessed via MTT assay. Apoptotic effects of hexane extracts on HT-29 cells were analysed by using flow cytometry annexin V analyse. Anti proliferative effects of compounds were determined through BrdU Elisa assay. Intra-cellular accumulation of reactive oxygen species (ROS) and mitochondrial membrane potential (MMP) was determined via using the fluorescent probes. Genotoxicity was evaluated by alkaline single cell gel electrophoresis assay (Comet Assay) methods. The quail / quantitative determination of phenolic compounds in hexane extracts were determined by GC/MS-MS and LC/MS-MS.

Results: The best anti-cancer activity was observed for the hexane (Hex) extract of P. vera green hull on HT-29 cell lines. Its hexane (Hex) extract showed a low activity against PNT-1A cancer cell lines. Hexane extract has also shown cytotoxic, genotoxic, apoptotic and ROS generating effects in a dose-dependent manner.
However, further studies at molecular level are required to support our findings and to elucidate chemotherapeutic effects of this extract on colon cancer.

**Keywords:** Pistacia Vera, Colon Cancer, Apoptosis

*This study supported by HÜBAK. (HÜBAK Project no: 15057).
Malignant mesothelioma (MM) is the primary tumour affecting the mesothelial cell wall that form in the pleura (90%), the peritonea (6-19%) and the pericardia, which is often attributable to asbestos. It is usually an aggressive, incurable type of cancer, the global residence of which keeps increasing. While clinical findings are not restricted to its early symptoms, a large number of patients with malignant mesothelioma are diagnosed late. Unfortunately, chemotherapy is the only choice for an anti-tumour treatment, and the average survival time is about 13 months. Therefore, however difficult it may be, an early diagnosis is a potential key factor to making good progress in treating Malignant Pleural Mesothelioma (MPM). Currently, there have been many commendable attempts to help early diagnosis and/or to provide more effective markers. Recent studies have introduced such promising biomarkers as CERC/M (mesothelin), NERC/M (megakaryocyte-potentiating factor), OSP (osteopontin) and HYA (Hyaluron). It is hoped that osteopontin (OPN) will be detected in early stages of MM. Osteopontin (OPN) is regulated by the protein in the cell-signal paths that mediates between cell-matrix interactions and cell signals by binding to integrin and CD44 receptors, which is also a protein associated with asbestos-based carcinogenesis. It is unfortunate that cases MPM are on the increase in Turkey, whether due to occupational reasons or due to exposure to asbestos and erionite in rural areas. The present study aims to investigate the effects of the difference in the levels of CERC / M, NERC / M, Fibulin 3, Syndecan 1, HYA, OPN and Midkine in the blood samples of patient with MPM, in addition to determining if these markers work in pre-treatment, especially in different responses to the treatment process like complete response, incomplete response, stable disease and progressive disease, and if they can be used in assessing the response of tumours.

Keywords: Asbestos, Biomarkers, Fibulin 3, Malignant Pleural Mesothelioma, Mesothelin

S-040 - THE ROLE OF BIOMARKERS IN THE FOLLOW-UP OF PATIENTS WITH MALIGNANT MESOTHELIOMA

Ayhanı Adnan1, Metin Taş Muzaffer2, Ak Günülü2, Yılmaz Şenay2, Boğar Filiz2, Teksoy Özgün1

1Eskişehir Osmangazi University, Faculty of Medicine, Department of Thorax, Eskişehir, Turkey
2Eskişehir Osmangazi University Faculty Science and Letters Department of Biology, Eskişehir, Turkey

S-041 - EFFECTS OF DIFFERENT DIET TYPES ON DNA DAMAGE AND INFLAMMATION IN BREAST CANCER

Çoban İlker1, Çiçekdal Burcu2, Güvenç Tuna Bilge3, Aydın Ahmet4, Doğan Soner5

1Department of Physiology, Yeditepe University Medical Faculty, Istanbul, Turkey
2Department of Biotechnology, Yeditepe University, Istanbul, Turkey
3Department of Biophysics, Yeditepe University Medical Faculty, Istanbul, Turkey
4Department of Toxicology, Yeditepe University Faculty of Pharmacy, Istanbul, Turkey
5Department of Medical Biology, Yeditepe University Medical Faculty, Istanbul, Turkey

Aim: Previous studies have reported that obesity has effects on all steps of carcinogenesis including cancer initiation by inducing DNA damage via the obesity induced chronic inflammation. Inflammation induced nuclear kappa B, reactive oxygen species, specific miRNAs and proinflammatory cytokines (PIC) may trigger the emergence of many cancer types including breast cancer (BC). Calorie restriction (CR) is suggested to be effective for the prevention of carcinogen induced or spontaneously emerged mammary tumors in rodents. Although exact mechanisms of CR on BC prevention could not totally be elucidated, the link might be attributed to diet induced changes in oxidative stress status and PIC levels. The aim of this study is to analyze the effect of different diet types on BC development and to understand the link between PIC (IL1-a, IL6, TNFα) levels and BC. Methods: C57/BL6 (MMTV-TGFα+) 10 weeks old mice were divided into 4 groups: Ad-libitum (AL), chronic calorie restriction (CCR), intermittent calorie restriction (ICR-R) and ICR-RF. Mice fed with different type of diets for the following 7-8 weeks. 8-OHdG levels (a biomarker for DNA damage) were measured from serum by, 8-OHdG ELISA assay kit, Elabscience and PIC levels were measured from liver homogenizates by Milliplex cytokine assay kit, Merck-Millipore. Results: Our results showed that CR has an impact on 8-OHdG and PIC levels. 8-OHdG levels were significantly decreased (%45) in CCR group compared to AL group. There was no significant difference between ICR groups. IL1-a levels significantly increased in CCR group compared to AL group. CR group had significantly more IL6 levels than AL group. However, TNFα levels of CCR group were not significantly different compared to other groups. Conclusions: We can conclude that CR might prevent or delay the development of BC by lowering 8-OHdG induced DNA damage and changing the expression of PIC. Acknowledgement: This project was supported by the grant from (project no: 114S100 and 114S894) Turkish Scientific and Technological Research Council (TUBITAK).

Keywords: Breast Cancer, Calorie Restriction, Dna Damage, Inflammation
S-042 - DIETARY CALORIE RESTRICTION ALTERS OXIDATIVE STRESS BIOMARKERS IN MMTV-TGF-ALPHA MICE

Cicekdal Munever Burcu1, Hamitoglu Muhammed2, Coban Ilker3, Aydin Ahmet2, Guvenc Tuna Bilge3, Dogan Soner1

1Yeditepe University Faculty of Medicine, Department of Medical Biology, Istanbul
2Yeditepe University Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Istanbul
3Yeditepe University Faculty of Medicine, Department of Biophysics, Istanbul

Objective: The objective of this study is to understand the effects of different calorie restriction (CR) types on oxidative stress biomarkers in a transgenic breast cancer mouse model.

Material and Methods: C57/BL6 (MMTV-TGF-a+) mice were enrolled in the study at 10 weeks of age into ad libitum-fed (AL), Chronic Caloric Restriction (CCR, %15 CR), and Intermittent Caloric Restriction [ICR, 3 weeks of AL (ICR-R) and 1 week of %60 CR (ICR-RF) in a cyclic periods] groups. Mice were euthanized at 10 (base), 18 or 50 weeks old. To determine the oxidative stress status lipid peroxidation as evidenced by malondialdehyde (MDA) and the status of the antioxidants superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were measured in erythrocytes and liver by using spectrophotometric methods.

Results: Lipid peroxidation in erythrocytes of AL group was enhanced by age compared to the base (p<0.05) while, there was no significant difference due to aging in CCR group. MDA levels of ICR-R group increased at week 18 and decreased at week 50 (p<0.05). MDA levels of liver were not different in all groups. GPx levels were higher in ICR-RF group compared to other groups at week 50 (p<0.05). SOD levels in erythrocytes were increased in AL group by age (p<0.05). CAT levels were decreased in all groups at week 18 compared to base in liver (p<0.05), an increase in CAT levels for ICR-R group were determined at week 50 compare to early ages.

Conclusion: These results displayed that CR has an impact on oxidative stress parameters. Moreover, ICR group demonstrated higher protective effect against oxidative stress than CCR group. This project is supported by TÜBİTAK (114S100).

Keywords: Oxidative Stress, Calorie Restriction, Transgenic Mice, Breast Cancer, Intermittent Calorie Restriction
S-044 - THERAPEUTIC EFFECT OF CANCER DRUGS ON MFE-319 ENDOMETRIAL CARCINOMA CELL LINE
Aydemir Isıl¹, Türköz Uluer Elgin¹, Korkmaz Oya¹, Tuğlu Mehmet İbrahim¹, Inan Sevinc²
¹Department of Histology and Embryology, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Turkey
²Department of Histology and Embryology, Faculty of Medicine, İzmir University of Economics, İzmir, Turkey

Introduction and Aim: Endometrial cancer is the most common carcinoma of the female reproductive tract. Various types of endometrial cancer are affected women such as type I and type II. Type II endometrial tumors are generally more invasive, estrogen receptor and progesterone receptor (ER/PR) negative. MFE-319 endometrial carcinoma cell line is an aggressive form like type II cancer. In our study we aimed to determine the therapeutic effect of metformin, cisplatin and paclitaxel on MFE-319 cell line using MTT and immunocytochemistry assay.

Materials and Methods: MFE-319 cells were seeded in 96-well plate and different dilutions of cancer drugs were applied and MTT assay was used. IC50 doses of metformin, cisplatin and paclitaxel were calculated. For immunocytochemistry, cells were exposed to the IC50 doses of metformin, cisplatin and paclitaxel alone and in combination for 24 h. Then cells were stained with PI3K/akt signal pathway which is critical for cell survival and cell growth markers PI3K, pErk1-2, akt-1, Pakt-1-2-3 and also angiogenic factor VEGF. Immunoreactivities were evaluated H-score and analyzed using One-Way ANOVA test statistically.

Results: Immunoreactivities of PI3K, pErk1-2, akt-1 and Pakt-1-2-3 were higher in metformin application than the other drugs. Cisplatin was decreased the immunoreactivities of PI3K, pErk1-2, akt-1 and Pakt-1-2-3. VEGF staining was the highest in control and was diminished in cisplatin application. It was ascertainment that these drugs caused decrease in the immunoreactivities in the following order of potency: cisplatin>paclitaxel>metformin. And also comparison of these drugs showed the same effect in the combination exposes: paclitaxel+cisplatin>metformin+paclitaxel>metformin+cisplatin.

Conclusion: These results were showed that cisplatin and paclitaxel were more effective than metformin. Cisplatin and paclitaxel can be used in the treatments of the invasive endometrial cancer focused PI3K/akt signal pathway. Metformin needs further studies for its use in the cancer therapies

Keywords: Endometrial Carcinoma, MFE-319, PI3K/akt, Apoptosis

S-045 - CYTOTOXIC, GENOTOXIC, APOPTOTIC AND REACTIVE OXYGEN GENERATING EFFECTS OF CARVACROL ON HUMAN FIBROBLAST (WS-1) AND GASTRIC ADENOCARCINOMA (AGS) CELLS
Günes Bayır Ayse¹, Kocyigit Abdurrahim², Güler Eray Metin²
¹Department of Nutrition and Dietetics, Faculty of Health Sciences, Bezmialem Vakif University, Istanbul, Turkey
²Department of Medical Biochemistry, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

Carvacrol is a natural phenolic compound from the plants of Family Lamiaceae. It’s some beneficial effects were reported such as antimicrobial, anti-inflammatory, and antioxidant. Additionally, anti-cancer effect was also determined on human colon carcinoma, liver carcinoma, ovarian adenocarcinoma, cervical, breast, lung cancer cells in vitro. Recently, it has been reported that loading of carvacrol in combination with chemotherapy agents into the human serum albumin nanoparticles may treat gastric cancer cells better than single drug loaded nanoparticles. However, anticancer mechanism of carvacrol has not yet been fully elucidated. Thus, the aim of this study was to explore the potential anticancer activity of carvacrol on human AGS cells. The results were statistically compared with human fibroblast (WS-1) cells which have also exposed to 0-600 μM carvacrol.

In both cell cultures carvacrol after 24 h of exposure showed cytotoxic, genotoxic, apoptotic and reactive oxygen species (ROS) generating effects in a dose-dependent manner. Significant differences exist after exposure of carvacrol in both cell cultures in the sense of cell viability, ROS generation, and DNA damage (p< 0.001). The results were statistically significant at the all same concentration which was applied to both cell cultures (p < 0.05). Interestingly, carvacrol at lower dose (10 μM) effect significantly on the proliferation of WS-1 cells (p < 0.01), and decrease the ROS generation (p < 0.01) in respect to the control cells. In general, a close negative relationship was found between cell viability and ROS level. In conclusion, carvacrol causes cytotoxic, genotoxic, apoptotic, and ROS generating effects on AGS cells more effectively than the WS-1 cells via its pro-oxidant activity.

Keywords: AGS Cells, Apoptosis, Carvacrol, Genotoxicity, WS-1 Cells
S-046 - EFFECTS OF FISETIN ON GLIOMA CELL PROLIFERATION AND APOPTOSIS

Öztopçu Vatan Pınar¹, Pak Fulya²
¹Department Of Biology, Faculty Of Arts And Sciences, Eskişehir Osmangazi University, Eskişehir, Turkey
²Graduate School Of Natural And Applied Sciences, Eskişehir Osmangazi University, Eskişehir, Turkey

Aims: Glioblastoma multiforme (GBM) remains the most aggressive and resistant brain tumor in adults. Besides a limited number of drugs, therapy resistance is the major obstacle for efficient treatment of GBM. Fisetin is a natural flavonoid. In this study the effects of fisetin on the cell morphology, proliferation and the apoptosis on glioma cells were evaluated.

Materials: The cytotoxic and the morphologic effects of fisetin (1 to 500 µM) were examined in T98G human glioma cells by inverted microscope and MTT assay. Carmustine was used as positive control and human bronchial epithelium (BEAS-2B) cells were used to see the morphological and the cytotoxic effects of the fisetin in healthy cells. Alterations on the T98G cell morphology by fisetin treatment were also analyzed by transmission electron microscopy. DNA fragmentation analysis and quantitative real time PCR (QRT-PCR) were used to evaluate the apoptotic effects of the treatment.

Results: The IC50 values of fisetin were determined as 93 and 75 µM for T98G, and 270 and 90 µM for BEAS-2B cells, respectively in 24 and 48 h. For the selected fisetin doses an increased apoptotic cell death on T98G cells when compared to BEAS-2B cells. We observed prominent expression of apoptotic genes CASPASE 3, 9, 8, BAX and decreased expression of BCL-2 and SURVIVIN in T98G cells.

Conclusion: According to the findings of this study, fisetin was found to have more efficient cytotoxic and apoptotic effects in T98G cells than normal cells, depending on the dose and the time. Additional in vivo and in vitro studies will show the place of this chemical in the treatment of glioma in the future.

Funding: This study was supported by Eskişehir Osmangazi University, Scientific Research Projects Committee (Project number: 201319A112).

Keywords: Apoptosis, Cytotoxicity, Fisetin, Glioma, QRT-PCR

S-047 - PREDICTION OF ENDOCRINE THERAPY RESPONSE AND RESISTANCE IN BREAST CANCER CELLS BY EXPLOITING THE MITOCHONDRIA AND ESTROGEN RECEPTOR STATUS

Karakas Bahriye¹, Giray Kurt Asli², Temel Sehime Gulsun³,⁴, Gul Ozgur⁵, Basaga Huveyda¹, Kutuk Ozgur²
¹Molecular Biology, Genetics and Bioengineering Program, Sabancı University, Istanbul, Turkey
²Department of Medical Genetics, Baskent University School of Medicine, Adana
²Dr. Turgut Noyan Medical and Research Center, Adana, Turkey
³Department of Histology and Embryology, Near East University School of Medicine, Nicosia, Northern Cyprus
⁴Department of Histology and Embryology, Uludag University School of Medicine, Bursa, Turkey
⁵Dept. of Genetics and Bioengineering, Bilgi University, Istanbul, Turkey

Background: Breast cancer is the leading cause of death among women globally. Estrogen receptor status is important prognostic factor and anti-estrogen (endocrine) therapy is the choice of first-line treatment in ER-positive breast cancer cases. Resistance to treatment and tumor recurrence often occur even though targeted therapies exist. Therefore, accurate biomarkers are needed to predict which individuals will respond to endocrine therapy.

Objective: In this study, we aim to explore how estrogen receptors affect mitochondrial cell death priming and endocrine therapy response in breast cancer cells.

Methods: We use a novel assay called BH3 profiling to measure how close the mitochondria for the apoptosis. ER status is determined with RT-qPCR and immunoblotting. CellTiter-Glo is used to measure cell viability in response to endocrine therapy. Confocal immunofluorescence microscopy is used to determine localization of ER isoforms.

Results: Differential expression of estrogen receptor isoforms were detected in both RNA and protein level. Endocrine therapy agents have similar EC50 values regardless of ER-α and ER-β expression status. Breast cancer cells have different mitochondrial priming status. Immunofluorescence analysis revealed mitochondrial localization of both receptors in addition to nucleus and cytoplasm.
Conclusion: Our initial results indicate mitochondria might be targeted by estrogens and this point out the role of estrogen receptors in endocrine therapy response and breast cancer progression. Our work highlights the promising potential of using BH3 profiling assay in prediction of breast cancer endocrine therapy response.

Keywords: Breast Cancer, Estrogen Receptor, Endocrine Therapy, Mitochondria, BH3profiling

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S-048 - INHIBITION OF O6-METHILGUANINE-DNA METILTRANSFERASE (MGMT) ACTIVITY ENHANCES MELPHALAN CYTOTOXICITY IN MULTIPLE MYELOMA

Akcora Yildiz Dilara1, Özkan Tülin2, Yükselten Yunus2, Özkanca Şeyma2, Beksaç Meral3, Sunguroğlu Asuman2

1Department of Biology, Art&Science Faculty, Mehmet Akif Ersoy University, Burdur, TURKEY
2Department of Medical Biology, Faculty of Medicine, Ankara University, Ankara, TURKEY
3Department of Hematology, Faculty of Medicine, Ankara University, Ankara, TURKEY

Background and Aim: Multiple Myeloma (MM) is the second most prevalent hematologic cancer manifested by proliferation of malignant plasma cells in the bone marrow. Despite introduction of novel agents such as new immunomodulators and proteasome inhibitors MM is still incurable. High-dose melphalan (L-PAM), an alkylating agent, used with stem cell transplant support increases response rates and progression-free survival. Melphalan is known to induce cytotoxicity because of the production of interstrand crosslinks, which are formed through the intermediate production of O6-alkylguanine. O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein, removes alkylating and methylating adducts from O6-guanine in DNA. As increased DNA repair activity has been implicated in protection of cancer cells from apoptosis, in this study we investigated whether pharmacological inhibition of MGMT activity enhances Melphalan cytotoxicity in MGMT proficient MM cells.

Materials and Methods: Protein expression of MGMT was investigated in MM cells by Western blotting and found that RPMI 8226 and NCI H929 cells have MGMT protein expression, whereas U266 cells are MGMT deficient. Then, RPMI 8226 and NCI H929 were incubated with MGMT inhibitor Lomeguatrib alone, Melphalan alone and Lomeguatrib in combination with Melphalan for 48 hr. Cell viability and apoptosis were assessed by MTT and Annexin V assays, respectively. DNA damage levels were examined by alkaline comet assay and immunoblotting of DNA repair proteins and Ƴ-H2AX phosphorylation.

Results: Apoptosis was found to be further increased by combined treatment with Lomeguatrib and Melphalan in MGMT proficient MM cells. In RPMI 8226 cells

This work was supported by grants from TUBITAK (SBAG-113S481), Baskent University Research Fund and The Science Academy.
S-049 - CYTOTOXIC, GENOTOXIC AND APOPTOTIC EFFECTS OF CURCUMIN IN DIFFERENT CELL LINES
Guler Fray Metin, Kocyigit Abdurrahim
Bezmialem Vakif University School of Medicine Department of Medical Biochemistry

Background: Gliomas are aggressive brain tumors with poor prognosis. Curcumin is one of the phenolic compounds. It has been known that turmeric compounds are used to treatment of many diseases due to its anti-inflammatory, anti-oxidant and anti-cancer properties. Curcumin inhibits the growth of some kinds of tumors. However, the effect of curcumin on cancer senescence is unclear.

Purpose: In this study we performed in vitro experiment to determine prooxidant, cytotoxic, genotoxic, and apoptotic effect of curcumin on different cell lines.

Materials and Methods: Glioma and healthy cell lines were treated with different doses of curcumin and incubated for 24 h. After incubation, genotoxic effect of curcumin was measured by comet assay. Cytotoxic effect was evaluated by ATP cell viability assay. Phenol & flavonoid and antioxidant effects are measured by prooxidant activities. To determine apoptotic effect of curcumin by western blotting and acridine orange staining methods at below the half maximal inhibitory concentrations (IC50) levels. Mitochondrial membrane potential (MMP) methods were performed and observed by using flow cytometer. Intracellular accumulation of reactive oxygen species (ROS) was determined using the fluorescent probes 2’, 7’-dichloro-dihydrofluorescein-diacetate.

Results: It was found that curcumin has a remarkable effect on the rate of cancer proliferation. Cytotoxic, genotoxic apoptotic and ROS generating effects in a dose dependent manner of curcumin. There was a statistically significant negative relationship between cell viability and ROS and, positive correlation between DNA damage, apoptosis and ROS levels. These results revealed that curcumin induced DNA damage and apoptosis by generating much more ROS via its pro-oxidant activity in glioma cells than in normal cells.

Conclusion: Although we found the effect of curcumin on the glioma and healthy cell lines, further studies will be needed to identify the inhibition mechanism of curcumin clearly. Further analyses are needed to understand the cancer inhibition mechanism.

Keywords: Apoptosis, Curcumin, DNA damage, Oxidative stress
S-050 - CYTOTOXIC, GENOTOXIC AND APOPTOTIC ACTIVITIES OF OLIVE LEAF AND SUMAC EXTRACTS ON CANCER AND HEALTHY CELLS

Kaleli Hümeysra Nur, Güler Eray Metin, Koçyiğit Abdurrahim

Department of Medical Biochemistry, Faculty of Medicine, Bezmialem Vakıf University, Istanbul, Turkey

**Background:** Olive leaf and sumac have been known as an antioxidant and anti-cancer agents. The anti-cancer properties are thought to be mediated by phenolic compounds present in olive leaf and sumac. Their effects on the different cells by measuring the level of cytotoxicity, genotoxicity, apoptosis, mitochondrial membrane potential and reactive oxygen species have been studied.

**Objective and Purpose:** The aim of this study is to investigate antioxidant, cytotoxic, genotoxic and apoptotic effect of olive leaf & sumac extracts on the human brain (C6) adenocarcinoma and human skin fibroblast cell lines.

**Material and Methods:** Total phenolic, flavonoid content, and antioxidant activities were determined using suitable methods as DPPH, antocyanin and prooxidant activity. C6 and CCD cells were incubated with different doses of olive leaf extract and sumac extract separately. After 24 h incubation of cells cytotoxicity, apoptosis and reactive oxygen species (ROS) generation were analyzed. Apoptotic effects were determined by annexin and mitochondrial membrane potential (MMP) methods. Genotoxicity was evaluated by Comet Assay. Cytotoxicity was analyzed by using ATP cell viability assay. Intracellular accumulation of ROS was determined using the fluorescent probes 2’7’-dichloro-dihydrofluorescein-diacetate.

**Results:** It was determined that extract have shown antioxidant activity in all tests and that they could be considered as a source of natural antioxidants. Cytotoxic effects were concentration-dose dependent manner. Specifically, apoptotic and genotoxic effect increased at 100 and 200 μg/ml concentrations by 24 hours. Our results shown that olive leaf and sumac extracts had more antiproliferative, genotoxic and apoptotic effects on the human cancer cell line than skin fibroblast normal cell line.

**Conclusion:** Further studies will be needed to use olive leaf and sumac extracts as phytotherapeutic agents for cancer therapy.

**Keywords:** Olive Leaf & Sumac Extracts, Antioxidant, Anticancer, Apoptosis, Genotoxicity

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S-051 - HDAC INHIBITORS, MS-275 AND SALERMIDE, POTENTIATES THE ANTICANCER EFFECT OF EF24 IN HUMAN PANCREATIC CANCER CELLS

Yar Sağlam Atıve Seda¹, Yılmaz Akın², Önen Hacer İlke¹, Alp Ebru³, Kayhan Handan³, Ekmecki Abdullah¹

¹Department of Medical Biology and Genetics, Faculty of Medicine, Gazi University, Beseveler, Ankara, Turkey
²Department of Medical Biology, Faculty of Medicine, Hitit University, Çorum, Turkey
³Department of Medical Biology, Faculty of Medicine, Giresun University, Giresun, Turkey

**Keywords:** HDAC inhibition in pancreas cancer cells.

Histone deacetylases (HDACs) play a major role in the regulation of chromatin structure and gene expression by changing acetylation status of histone and nonhistone proteins. MS-275 (entinostat, MS) is a well-known benzamide-based histone deacetylase inhibitor (HDACI) and Salermide (SAL), a reverse amide compound HDACI, have antiproliferative effects on several human cancer cells. In this study, we aimed to investigate the effects of HDACIs (MS and SAL) alone and/or combined use with EF24 (EF), a novel synthetic curcumin analog, on human pancreatic cancer cell line (BxPC-3). In vitro, BxPC-3 cells were exposed to varying concentrations of MS, SAL with or without EF, and their effects on cell viability, acetylated Histone H3 and H4 levels, cytotoxicity, cleaved caspase 3 levels, and cell cycle distribution were measured. The viability of BxPC-3 cells decreased significantly after treatment with EF, MS and SAL treatments. MS and SAL treatment increased the acetylation of histone H3 and H4 in a dose dependent manner. MS and SAL alone or combined with EF were increased the number of cells in G1 phase. In addition, treatment with agents significantly decreased the ratio of cell in G2/M phase. There were significant dose dependent increases at cleaved Caspase 3 levels after MS treatment but not after SAL treatment. Our results showed that HDAC inhibitors (MS and SAL), when combined with EF, may effectively reduce pancreatic cancer cell (BxPC-3) progression and stop the cell cycle at G1 phase. Further molecular analyses are needed to understand the fundamental molecular consequences of HDAC inhibition in pancreas cancer cells.

**Keywords:** EF24, HDACI, MS-275, Pancreatic Cancer, Salermide
S-052 - DOES CHEMOTHERAPEUTICS CONTRIBUTE TO DNMT1 EXPRESSION LEVEL IN COLORECTAL CANCER CELLS?

Varol Nuray¹, Arıkan Terzi Evrim Suna², Soylemez Zafer³, Yıldız Salına Handan¹, Ozdemir Erdogan Muğan⁴, Solak Mustafa¹

¹Afyon Kocatepe University, Faculty of Medicine, Department of Medical Genetics, Afyonkarahisar
²Afyon Kocatepe University, Faculty of Medicine, Department of Medical Biology, Afyonkarahisar

Introduction and Aim: Epigenetic modifications, particularly DNA methylation in selected gene promoters is a pivotal role in the development of colorectal cancer. DNA methylation is considered as one of the most important epigenetic mechanisms and it is catalyzed by DNA methyltransferases (DNMTs). DNMT1 abundance has been frequently seen in colorectal cancers but the reasons are not well understood. We investigated to the effect of chemotherapeutics used in treatment of colorectal cancer on expression of DNMT1 and this effect is achieved over which signalling pathway.

Materials and Methods: Cell proliferation levels in HT29 cells treated with specific inhibitors (LY294002 for Akt1; SB216763 for GSK3β; IWP2 for β-catenin) and chemotherapeutics (oxaliplatin, fluorouracil, irinotecan) were detected by WST1. DNMT1 expression level was determined by real-time PCR; and protein levels of GSK3β, pGSK3β(Ser9), Akt1, pAkt1(Ser473), β-catenin, pβ-catenin(Ser675) and DNMT1 by western blot.

Results: Our results indicated Akt1 increased the protein level of DNMT1 expression without coordinate transcriptional change via β-catenin pathway. Fluorouracil and irinotecan decreased DNMT1 expression both transcriptional and translational levels but not oxaliplatin. Oxaliplatin increased DNMT1 expression at mRNA and protein levels. This effect is achieved by specific phosphorylation of β-catenin protein.

Conclusion: The results revealed that use of some chemotherapeutic, particularly oxaliplatin, with specific inhibitors combination led to a reduced DNMT1 expression. Our findings may offer a new approach for determination of molecular effects of β-catenin signal pathway on DNMT1. This may allow us to identify new molecular targets for the treatment of colorectal cancers. However, the results revealed that some chemotherapeutics may contribute aberration of DNA methylation.

Keywords: Chemotherapeutics, DNMT, Akt1 signalling pathway, β-catenin signalling pathway, Colorectal cancer

S-053 - INVESTIGATING THE ROLE OF ALTERNATIVE POLYADENYLATION IN LUNG SQUAMOUS CELL CARCINOMA

Kazan Hilal

Department of Computer Engineering, Uluslararası Antalya Üniversitesi, Antalya, Turkey

Introduction: Polyadenylation is an RNA processing step that involves the cleavage of pre-mRNA at a poly(A) site and addition of the poly(A) tail. Approximately 70% of human genes contain multiple poly(A) sites and can undergo alternative polyadenylation (APA). APA could lead to the production of mRNA isoforms with variable lengths of 3'UTRs. Gain or loss of cis-regulatory regions in 3’UTR isoforms can alter mRNA stability and translation dramatically. In particular, a strong association has been found between proliferation and 3’UTR shortening through the use of proximal polyA sites. Previous studies that explored the effects of 3’UTR shortening have mainly focused on the regulatory effects of microRNAs (miRNAs); however, it is well known that 3’UTRs also harbor sites for several RNA-binding proteins (RBPs).

Methods: In this study, we developed a computational model that incorporates APA-related changes in both miRNA and RBP sites. To map miRNA sites, we utilized TargetScan predictions as well as Ago-CLIP-derived peaks. For RBP sites, we scanned the 3'UTRs with RNAcompete motifs, and also included CLIP-derived peaks. We developed a regression model that links these alterations with gene expression changes [3]. Our analysis revealed a strong association between the loss of binding sites and downregulation for a number of RBPs. One of these RBPs is ELAVL1, a well-characterized stabilizing factor. Altogether, these results indicate that future studies of APA must incorporate the regulatory effects of RBPs in addition to miRNAs.

Results: We identified the RBP and miRNA sites that are lost or gained due to APA and developed a regression model that links these alterations with gene expression changes [3]. Our analysis revealed a strong association between the loss of binding sites and downregulation for a number of RBPs. One of these RBPs is ELAVL1, a well-characterized stabilizing factor. Altogether, these results indicate that future studies of APA must incorporate the regulatory effects of RBPs in addition to miRNAs.

Keywords: post-Transcriptional Regulation, Alternative Polyadenylation, RNA-Binding Proteins, miRNAs, Regression
S-054 - CTLA-4 GENE +49 A/G POLYMORPHISM IN PROSTATE CANCER PATIENTS

Budak Diler Songül

University of Niğde, Faculty of Art and Science, Department of Biotechnology, 51200, Niğde, Turkey.

Background and Aim: Prostate cancer are the most common cancers in Western population and its rate is increasing in the Eastern World. The aim was to evaluate cytotoxic T lymphocyte associated antigen-4 (CTLA-4) gene +49 A/G polymorphisms in prostate cancer patients.

Methods: This study included 119 (68.94±8.38) healthy controls and 62 (72.83±7.60) patients with prostate cancer. The CTLA-4 +49 A/G (rs231775) gene regions were amplified using polymerase chain reaction (PCR), detected by restriction fragment length polymorphism (RFLP).

Results: At the end of our research, we found that the prevalence of genotypes of AA (wild-type), AG (heterozygous mutant) and GG (homozygous mutant) profiles for the CTLA-4 +49 A/G polymorphism were 50%, 45% and 5% respectively in prostate cancer patients, and 56%, 36% and 8% respectively in healthy control groups.

Conclusions: Any association was not found for CTLA-4 +49 A/G polymorphism between prostate cancer patients and the control groups in Turkish population.

Keywords: CTLA-4 +49 A/G polymorphism, Prostate cancer, PCR, RFLP

S-055 - DEMONSTRATION OF THE EFFECTIVENESS OF NEOADJUVANT CHEMOTHERAPY AND RADIOTHERAPY BY 18F-FDG PET-CT AND MRI IN PATIENTS WITH COLORECTAL CANCER

Gül Serdar Savas1, Rahatlı Samed2, Güler Avci Gülhan3, Sönmezgöz Fitnet4, Hasbek Zekiyе5

1Gaziosmanpaşa University, School of Medicine, Department of Nuclear Medicine, Tokat, Turkey
2Gaziosmanpaşa University, School of Medicine, Department of Internal Medicine, Tokat, Turkey
3Gaziosmanpaşa University, School of Medicine, Department of Radiation Oncology, Tokat, Turkey
4Gaziosmanpaşa University, School of Medicine, Department of Radiology, Tokat, Turkey
5Cumhuriyet University, School of Medicine, Department of Nuclear Medicine, Sivas, Turkey

Aim: Colorectal cancer is one of the most common tumors of the gastrointestinal tract. The adjuvant therapy selected according to the stage and location of the disease affects the prognosis. In our study, the effectiveness of preoperative chemotherapy and radiotherapy in patients with colorectal cancer was evaluated by using Fluor-18 Fluorodeoxyglucose Positron Emission-Computerized Tomography (18F-FDG PET-CT) and Magnetic Resonance Imaging (MRI).

Methods: Twelve patients with a diagnosis of colorectal adenocarcinoma were included in the study (5 females and 7 males; mean age 68.1±11.8 years). Patients were treated with concomitant chemotherapy and radiotherapy before the surgery. Preoperative and postoperative F-18 FDG PET-CT and MRI images were obtained. PET-CT images were used to determine the tumor size, area and volume with the SUVmax and were compared to the tumor size, area and volume on MRI.

Results: Chemotherapy regimen of capacitamine 825mg/m2 two times daily for 5days/week was given to 8patients and 5-Fluouracil 225mg/m2 with an infusion pump for 7days was given to the remaining 4patients. Simultaneous radiotherapy included a total of 45Gy with a fractioned dose of 1.8Gy/day to the areas with standard risk and a total of 50Gy with a fractioned dose of 2Gy/day to the high-risk areas. Preoperative and postoperative F-18 FDG PET-CT and MRI images were obtained (Figure1). Both imaging methods revealed a significant decrease in the tumor size, volume and area after the treatment (Table1).
Conclusion: Effect of perioperative chemotherapy and radiotherapy on survival rate is an important research area in terms of adjuvant therapy with no available clear conclusions. Results of the present study suggest that chemotherapy and radiotherapy given before the surgery is an effective treatment method resulting in a significant decrease in tumor size which was shown in both PET-CT and MR images. In conclusion, F-18 FDG-PET-CT is considered to be a good alternative for conventional MRI.

Keywords: Neoadjuvant Chemotherapy, Radiotherapy, 18F-FDG PET-CT, MRI, Colorectal cancer

Figure 1

The decrease in tumor size (white arrow) on transaxial and sagittal F-18 FDG-PET-CT images obtained before and after the surgery in patients with colorectal cancer.

Table 1

Comparison of the decrease in tumor size after the neoadjuvant chemotherapy and radiotherapy by using MRI and PET-CT in patients with colorectal cancer.
S-056 - FACTORS EFFECTING MORTALITY IN PATIENTS OPERATED DUE TO GASTRIC CARCINOMA

Kayıhoğlu Selami Ilgaz, Dinç Tolga, Göktuğ Ufuk Utku, Bostanoğlu Akın, Sonişık Muhittin, Coşkun Faruk

General Surgery, Ankara Numune Research and Training Hospital, Ankara, Turkey

The purpose of this study is to investigate the results of data obtained from the records of patients who were operated due to gastric carcinoma in our hospital, to determine whether the evaluated variables have an effect on mortality. Demographic information (age, gender, contact information, hospital registration, and citizenship number), types of surgery performed (total/subtotal gastrectomy), histopathological diagnosis (tumor size, lymph node calculation and status), pathological stage, serum albumin levels, tumor markers, complete blood count, and survival status of 170 patients who underwent surgery due to gastric carcinoma were observed and recorded. According to these data, metastatic lymph node ratio (MLR), red cell distribution width - platelet ratio (RPR), neutrophil - lymphocyte ratio (NLR), platelet - lymphocyte ratio (PLR), and prognostic nutritional index values were calculated.

Results: According to the univariate analysis of the independent variables which effect mortality, NLR, MLR, age, stage, and gender parameters were found statistically significant (p<0.05). According to the multivariate analysis (Cox regression analysis), age, the stage of disease, and RPR were found statistically significant. For patients who underwent surgery due to gastric carcinoma, being over the age of 68, RPR rate higher than 0.038, and disease in stage 4 have been determined as prognostic factors which have negative effects on mortality.

Keywords: Gastric Carcinoma, Mortality, Prognostic Factors

Multivariate logistic regression model for the factors effecting general survival (95% CI)

| Variables | Odds Ratio | 95% CI          | p value |
|-----------|------------|-----------------|---------|
| Age       | 1.0475     | 1.0100 to 1.0864| 0.0130* |
| Stage     | 2.6539     | 1.0277 to 6.8532| 0.0448* |
| RPR       | 4.0480     | 1.2362 to 13.2555| 0.0215* |

RDW: Red cell distribution width, RPR: red cell distribution width - platelet ratio, CI: Confidence Interval *P<0.05 significant.
S-057 - BRCA2 AND RAD51 GENE EXPRESSION ANALYSIS OF CMTS

Özmen Özge¹, Kul Selim², Rışvanlı Ali³, Kul Oğuz⁴

¹Ankara University, Faculty of Veterinary Medicine, Department of Genetics, Ankara, Turkey.
²Firat University, Faculty of Veterinary Medicine, Department of Animal Breeding, Elazığ, Turkey.
³Firat University, Faculty of Veterinary Medicine, Department of Obstetrics and Gynecology, Elazığ, Turkey.
⁴Kirikkale University, Faculty of Veterinary Medicine, Department of Pathology, Kirikkale, Turkey.

Tumors of the mammary glands are the most common tumors to affect entire female dogs representing between 50-70% of all tumors types, which is three times higher rate of incidence than humans. No other animal species has such high probability of onset of mammary tumors. In humans, heritable breast cancers have been linked with mutations in the breast cancer susceptibility gene BRCA2. The primary function of BRCA2 is homologous recombination, and its mediates the recruitment of recombinase RAD51 to DNA double-strand breaks; RAD51 recruitment is not only essential for homologous recombination but also responsible for the tumor-suppressive function of this repair process. In this study, BRCA2 and RAD51 mRNA expression was measured in tissue samples of adenomas and adenocarcinomas of the mammary gland by real-time quantitative reverse transcription polymerase chain reaction. Tumoral biopsies taken from the mammary gland regions of 64 canine patients were examined histopathologically and a total of 22 mammary tumors (benign n=10 and malign n=12) were used for the study. Expression levels in the tumors were normalized to the geometric mean of two housekeeping genes (ATP5B, HPRT) and quantified relative to normal mammary epithelium of the same dog. In adenomas, mRNA expression was reduced for BRCA2 (2/10, 20%) and RAD51 (4/10, 40%). BRCA2 and RAD51 were overexpressed in 9 of 12 (75%) and 10 of 12 (83%) of adenocarcinomas, respectively. The results of this study indicate that BRCA2 and RAD51 genes are overexpressed in malignant canine mammary tumors (CMTs).

Keywords: BRCA2, RAD51, Gene Expression, CMTs
S-058 - FLUORESCENCE MICROSCOPIC DETECTION OF SOME TERMINAL SUGAR MOIEITIES ON THE CELL SURFACE OF HUMAN THYROID CARCINOMA CELL LINES

Sancar Baş Serap¹, Kaptan Engin¹, Sancaklı Aylin², Bolkent Şehnaz¹

¹Istanbul University, Faculty of Science, Department of Biology, Section of Molecular Biology Vezneciler 34134 Istanbul/Turkey
²Istanbul University, Graduate School of Engineering and Science, Department of Biology, Vezneciler, Istanbul/Turkey

Background: Aberrant glycosylation is a common phenomenon in various pathological processes. Differences in the enzyme expressions induce changes in the composition of membrane glycans conjugated with glycolipids and glycoproteins. Thyroid cancers root from follicular cells of thyroid gland and it is the most common type of endocrine cancers.

Objective: In this study, we aimed to show terminal α-2,3, α-2,6 sialic acid and α-1,6 fucose residues, which are known to be effective in malignancy in several cancer types, on cell surface glycan chains in anaplastic 8505C, follicular FTC-133 and papillary K1 thyroid cell lines.

Material and Methods: The cells were treated with determined doses of the biotinylated lectins; Maackia amurensis lectin-I (MAL-II; Neu5Ac α-2,3Galβ1-4GlcNAc), Sambucus nigra agglutinin (SNA; Neu5Ac α-2,6 GalNAc), Aleuria aurantia lectin (AAL; GlcNAcβ1-4(Fucα-1,6) GlcNAc) for lectin binding assay. The cells were examined under fluorescent microscope after incubation of streptavidin-Texas red. Surface glycosylation patterns of the cell lines were compared with human thyroid follicular epithelial cell line Nthy-ori 3-1 by considering fluorescent density.

Results: We found that α-1,6 fucosylated glycan chains, α-2,3 and α-2,6 sialylated glycan chains were dramatically high on all cells lines we used when compared to human thyroid epithelial cell line Nthy-ori 3-1. MAL-II binding of K1 was lower than those of FTC-133 and 8505C. AAL binding of FTC-133 was lower than those of K1 and 8505C. Also, SNA binding of 8505C was lower than those of FTC-133 and K1.

Discussion: It is suggested that predominantly found α-1,6 fucosylated, α-2,3 and α-2,6 sialylated glycan chains can be indicators of the aberrant glycosylation. Each of the aberrant glycosylation moieties that we detected may be responsible for different tumorigenic and malignant characters.

Conclusion: The cell surface glycosidic properties of thyroid carcinoma cells we detected can be used as a target for developing new strategies in diagnosis and therapy.

Keywords: Aberrant glycosylation, Aleuria aurantia lectin (AAL), Maackia amurensis

Lectin (MAL II), Sambucus nigra agglutinin (SNA), Thyroid carcinoma
S-059 - NEAR-INFRARED FLUORESCENT CARBON NANOTUBE BASED SENSORS FOR IN VITRO AND IN VIVO CANCER APPLICATIONS

Sen Fatih
Department of Biochemistry, Dumlupinar University

Since carbon nanotubes exhibit a fluorescent signal in a spectral region where there is minimal interference from biological media, they are particularly attractive for biomedical applications. Even though carbon nanotubes have been used as highly sensitive detectors for cancer applications, their use as in vivo biomarkers requires the simultaneous optimization of various parameters, including biocompatibility, molecular recognition, high fluorescence quantum efficiency and signal transduction. Addressed herein, a polyethylene glycol ligated copolymer stabilizes near infrared-fluorescent single-walled carbon nanotubes sensors in solution, enabling intravenous injection into mice and the selective detection of local nitric oxide concentration with a detection limit of 1 mM. The half-life for liver retention is 4 h, with sensors clearing the lungs within 2 h after injection, thus avoiding a dominant route of in vivo nanotoxicology. After localization within the liver, it is possible to follow the transient inflammation using nitric oxide as a marker and signalling molecule. Finally, we demonstrate that alginate-encapsulated single-walled carbon nanotubes can function as implantable inflammation sensors for nitric oxide detection, with no intrinsic immune reactivity or other adverse response for more than 400 days.

Keywords: Biosensor, Carbon Nanotube, Infrared, NO

S-060 - SEX HORMONE DEPENDENT TOXICITY OF OCHRATOXIN A IN THE KIDNEY OF FEMALE RATS

Kılıç Mehmet Akif1, Mor Firdevs2, Özmen Özlem3

1Akdeniz University, Science Faculty, Department of Biology, Antalya, Turkey.
2Mehmet A. Ersoy Univ., Veter. Faculty, Dept. of Pharm. and Toxicology, Burdur, Turkey
3Mehmet Akif Ersoy University, Veterinary Faculty, Dept. of Pathology, Burdur, Turkey.

Introduction and Aim: Ochratoxin A (OTA) could cause pathological lesions, including renal cancers. Female rodents ought to be less susceptible to OTA toxicity. The objective of this study was to deduce the role of sex hormones in the OTA-related pathogenesis in female rat kidneys.

Material and Methods: Female rats, 16-weeks old, were divided into 5 different groups (n=7): intact females (F), ovariectomised (F-OVA), testosterone injected (F-TEST), antitestosterone injected (F-AntiTEST) and ovariectomised and testosterone injected (F-OVA+TEST) and fed with a diet containing 3 ppm of OTA for 9 weeks. Lesions in kidney parts were evaluated and scored in a range 0-3. A score of 3 was used for the most prominent histological change.

Results: In all experimental groups, the outer medulla had the highest karyomegalic cells. Karyomegaly scores of rats were: F-OTA (2.00±0.00), F-OVA-OTA and F-TEST-OTA (2.28±0.48), F-OVA+TEST-OTA (2.66±0.57) and F-AntiTEST-OTA (1.00±0.00). The results showed that although ovariectomy or testosterone treatment did not significantly change number of karyomegalic cells in kidneys, testosterone injection to ovariectomised females markedly increased karyomegalic lesions and conversely, antitestosterone injection significantly reduced karyomegalic lesions. The number of apoptotic cells and their localization were also evaluated and the cortex was more affected than other parts. The F-OVA+TEST-OTA had the highest apoptosis score (1.33±0.57) and antitestosterone treatment significantly reduced apoptotic cell death (0.28±0.48). All these findings suggest that testosterone also plays an important role in the OTA-related pathogenesis in female rats.

Conclusion: Although OTA is toxic to all parts of the kidney, 1- the outer medulla seems to be more sensitive to OTA toxicity, 2- testosterone remarkably increases its deleterious effects and 3- testosterone repression in female rats significantly reduces its side effects. We suggest that testosterone is the major player in the OTA-
related sex dependent toxicity differences observed in rats.

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Keywords: Ochratoxin A, Testosterone, Antitestosterone, Kidney, Female rats

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S-061 - P-COUMARIC ACID ATTENUATE ON CISPLATIN-INDUCED OXIDATIVE STRESS IN RAT’S HEART

Ekinci Akdemir Fazile Nur¹, Gürsul Cebrail², Gülçin İlhami³, Alvasel Saleh H.⁴, Gözcü Dusak Lale⁵, Bayır Yasin⁵

¹Department of Nutrition and Dietetics, Health School, Ağrı İbrahim Çeçen University, Ağrı, Turkey
²Department of Physiology, Faculty of Medicine, Erzincan University, Erzincan, Turkey
³Department of Biochemistry, Faculty of Science, Atatürk University, Erzurum, Turkey
⁴Department of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia
⁵Department of Biochemistry, Faculty of Pharmacy, Atatürk University, Erzurum, Turkey

Aim: The healing importance of cisplatin as anticancer treatment is limited via its cardiotoxicity. The most of natural phenolic acids in the protection from many pathological events have been determined in the previous study. In the present study, we were aimed to investigate the protective effect of p-coumaric acid, as a phenolic acid, against cisplatin-induced oxidative damage on the rat’s heart.

Material and Methods: In our experimental study thirty Sprague-Dawley type adult rats were used. The rats were divided into five groups; control, control+ethanol, cisplatin, p-coumaric acid, and p-coumaric acid+cisplatin. Cisplatin was administered i.p. in a single dose of 10 mg kg⁻¹. p-Coumaric acid was used in a doses of 100 mg kg⁻¹ i.p. for three sequential days. In cisplatin group, rats were sacrificed after for 72 hours administration of cisplatin. At the end of the experiment, rats were sacrificed with high dose anesthetic agent and heart tissues removed quickly. The biochemical measurements were performed in tissue samples.

Results: Pretreatment with p-coumaric acid was improved the tissue content of glutathione level, and superoxide dismutase activities, compared to cisplatin-received rats. Also, tissue MDA decreased following p-coumaric acid pretreatment, compared to cisplatin-treated rats. But this damage was decreased in group of p-coumaric acid treatment.

Conclusions: Our results were indicated that p-coumaric acid can prevent heart tissue against cisplatin-induced oxidative damage. We have believed that p-coumaric acid may have valuable benefits in cancer treatment.

Keywords: Cardiotoxicity, p-coumaric acid, Cisplatin, Oxidative stress
S-062 - FLOW CYTOMETRIC ASSESMENT OF THE ROSA CANINA EXTRACTS ON DIFFERENT CANCER TYPES

Kılınç Kağan¹, Turan İbrahim¹, Demir Selim², Burnaz Nesibe Arslan⁴, Genç Berna¹, Örem Asım³, Alver Ahmet¹

¹Gumushane University Faculty of Engineering and Naturel Science Department of Genetic and Bioengineering Gumushane Turkey
²Karadeniz Technical University Faculty Of Health Sciences Department of Nutrition and Dietetics, Trabzon, Turkey
³Karadeniz Technical University Faculty of Medicine Department of Medical Biochemistry, Trabzon, Turkey
⁴Gumushane University Faculty of Health Department of Nutrition and Dietetic Gumushane Turkey

Introduction: Rosa canina is the rich including polyphenols, carotenoids, ascorbic acid and fatty acids. Several studies have indicated that Rosa canina hips show antioxidant, anti-inflammatory, anticancer, properties. Rosa canina is also used in the treatment of several illnesses and disfunctions in traditional medicine due to the above mentioned compounds. In this study we aimed to investigating anticancer effect and their apoptotic ways of different Rosa canina extracts.

Material and Methods: Rosa canina samples were extracted by using different solvents and solvents plus 0,5% hydrogen chloride. Rosa canina extracts (RCE) analyzed with spectrophotometric and HPLC methods to detect their antioxidant capacity, species of phenolic compounds. We were chose the most appropriate RCE sample for anticancer and flow cytometry analyzes according to their values. This RCE sample extracted with dimethyl sulfoxide (DMSO), DMSO-acetic acid(DMSO-AA) and DMSO-hydrogen chloride (DMSO-HCl).

Human lung carcinoma (A549) and human prostate adenocarcinoma (PC-3) cell lines were used to detect antiproliferative and possible apoptotic effects of RCE on cancer. Flow cytometrically, Cell cycle, Annexin V, mitochondrial membrane potential and caspase 3/7 activities tests carried out on significantly antiprolifreative cell lines.

Results: In A549 and PC-3 cell lines, during cell cycle test, RCE with DMSO-AA IC90 value has shown significantly differences (P<0.01) during Annexin V and mitochondrial membrane potential tests according to number of necrotic cells. RCE with DMSO-AA was induced the caspase 3/7 activities significantly in A549 line (P0.01) whereas RCE has no effect on PC-3 cell line.

Discussion: It was concluded that Rosa canina may have anticancer activity by different signal ways necrotic, apoptotic and cell cycle mechanisms.

Keywords: Anticancer, Flow cytometry, Dimethyl sulfoxide, Rosa canina
S-063 - FHit DEFICIENCY DRIVES NEOPLASTIC INITIATION AND PROGRESSION

**Batar Bahadır**1*, Karras Jenna R.1, Schrock Morgan S.1, Zhang Jie2, Perle Krista L3, Druck Tresa1, Huebner Kay1

1Department of Cancer Biology and Genetics, Ohio State University Wexner Medical Center, Columbus, Ohio, USA.
2Department of Biomedical Informatics, Ohio State University Wexner Medical Center, Columbus, Ohio, USA.
3Department of Veterinary Biosciences, College of Veterinary Medicine, Ohio State University, Columbus, Ohio, USA.

*Current address: Department of Medical Biology, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey

**Background:** The Fragile Histidine Triad (FHit) gene, spans the most active common fragile site, FRA3B, is one of the earliest and frequently altered genes in preneoplasia and cancer. Fhit protein, which is reduced in expression in the majority of human cancers, is a genome ‘caretaker’ whose loss initiates genome instability in preneoplastic lesions. Our goal was to demonstrate that Fhit deficiency supports tumorigenic initiation and progression.

**Material and Methods:** We established epithelial cell lines from kidney tissues of Fhit-/- and +/- mouse pups early after weaning and subjected cell cultures to nutritional and carcinogen stress, to assess the early genetic alterations and functional changes. Through transcriptome profiling and protein expression analysis, we defined alterations in proteins in signal pathways that are frequently altered in cancers.

**Results:** Fhit-deficient cells exhibited alterations in Trp53/p21 and survivin apoptotic pathways and in expression of proteins involved in the epithelial-to-mesenchymal transition (EMT). Some Fhit-/- cell lines displayed anchorage-independent colony formation and increased invasive capacity in vitro. Furthermore, cells of stressed Fhit-/- cell lines formed subcutaneous and metastatic tumors in nude mice.

**Conclusions:** Fhit-deficient cells are more susceptible to acquire cancer-promoting mutations. Thus, Fhit loss provides a ‘mutator’ phenotype. Loss of Fhit leads to survival and selective expansion advantage for transformation and cancer progression.

**Keywords:** Fhit, Genome Instability, Cell Transformation

S-064 - ARE THERE POSSIBLE ASSOCIATIONS BETWEEN MNSOD AND GPX1 GENE VARIANTS FOR LARYNGEAL CANCER RISK OR DISEASE PROGRESSION?

**Censoğlu Cihan**1, Verim Ayşegül2, Farooqi Ammad Ahmad3, Turan Saim4, Mezani Brunilda5, Küçük hüseyin Özlem5, Hakan Mehmet Tolgahan5, Ergen Arzu1, Yao lim Ilhan1

1Department of Biochemistry, Haseki Training and Research Hospital, Istanbul, Turkey
2Otorhinolaryngology Clinic, Haydarpasa Training and Research Hospital, Istanbul, Turkey
3Laboratory for Translational Oncology and Personalized Medicine, Rashid Latif Medical College, Lahore, Pakistan
4Department of Molecular Medicine, Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey

**Introduction:** Laryngeal squamous cell carcinoma (LSCC) is a multifaceted and genomically complex disease and cellular and preclinical studies have demystified wide ranging molecular mechanisms which underpin its development and progression and resistance against wide ranging molecular therapeutics. Oxidative stress is a widely studied molecular mechanism and reportedly involved in carcinogenesis. Increasingly it is being realized that accumulation of Reactive Oxygen Species (ROS) activates defensive mechanism to counteract oxidative stress induced damage. Manganese superoxide dismutase (MnSOD) and glutathione peroxidase (GPx) are important members of defensive machinery. We investigated whether the polymorphisms of MnSOD (Ala-9Val, rs4880) and GPx1 (Pro198Leu, rs1050450) are associated with LSCC and also evaluated possible interactions between these polymorphisms and various lifestyle factors or pathological features of patients.

**Material and Method:** For this purpose, 67 LSCC patients and 73 healthy controls were enrolled. Molecular assessment of MnSOD and GPx1 variants were determined with polymerase chain reaction-restriction fragment length polymorphism techniques.

**Result:** We found that the frequency of both heterozygous PL genotype and P allele was considerably higher in patients with advanced tumor stage (T3/T4) than in those with early tumor stage (T1/T2) (OR= 5.106; 95% CI=1.372-19.004; p<0.001, OR=5.787; 95% CI =1.564-21.414; p<0.001 respectively). Although the frequency of ValVal/LL combine genotype was significantly decreased (OR=0.204,
95% CI=0.055-0.760; p=0.021), the frequency of ValAla/PL combine genotypes was higher in patients with stage T3/T4 than in those patients with stage T1/T2 (p=0.027).

**Conclusion:** Consequently, we have concluded that variants of GPx1 and MnSOD should not be considered as a risk factor of LSCC, only may be accepted as a prognostic markers. Use of new technologies such as metabolomics and deep DNA sequencing will prove to be helpful in developing a deeper knowledge related to how cancer cell metabolism adapts and provides a buffer against increased oxidative stress.

**Keywords:** Larynx cancer, Genotype, MnSOD, GPx1, Polymorphism