CAN WE EAT TO PREVENT COLORECTAL CANCER?

Introduction Industrialization, western lifestyle and changes in environmental and dietary factors are possible causes of the increasing prevalence of colorectal cancer (CRC). Mediterranean diet (MDiet) is considered one of the healthiest diet models because it has positive functional effects on the health and wellbeing of the individual. Several studies suggest that the adherence to a dietary pattern based on MDiet prevents the development of certain types of cancer, due to the role of dietary fibre, as well as the diversity of vitamins and substances with antioxidant properties. To date, there are few studies conducted in the Portuguese population. This work constitutes an exploratory study in the 'Região Centro' of Portugal and aims to understand the impact of diet on CRC.

Material and methods In order to explore this question, we conducted a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to investigate the association between serum calcium levels and the risk of colorectal cancer (CRC) development. 975 first incident CRC cases were matched to 975 matched controls from within the cohort by sex, age, study centre, length of follow-up and some additional relevant variables. Serum calcium levels were measured using reflection X-ray fluorescence spectrometry on the pre-diagnostically-collected serum samples from cases and matched controls. Conditional logistic regression was used to calculate multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CIs).

Results and discussions Higher levels of serum calcium were associated with reduced risk of CRC (OR Q5 vs Q1=0.69, 95% CI: 0.48–0.99; p trend=0.02). Sub-group analyses by anatomical sub-site suggest that the observed inverse cancer risk association is apparent in the colon (OR Q5 vs Q1=0.61, 95% CI: 0.38–0.98; p trend=0.04) and not in the rectum (OR Q5 vs Q1=0.99, 95% CI: 0.53–1.85; p trend=0.54) where the association appeared to be non-linear. The magnitude of the association in the colon is similar to that observed with diet-related to higher CRC risk.

Conclusion In conclusion, elevated serum calcium levels are inversely associated with risk of CRC development, with some evidence for heterogeneity by anatomical sub-site and sex. Additional studies are necessary to confirm these findings and to further investigate potential underlying mechanisms for the role of serum calcium in CRC development.
with high-LET carbon beams, pretreatment of 10 µM DADS resulted in more significant decrease in cell viability, weaker G2/M phase arrest, more significant increase in apoptosis were observed in comparison with HeLa cells exposed to radiation group alone. Furthermore, combination DADS and high-LET carbon beams exacerbated the activation of apoptosis pathways through up-regulated ration of pro-apoptotic Tap73 to anti-apoptotic ΔNp73, and its downstream protein such as FASLG, and APAF1 in contrast to radiation group alone.

**Results and discussions** These observations indicate that DADS is a very promising candidate as radio sensitive agent for cervical cancer and the ratio of pro-apoptotic Tap73 to anti-apoptotic ΔNp73 might be a molecular predictor of tumour responsiveness to radiation in a p53-independent manner. This study highlights a potential role of DADS and the ratio of Tap73/ΔNp73 in radiotherapy.

Taken together, our results strongly suggest that DADS enhances high-LET carbon beams induced apoptotic cell death in human cervical cancer cells via regulating balance between Tap73 and ΔNp73. We propose that DADS could be an a very promising candidate as radio sensitive agent for cervical cancer and the ratio of pro-apoptotic Tap73 to anti-apoptotic ΔNp73 might be a molecular predictor of tumour responsiveness to radiation in a p53-independent manner. However, this would require further investigation using tumor-bearing animal model and clinical trials to understand the effects of the DADS.

**Conclusion** These observations indicate that DADS is a very promising candidate as radio sensitive agent for cervical cancer and the ratio of pro-apoptotic Tap73 to anti-apoptotic ΔNp73 might be a molecular predictor of tumour responsiveness to radiation in a p53-independent manner. This study highlights a potential role of DADS and the ratio of Tap73/ΔNp73 in radiotherapy.

**PO-106 UNIQUE AND OVERLAPPING ROLE OF HIF PROTEINS IN RADIATION RESPONSE AND TUMOUR CELL METABOLISM**

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**Introduction** Hypoxia is a common feature of human solid tumours and caused by limited diffusion and structural aberrations of tumour vasculature. Tumour hypoxia in cancer is linked to worse outcome and treatment resistance. Hypoxic cells are also characterised by changes in their energy requirements and radiation response. Many of these adaptations are driven by the hypoxia-inducible transcription factors or HIFs. Mammalian cells encode for three HIF1–3 proteins which are O2 regulated. The similarities and differences between HIF proteins in regulating tumour cell metabolism and radiation response are still understudied.

**Material and methods** Using gene-editing with the CRISPR/CAS9 system we generated isogenic series of cells lacking HIF1, HIF2 or both HIF1,2 in the H1299 non-small cell lung cancer cell line. We analysed the differences in hypoxia response on downstream target gene activation. In parallel, we analysed the upregulation of HIF protein expression under hypoxic conditions for each cellular model. Proliferative capacity and hypoxic tolerance were assessed for each cell line. We determined the metabolic consequences of silencing HIF by measuring oxygen consumption rate, extracellular acidification rate, extracellular pH and lipid droplet accumulation. We determined the radiation response of each cellular model under both normoxic and hypoxic conditions using clonogenic survival assays, gamma-H2AX staining and cell cycle analysis.

**Results and discussions** We found that HIF2 compensates for the depletion of HIF1, but HIF1 is not upregulated upon HIF2 depletion. Both HIF1 and HIF2 proteins appear to be crucial for the upregulation of downstream HIF target genes such as CAIX, GLUT1 or TWIST. HIF depleted cells appear to be less glycolytic and at the same time trigger mitochondrial activity. The radiation response of the different cellular models shows a specific profile in terms of clonogenic survival and double-strand break formation in both normoxic and hypoxic conditions.

**Conclusion** Taken together these genetically-modified cell models may help us to further define the radiation response of hypoxic tumour cells for therapeutic interventions.

**PO-107 NOTCH SIGNALLING PATHWAY IS REQUIRED FOR PROLIFERATION, REPAIR AND DIFFERENTIATION OF PRIMARY HUMAN LUNG STEM CELLS UPON IRRADIATION**

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**Introduction** Lung cancer is the leading cause of cancer death in western countries. While significant progress has been made in terms of treatment, radiotherapy is limited by dose-limiting side-effects. Reducing side-effects may improve tumour control by dose-escalation and treatment-time. The NOTCH signalling pathway plays an important role in differentiation of the airway epithelium and its deregulation is associated with lung cancer. However, the mechanism by which NOTCH inhibition integrates with airway repair is unknown. What is currently lacking are primary human lung tissue models that enable robust evaluation of the effects of treatment which can guide the selection of combination treatments for lung cancer.

**Material and methods** We therefore investigated the effects of inhibiting NOTCH in human basal stem cells from normal primary bronchial epithelial cells isolated from lung cancer patients undergoing lobectomy. Basal stem cells isolated from 3 different patients were treated with the pan NOTCH inhibitor (DBZ) and irradiated with 2–4 Gy. Incucyte experiment, Edu/PI staining and clonogenic assay were used to evaluate proliferation and clonal capacity. To evaluate DNA damage response S3 bp1 staining was performed. To study Notch inhibition in basal cells differentiation the tracheal epithelium of 2–5 Gy irradiated mice was seeded in ALI system and confocal stainings were performed.

**Results and discussions** Incucyte experiment revealed a reduced proliferation of stem cells upon NOTCH inhibition which is further reduced upon irradiation. NOTCH inhibition induces accumulation of the cells in GO-G1 phase and a significant reduction in S phase which was exacerbated upon irradiation. The reduction in proliferation also led to a reduction in long term survival. We observed activation of the DNA damage response pathway by expression of pCHK2, pATM upon NOTCH inhibition which was enhanced by radiation. S3 BP1