Combined treatment with lexatumumab and irradiation leads to strongly increased long term tumour control under normoxic and hypoxic conditions

Patrizia Marini¹, Dorothea Junginger¹, Stefan Stickl¹, Wilfried Budach³, Maximilian Niyazi¹ and Claus Belka*¹,²

Address: ¹CCC Tübingen, Dept of Radiation Oncology, University of Tübingen, Hoppe-Seyler-Str 3, 72076 Tübingen, Germany, ²Dept of Radiation Oncology, LMU University of München, Marchioninistr 15 81377 München, Germany and ³Dept of Radiation Oncology and Radiotherapy, University of Düsseldorf, Moorenstr 5, 40225 Düsseldorf, Germany

Email: Patrizia Marini - patrizia.marini@uni-tuebingen.de; Dorothea Junginger - dorothea.junginger@gmx.de; Stefan Stickl - stefan.stickl@gmx.de; Wilfried Budach - wilfried.budach@med.uni-duesseldorf.de; Maximilian Niyazi - maxi.niyazi@t-online.de; Claus Belka* - claus.belka@med.uni-muenchen.de

* Corresponding author

Abstract

Purpose: The combination of ionizing radiation with the pro-apoptotic TRAIL receptor antibody lexatumumab has been shown to exert considerable synergistic apoptotic effects in vitro and in short term growth delay assays. To clarify the relevance of these effects on local tumour control long-term experiments using a colorectal xenograft model were conducted.

Materials and methods: Colo205-xenograft bearing NMRI (nu/nu) nude mice were treated with fractionated irradiation (5× 3 Gy, d1-5) and lexatumumab (0.75 mg/kg, d1, 4 and 8). The tumour bearing hind limbs were irradiated with graded single top up doses at d8 under normoxic (ambient) and acute hypoxic (clamped) conditions. Experimental animals were observed for 270 days. Growth delay and local tumour control were end points of the study. Statistical analysis of the experiments included evaluation of tumour regrowth and local tumour control.

Results: Combined treatment with irradiation and lexatumumab led to a pronounced tumour regrowth-delay when compared to irradiation alone. The here presented long-term experiments revealed a highly significant rise of local tumour control for normoxic (ambient) (p = 0. 000006) and hypoxic treatment (p = 0. 000030).

Conclusion: Our data show that a combination of the pro-apoptotic antibody lexatumumab with irradiation reduces tumour regrowth and leads to a highly increased local tumour control in a nude mouse model. This substantial effect was observed under ambient and more pronounced under hypoxic conditions.

Background

Lexatumumab is a fully human agonistic antibody with a distinct tumour cell specificity via activation of TRAIL (TNF-related apoptosis inducing ligand) receptor 2 (TRAIL-R2) induced apoptosis. Although TRAIL-R2 stimulation alone is highly effective in a wide range of cancer cell lines, effi-
cacy can be increased by combination with other gyrostatic drugs (for review see [1]). We have already shown that a combined treatment with TRAIL and irradiation exerts highly synergistic effects regarding apoptosis induction. This enhanced efficacy was detectable in various solid tumour cell lines and lymphoid tumour cells[2,3].

Since discovery of TRAIL and its receptors in 1997 a panel of agonistic antibodies for TRAIL-receptors R1 and R2 have been developed and tested in clinical phase I and II trials [4-18]. However, up to now only little data are available concerning interaction of agonistic TRAIL receptor antibodies and irradiation ([7,19,20]. Besides our recently published report no data on experiments with a combination of a fully human TRAIL receptor antibody and irradiation have been published[21].

Combining mapatumumab or lexatumumab with irradiation, we have demonstrated that this combination exerts strong additive and synergistic effects on apoptosis induction in vitro and in short-term growth delay experiments[10]. However, to proof that induction of apoptosis evidently translates into definitive tumour stem cell eradication long-term experiments with local tumour control as primary endpoint might provide a reliable model for clinical potency [22-26].

Therefore, we decided to perform long-term experiments in a nude mouse xenograft model. As radiation sensitivity becomes affected by limiting intratumoural hypoxia we run experiments under both ambient and hypoxic conditions to mimic realistic tumour conditions[27].

Taken together, our experimental series was designed to confirm the striking principle that radiation mediated TRAIL sensitization effectively increases long-term local tumour control.

**Materials and methods**

**Animals and tumours**

Immunodeficient NMRI-(nu/nu)-nude mice were purchased from a specific pathogen free colony at the University of Essen (Germany) at the age of 4-6 weeks. Animals were kept in an individually ventilated cage rack system (Techniplast, Italy) and fed with sterile high calorie laboratory food (Sniff, Germany). Drank water was supplemented by chlorotetracycline and potassium sorbate acidified to a pH of 3.0 with hydrochloric acid.

The Colo205 tumour cell line (established from a colorectal adenocarcinoma) was acquired from ATCC (Bethesda, MD, USA). In NMRI-(nu/nu)-nude mice Colo205 cells form solid, roundly shaped tumours without indication for metastasis.

**Transplantation and experimental design**

Tumour lumps of about 2 mm diameter from a source tumour were implanted subcutaneously into the right hind limb of 6-10 week old animals. Approximately 2-3 weeks after transplantation tumour growth was measurable. Tumour size was quantified with calipers in two perpendicular diameters. The tumour volume (V) was calculated as $V = (a \times b^2)/2$, where $a$ and $b$ are the long axis and the short axis, respectively. Scoring of tumour sizes took place three times per week before start of treatment. Body weight was monitored once a week.

The median tumour volume at the start of experiments was $116 \pm 31 \text{ mm}^3$. Animals were randomly allocated to 24 treatment arms (scheme see Figure 1): lexatumumab at day 1, 4 and 8 (0.75 mg/kg body weight intraperitoneally (i.p.)) alone, fractioned radiotherapy (5 × 3 Gy within five subsequent days) alone. Single dose top up irradiations (0, 10.0, 14.5, 21.0, 30.4, 44.2 Gy) were performed on day 8. Combined treatment was performed at day 1, 4 and 8 with lexatumumab (0.75 mg/kg) (figure 1). Control ani-
mals were treated only with an i.p. injection of medium without antibody or irradiation.

To minimize toxic side effects and to apply high irradiation doses in an easy comparable, time saving schedule we choose a combination of fractionated and graded single high dose (top up) irradiation. 3 Gy single dose was chosen for fractionated irradiation based on previous experiments (Marini et al., Oncogene 2006). Fractionated irradiation of tumours was applied in inhalation (Isoflurane) narcosis. Top up irradiation under ambient conditions or under clamped hypoxia was performed with i.p. narcosis (fentanyl, midazolam, medetomidine), as recommended by the university veterinarian department. For animals, whose tumours were clamped irradiation was performed 10 minutes after applying a narrow lace to the right hind limb just at the proximal end of the tumour to make the hypoxic radiation conditions as consistent as possible. Experiments were performed in one run with 252 animals.

Tumour volumes were scored twice a week, no blinding took place. Follow up was discontinued after 270 days or in case of intercurrent death or if tumours had grown to eight-times the initial tumour volume at the start of treatment. Growth delay and local tumour control were endpoints of the study. All animal experiments were accomplished in accordance with the guidelines of the local authorities (Regional Board Tuebingen, Germany, appl.no. R4/04) and the German animal welfare regulations.

**Statistical Analysis**

Statistical analysis was performed as described before[21]. In short terms, an exponential regression model was used to interpolate median tumour regrowth times. Regrowth delay was compared by unparametric Kruskal-Wallis tests with Dunn’s post tests. Tumour control rates were calculated accounting for censored animals as described by Walker and Suit[28]. Data were analysed by a probit non linear regression analysis. Parameters were estimated using the maximum likelihood method. Statistical significance was calculated asymptotically by means of a Hessian matrix (STATISTICA 6.0 StatSoft, Hamburg, Germany).

**Results**

Treatment with lexatumumab failed to induce any immune reactions of the irradiated skin. No evidence of acute toxicity was observed. Follow up revealed no significant differences in frequency of intercurrent deaths after irradiation alone or combined treatment with lexatumumab (5.6% vs. 4.6%).

Figure 2 shows a chronological sequence of the impressive tumour regression after treatment with lexatumumab (0.75 mg/kg) for one test animal, exemplarily. Obviously, tumour growth reduction started after the second application i.p., already. However, lacking consolidating irradiation in this example tumour regrowth is evident four weeks after start of treatment.

However, combination of very low doses of irradiation with lexatumumab led to an unexpected high local tumour rate, already. Tumour regrowth after combined treatment was observed in less than 50% of the animals. Figure 3 shows data on the 2-, 4- and 8-fold tumour regrowth after single and combined treatment with a 10 Gy top up dose, exemplarily. In this subset of experiments, five of nine mice were lacking any tumour regrowth 270 days after start of treatment. Analysis of the median time of tumour regrowth after combined treatment was impaired by an unexpected high rate of local control (figure 3). Therefore, we decided to choose the more complex probit non linear regression analysis.

Figure 4 depicts the extraordinary efficacy of the combined treatment by the probit analysis. Irradiation with graded top up doses from 0 to 44.2 Gy alone resulted in local tumour control from 0 to 52% under ambient conditions (figure 4a, grey solid line). Addition of lexatumumab after fractionated irradiation alone already caused very high tumour control rates of 85-87%, regardless of the top up dose (p = 0.000006, figure 4a, black solid line). Under clamped bloodflow, treatment with lexatumumab enhanced local tumour control after irradiation with fractionated irradiation and graded top up doses (0 to 44.2 Gy) alone from 0% - 30% (figure 4b, grey solid line) up to 43 - 87% (p = 0.00003, figure 4b, black solid line). Statistical analysis unveiled a highly significant increase of tumour control rates under both, ambient (p < 0.0001) and hypoxic (p < 0.0001) conditions (table 1).

**Discussion**

Our data prove that the combination of the proapoptotic human antibody lexatumumab with ionizing radiation has an obvious influence on local tumour control in a long-term xenograft model. The effect is evident after irradiation with low doses, already.

It is important to note that these experiments with an agonistic antibody against TRAIL receptor DR5 corroborate our recently published data on a high efficacy of a combined treatment with another proapoptotic antibody (mapatumumab, anti-DR4) and irradiation. Both models are in line with in vitro data from our and other labs demonstrating that irradiation acts as a TRAIL sensitizer and not obversely[3,29,30].
Figure 2
Photographic showcase of the chronological sequence of tumour regression and tumour regrowth after i.p. application of lexatumumab (0.75 mg/kg; d 1, 4 and 8) from day 1 (d1) up to day 81 (d81) of treatment.
This principle diverges from other combined approaches where classical chemotherapeutic or other molecular targeted agents act as radiosensitizer. E.g. the synergizing efficacy of cisplatin is based on increased oxygenation of hypoxic cells and an influence in DNA-repair and cell cycle regulation [31-33]. Cetuximab, an antibody against epidermal growth factor receptor, seems also to influence long-term tumour control by affecting DNA damage repair [34,35]. In contrast to former reports the mitochondrial pathway has a strong impact in TRAIL induced apoptosis. Depending on the cell system applied mitochondrial amplification loops account for its high efficacy [36,37]. Cetuximab, an antibody against epidermal growth factor receptor, seems also to influence long-term tumour control by affecting DNA damage repair [34,35].

In contrast to former reports the mitochondrial pathway has a strong impact in TRAIL induced apoptosis. Depending on the cell system applied mitochondrial amplification loops account for its high efficacy [36,37]. In combination with TRAIL, irradiation increases apoptosis in tumour cells with an impaired mitochondrial pathway. Furthermore, preirradiation of bcl-2 overexpressing lymphoma cells raises cell death rates after TRAIL receptor stimulation [38]. In several tumour cell systems, the proapoptotic molecule Bax was shown to be essential for the combined effect of TRAIL and ionizing radiation suggesting a considerable mitochondrial relevance for this synergizing principle [10,39,40].

The role of radiation induced TRAIL receptor upregulation has been discussed extensively. However, we and others found an only weak or lacking correlation between upregulation and synergism [10,41,42]. Although, other mechanisms like cell cycle regulation might play a role [43].

It is important to note, that this synergistic principle works under ambient and hypoxic conditions as well. Weinmann et al. demonstrated an undiminished efficacy of TRAIL alone under hypoxia in a lymphoma cell model [44]. Takahashi et al. reported similar observations on clonogenic cell kill of A549 cells after treatment with TRAIL and irradiation [45]. However, it remains speculative why this effect on local tumour control is more pronounced under normoxia than under hypoxia. The known increase of intrinsic radioresistance of hypoxic cells will be responsible for this reduced susceptibility.
The strong request on the development of personalized targeted therapies has amazingly changed the general approach to cancer treatment. In contrast to cytostatic drugs being prescribed on base of classical features as TNM classification and histology, targeted drugs require an accurate identification of patient collectives who benefit from a given treatment. Therefore, a specific subset of marker molecules should be identified for each targeted drug [46-48].

**Conclusion**

The here presented data provide evidence that the combination of apoptosis inducing antibodies with irradiation strongly increases long-term tumour control. Since murine long-term control experiments are the only currently accepted functional approach to simulate the efficacy of radiation based treatments the given data are an optimal scientific base for subsequent clinical trials.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

PM conceived and drafted the manuscript. DJ and SS carried out the animal experiments to the same portion. WB performed the statistical analysis. MN participated in the statistical analysis and in the drafting of the manuscript. CB contributed to interpretation of the data and critically reviewed the article. All authors read and approved the final manuscript.
Acknowledgements

We thank Human Genome Sciences, Inc. for providing lexatumumab and Dirk Schiller, University of Tübingen, for providing the pictures on tumour growth after treatment with lexatumumab. In addition, we like to thank Katrin Stasch and Stefan Ablasser for technical assistance. This work was supported by a grant from the Federal Ministry of Education and Research (Fo: 1456-00) to CB and VJ and by the ’Deutsche Krebshilfe’ (Grants 10-1764 B1 and 10-2220 B6) to CB, PM and WB.

References

1. Ashkenazi A, Holland P, Eckhardt SG: Ligand-based targeting of apoptosis in cancer: The potential of recombinant human antiapoptosis ligand 2/tumor necrosis factor-related apoptosis-inducing ligand (rhapo2l/trail). J Clin Oncol 2006, 24:3621-3630.

2. Belka C, Schmid B, Marini P, Durand E, Rudner J, Faltin H, Bamberg M, Schlue-Ohstorf K, Budach W: Sensitization of resistant lymphoma cells to irradiation-induced apoptosis by the death ligand trail. Oncogene 2001, 20:2993-3003.

3. Marini P, Schmid A, Jendrossek V, Faltin H, Daniel PT, Budach W, Belka C: Irradiation specifically sensitizes solid tumour cell lines to trail mediated apoptosis. BMC Cancer 2005, 5:5.

4. Pan G, O’Rourke K, Chinnaiyan AM, Gentz R, Ebner R, Ni J, Dixit VM: The receptor for the cytotoxic ligand trail. Science 1997, 276:111-113.

5. Walczak H, Miller RE, Arai K, Gliniak B, Griffith TS, Kubin M, Chin W, Jones J, Woodward A, Le T, Smith C, Smolak P, Goodwin RG, Rauch CT, Schuh JC, Lynch DH: Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo. Nat Med 1999, 5:157-163.

6. Camidge DR: An agonist monoclonal antibody directed against death receptor 5/trail-receptor 2 for use in the treatment of solid tumors. Expert Opin Biol Ther 2008, 8:1167-1176.

7. Fisher SB, Gillis GD, Oliver PG, Zhou T, Beleksy-Desilets DJ: Enhancement of glioma radiotherapy and chemotherapy response with targeted antibody therapy against death receptor 5. Int J Radiat Oncol Biol Phys 2008, 71:507-516.

8. Humphreys R, et al.: HGS-TR2J, a human, agonistic, trail receptor-2 monoclonal antibody, induces apoptosis, tumor regression and growth inhibition as a single agent in diverse human solid tumour cell lines. Abstract #204: 16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Geneva, Swizrs 2004.

9. Ichikawa K, Liu W, Zhao L, Wang Z, Liu D, Ohtsuka T, Zhang H, Moutz JD, Koopman WJ, Kimberly RP, Zhou T: Tumooricidal activity of a novel anti-human dr5 monoclonal antibody without hepatotoxicity. Nat Med 2001, 7:954-960.

10. Marini P, Denzinger S, Schiller D, Kauder S, Welz S, Humphreys R, Daniel PT, Jendrossek V, Budach W, Belka C: Combined treatment of colorectal tumours with agonistic trail receptor antibodies HGS-ETRI and HGS-ETR2 and radiotherapy: Enhanced effects in vitro and dose-dependent growth delay in vivo. Oncogene 2006, 25:1545-1554.

11. Mom CH, Sleijfer S, Gietema JA, Fox NL, Piganeau C, Lo L, Uges DRA, Petersen C, Bruchner K, Hilberg F: Enhanced effects in vitro and dose-dependent growth delay in vivo. Int J Radiat Oncol Biol Phys 2004, 59:890-899.

12. Motoki K, Mori E, Matsuzono T, Ackerman E, Kramer J, Shiu T, Wang G, Yoon SS, Chuang E, Schimitz K, et al.: HGS-ETR1, a human monoclonal antibody to TRAIL-R2, in combination with gemcitabine and cisplatin. A phase 1b study in patients with advanced solid malignancies. EORTC-NCI-AACR Prague, Czech Republic, 2006.

13. Motoki K, Mori E, Matsumoto A, Thomas M, Tomura T, Humphreys R, Albert V, Muto M, Yoshida H, Aoki M, Tamada T, Kuroki R, Yoshida H, Ishida I, Ware CF, Kataoka S: Enhanced apoptosis and tumour regression induced by a direct agonist antibody to tumour necrosis factor-related apoptosis-inducing ligand receptor 2. Clin Cancer Res 2005, 11:3126-3135.

14. Pacey S, Smurley RE, Attard G, Bale C, Calvert AH, Blagden S, Fox NL, Corey A, de Bono JS: Phase I and pharmacokinetic study of HGS-ETR2, a human monoclonal antibody to TRAIL R2 in patients with advanced solid malignancies. J Clin Oncol 2005, 23:3055. abstr.

15. Saleh MN, Percent I, Wood TE, Posej J, Shah J, Carlisle R, Wojtowicz-Praga S, Forero-Torres A: A phase I study of CS-1008 (humanized monoclonal antibody targeting death receptor 5, DRS), administered weekly to patients with advanced solid tumours or lymphomas. ASCO Annual meeting. Orlando, Florida, USA, J Clin Oncol 2008, May 20 suppl; abstr 3357.

16. Siwik D, Wakayama H, von Mehren M, Lee KS, Calvert AH, Salvert AH, Fox NL, Kumm EA, Jones DF, Burris HA: A phase 1b study to assess the safety of lexatumumab, a human monoclonal anti-body that activates TRAIL-R2, in combination with gemcitabine, pemetrexed, doxorubicin or FOLFIRI. Abstract. 2007. Proceedings of the American Society of Clinical Oncology 25:14006.

17. Tolcher AW, Mita M, Mergo NL, von Mehren M, Pataki A, Padavich K, Hill M, Mays T, McCoy T, Fox NL, Halpern W, Corey A, Cohen RB: Phase I pharmacokinetic and biologic correlative study of mapatumumab, a fully human monoclonal antibody with agonist activity to tumor necrosis factor-related apoptosis-inducing ligand receptor-1. J Clin Oncol 2007, 25:1390-1395.

18. Vullivoich M, Saba N: Mapatumumab, human genome sciences/ glaxosmithkline/takeda. Curr Opin Mol Ther 2005, 7:502-510.

19. Younes A, Vose JM, Zeleznay AD, Smith MR, Burris H, Ansell S, Klein J, Hams R, Cauvez J, Platten M: Results of a phase 2 trial of HGS-ETRI (agonistic human monoclonal antibody to TRAIL receptor 1) in subjects with relapsed/refractory non-hodgkin’s lymphoma (NHL). Blood 2005, 106:489. abstr.

20. Buchsbaum D, Zhou T, Grizzle WE, Oliver PG, Hammond CJ, Zhang S, Herper M, LoBuglio AF: Anti-tumor efficacy of bds-8 anti-death receptor 5 (DR5) monoclonal antibody in combination with chemotherapy and radiation therapy in a cervical cancer model. Gynecol Oncol 2006, 101:46-54.

21. Baumann M, Krause M, Lips A, Eicheler W, Dorfler A, Alvens J, Petersen C, Bruchner K, Hilberg F: Selective inhibition of the epidermal growth factor receptor tyrosine kinase by BIBX1382BS and the improvement of growth delay, but not local control, after fractionated irradiation in human fadu squamous cell carcinoma in the nude mouse. Int J Radiat Biol 2003, 79:547-559.

22. Borst P, Borst J, Smets LA: Does resistance to apoptosis affect clinical response to antitumor drugs? Drug Resist Updat 2001, 4:129-131.

23. Brown JM, Wouters BG: Apoptosis, p53, and tumor cell sensitivity to anticancer agents. Cancer Res 1999, 59:1391-1399.

24. Krause M, Prager J, Zhou Y, Yaromina A, Dorfler A, Eicheler W, Baumann M: EGFR-TK inhibition before radiotherapy reduces tumour volume but does not improve local control: Differential response of cancer stem cells and non-tumourcellular tumours? Radiat Oncol 2007, 8:316-325.

25. Schmitt CA, Lowe SW: Apoptosis is critical for drug response in vivo. Drug Resist Updat 2001, 4:132-134.

26. Harris AL: Hypoxia-a key regulatory factor in tumour growth. Radiother Oncol 2003, 67:132-134.

27. Luthra R, Sausen R, Otto W, Mohr F, Aigner M, Hunger H, Reichardt P: Ionizing radiation enhances chemotherapy and hormone therapy in prostate cancer cell models. Int J Radiat Oncol Biol Phys 2004, 60:691-701.

28. Shankar S, Singh TR, Chen X, Thakkar H, Firnin J, Srivastava RK: Ionizing radiation enhances the therapeutic potential of trail in prostate cancer in vitro and in vivo: Intracellular mechanisms. Prostate 2004, 61:35-49.

29. Shankar S, Singh TR, Srivastava RK: Ionizing radiation enhances the therapeutic potential of trail in prostate cancer in vitro and in vivo: Intracellular mechanisms. Prostate 2004, 61:35-49.

30. Shankar S, Singh TR, Chen X, Thakkar H, Firnin J, Srivastava RK: Ionizing radiation enhances the therapeutic potential of trail in prostate cancer in vitro and in vivo: Intracellular mechanisms. Prostate 2004, 61:35-49.

31. Shankar S, Singh TR, Chen X, Thakkar H, Firnin J, Srivastava RK: Ionizing radiation enhances the therapeutic potential of trail in prostate cancer in vitro and in vivo: Intracellular mechanisms. Prostate 2004, 61:35-49.

32. Shankar S, Singh TR, Chen X, Thakkar H, Firnin J, Srivastava RK: Ionizing radiation enhances the therapeutic potential of trail in prostate cancer in vitro and in vivo: Intracellular mechanisms. Prostate 2004, 61:35-49.

33. Shankar S, Singh TR, Chen X, Thakkar H, Firnin J, Srivastava RK: Ionizing radiation enhances the therapeutic potential of trail in prostate cancer in vitro and in vivo: Intracellular mechanisms. Prostate 2004, 61:35-49.
33. Chu G: Cellular responses to cisplatin. The roles of DNA-binding proteins and DNA repair. J Biol Chem 1994, 269:787-790.
34. Dittmann K, Mayer C, Rodemann HP: Inhibition of radiation-induced egfr nuclear import by c225 (cetuximab) suppresses DNA-PK activity. Radiother Oncol 2005, 76:157-161.
35. Huang SM, Harari PM: Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: Inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. Clin Cancer Res 2000, 6:2166-2174.
36. Suliman A, Lam A, Datta R, Srivastava RK: Intracellular mechanisms of trail: Apoptosis through mitochondrial-dependent and -independent pathways. Oncogene 2001, 20:2122-2133.
37. Cuello M, Coats AO, Darko I, Ettenberg SA, Gardner GJ, Nau MM, Liu JR, Birrer MJ, Lipkowitz S: N-(4-hydroxyphenyl) retinamide (4HPR) enhances trail-mediated apoptosis through enhancement of a mitochondrial-dependent amplification loop in ovarian cancer cell lines. Cell Death Differ 2004, 11:527-541.
38. Belka C, Schmid B, Marini P, Durand E, Rudner J, Faltin H, Bamberg M, Schulze-Osthoff K, Budach W: Sensitization of resistant lymphoma cells to irradiation-induced apoptosis by the death receptor TRAIL. Oncogene 2001, 20:2190-2196.
39. von Haefen C, Gillissen B, Hemmati PG, Wendt J, Guner D, Mrozek A, Belka C, Dorken B, Daniel PT: Multidomain Bcl-2 homolog barna but not Bak mediates synergistic induction of apoptosis by TRAIL and 5-FU through the mitochondrial apoptotic pathway. Oncogene 2004, 23:8320-8332.
40. Deng Y, Lin Y, Wu X: TRAIL-induced apoptosis requires Bax-dependent mitochondrial release of smac/diablo. Genes Dev 2002, 16:33-45.
41. Griffith TS, Rauch CT, Smolak PJ, Waugh JY, Boiani N, Lynch DH, Smith CA, Goodwin RG, Kubin MZ: Functional analysis of TRAIL receptors using monoclonal antibodies. J Immunol 1999, 162:2597-2605.
42. Luciano F, Ricci JE, Herrant M, Bertolotto C, Mari B, Cousin JL, Auberger P: T and B leukemic cell lines exhibit different requirements for cell death: Correlation between caspase activation, dff40/dff45 expression, DNA fragmentation and apoptosis in T cell lines but not in Burkitt's lymphoma. Leukemia 2002, 16:700-707.
43. Wu F, Hu Y, Long J, Zhou Y, Zhong YH, Liao ZK, Liu SQ, Zhou FX, Zhou YF, Xie CH: Cytotoxicity and radiosensitization effect of TRA-8 on radioresistant human larynx squamous carcinoma cells. Oncol Rep 2009, 21:461-465.
44. Weinmann M, Marini P, Jendrossek V, Betsch A, Gocek B, Budach W, Belka C: Influence of hypoxia on TRAIL-induced apoptosis in tumor cells. Int J Radiat Oncol Biol Phys 2004, 58:386-396.
45. Takahashi M, Inanami O, Kubota N, Tsujitani M, Yasui H, Ogura A, Kiwabara M: Enhancement of cell death by TNF alpha-related apoptosis-inducing ligand (TRAIL) in human lung carcinoma A549 cells exposed to x rays under hypoxia. J Radiat Res (Tokyo) 2007, 48:461-468.
46. Sturm I, Rau B, Schlag PM, Wust P, Hildebrandt B, Riess H, Hauptmann S, Dorken B, Daniel PT: Genetic dissection of apoptosis and cell cycle control in response of colorectal cancer treated with preoperative radiochemotherapy. BMC Cancer 2006, 6:124.
47. Mrozek A, Petrowsky H, Sturm I, Kraus J, Hermann S, Hauptmann S, Lorenz M, Dorken B, Daniel PT: Combined p53/Bax mutation results in extremely poor prognosis in gastric carcinoma with low microsatellite instability. Cell Death Differ 2003, 10:461-467.
48. Kallioniemi A: CGH microarrays and cancer. CurrOpin Biotechnol 2008, 19:36-40.