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THE ROLE OF IMAGE-GUIDED RADIOTHERAPY IN DOSE ESCALATION FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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Aim: To illustrate the potential role of image-guided radiotherapy (IGRT) in dose escalation for the treatment of patients with locally advanced non-small cell lung cancer. *Methods:* A literature review on the limitations of dose escalation in the thorax, and the potential role of IGRT to safely escalate the radiation dose to the primary tumor in locally advanced non-small cell lung cancer. *Results:* Image guided, intensity modulated radiotherapy may reduce radiation dose to normal thoracic structures, such as the normal lungs, the esophagus, the spinal cord, and the heart, which enables the safe escalation of radiation dose to the primary tumor in the treatment of locally advanced non-small cell lung cancer. This may ultimately lead to improved patient survival. *Conclusion:* There is a role for IGRT in dose escalation for the treatment of locally advanced non-small cell lung cancer, which warrants further exploration in future clinical studies.

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MAPK15 MEDIATES BCR-ABL-INDUCED AUTOPHAGY AND CELLULAR TRANSFORMATION

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MAPK15 (ERK8) is the last identified member of the MAP kinase family of proteins. Its activity is modulated by nutrient deprivation and important human oncogenes. We have previously shown that BCR-ABL stimulated MAPK15 activity and that the ABL1 proto-oncogene interacted with this MAP kinase and mediated its activation by upstream stimuli. Also, we have recently described a role for MAPK15 in the regulation of the autophagic process and demonstrated the feasibility of pharmacologically interfering with autophagy by modulating the activity of this MAP kinase. Autophagy has been demonstrated as necessary for BCR-ABL-induced leukemogenesis, as well as to protect cancer cells from apoptosis induced by antineoplastic drugs, such as imatimib. Based on this evidence, an inhibitor of autophagy is being tested for its ability to potentiate tyrosine kinase inhibitors (TKI)-induced cell death in chronic myeloid leukemia (CML) patients. The objective of our research was to investigate a role for MAPK15 in BCR-ABL-dependent autophagy. Indeed, while the use of imatinib and of related 2nd generation TKIs has clearly revolutionized the therapy of CML, these treatments face important problems of insurgence of primary and secondary resistance. Consequently, there is still need for alternative options to "integrate" current pharmacological approaches. We demonstrate that BCR-ABL stimulated autophagy in our cellular model system and that MAPK15 was able to mediate this effect. Interestingly, MAPK15 was able to physically recruit the oncogene to autophagosomal vesicles. Moreover, we did not only show that artificial depletion of the endogenous MAP kinase inhibited BCR/ABL-dependent autophagy, but we also showed that it was possible to pharmacologically interfere with this process. Ultimately, based on the role of autophagy in BCR-ABL-dependent transformation, we show that MAPK15 is required for cell proliferation and transformation induced by this oncogene, therefore establishing this MAP kinase as a novel feasible therapeutic target for human CML.

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THE COMBINATIVE EFFECTS OF DNA APEX1 GENOTYPE AND SMOKING HABITS ON TAIWAN LUNG CANCER RISK

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To evaluate the association and interaction of genotypic polymorphism, the gene for DNA-apurinic/apyrimidinic endonuclease (APEX1) with personal smoking habit and lung cancer risk in Taiwan, the polymorphic variants of APEX1, Asp148Glu (rs1130409), was analyzed in association with lung cancer risk, and its joint effect with personal smoking habits on lung cancer susceptibility is discussed. In this hospital-based case-control study, 358 patients with lung cancer and 716 cancer-free controls,

frequency-matched by age and sex, were recruited and genotyped by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). The results showed that the percentages of TT, TG and GG APEX1 Asp148Glu genotypes were not significantly different at 43.0%, 41.1% and 15.9% in the lung cancer patient group and 39.9%, 46.1% and 14.0% in non-cancer control group, respectively. We further analyzed the genetic lifestyle effects on lung cancer risk and found the contribution of APEX1 Asp148Glu genotypes to lung cancer susceptibility was neither enhanced in the cigarette smokers nor in the non-smokers (p=0.3550 and 0.8019, respectively). Our results provide evidence that the non-synonymous polymorphism of APEX1 Asp148Glu may not be directly associated with lung cancer risk, nor enhance the effects of smoking habit on lung cancer development.

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TCP-1 AS A NOVEL PHAGE-DISPLAY PEPTIDE TARGETING COLON CANCER

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TCP-1 is a novel vasculature-targeting peptide. It was discovered through the *in vivo* phage library selection. It was demonstrated that the TCP-1 peptide exhibited a homing ability to the tumor neovasculature and was capable of efficiently delivering imaging agents and chemotherapeutic drugs to this target site. The current study is to further investigate the targeting ability and the anti-cancer mechanisms of TCP-1 in order to strengthen the potential clinical applications of this peptide in the treatment of colon cancer. In this study, we showed that the TCP-1 peptide could deliver a fluorescein protein, GFP, only to the tumor blood vessels other than normal organs after TCP-1/GFP injection. This was not observed after GFP injection. With this protein-carrying property of TCP-1, we further biologically conjugated TCP-1 with a pro-inflammatory immunomodulator, TNF-α, as a potential therapeutic agent for colon cancer. Results showed that a high dose of TCP-1/TNF-α displayed stronger anti-cancer effects than TNF-α alone in the induction of apoptosis and reduction in number of microvessels in tumors without observable systemic toxicity. In the combined therapy with 5-FU, a standard drug for colon cancer, pretreatment with a low dose of TNF-α or TCP-1/TNF-α significantly potentiated the anti-cancer action of 5-FU on tumor size and weight. The new conjugate could normalize the tumor blood vessels and increased the concentrations of TNF-α and 5-FU in tumor tissues. This drug combination also promoted the immunotherapeutic reaction in tumors. Taken together, TCP-1 appears to be a promising agent in molecular imaging and drug delivery for colorectal cancer treatment.

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AN INTEGRATED VIEW OF THE TRANSCRIPTOME AND miRNOME OF GLIOBLASTOMA AND PERITUMOR TISSUES

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Glioblastoma multiforme (GBM) is the most common and most malignant primary brain tumour. Despite multimodal aggressive treatment, the prognosis of GBM patients is poor and the median survival time after diagnosis is still in the range of just 12 months with the interesting exception of a small fraction (less than 10%) of patients, referred to as long-term survivors (LTS), who survive longer than 36 months. In general, GBM recurrence occurs in peritumoral tissue in about 90% of patients, making this area a crucial one for studies about the molecular pathways perturbed early in GBM malignant evolution. By SAGE analysis, we studied the transcriptome and miRNome of GBM tissues from 13 patients classified as either short-term survivors (STS) or LTS. For each patient, we analysed one sample representing the center of the tumour (C) and another excised from the tumour-free peritumoral area (P). We describe a group of RNAs (coding and noncoding) found to be commonly modulated in P as well as in C samples compared to healthy white matter, that we think may represent early markers of GBM pathogenesis; we also present RNAs that differentiate ST from LT tumors. Among up-regulated RNAs in both comparisons, we found a remarkable enrichment of mesenchymal stem-like markers. For these comparisons, we also show the relevant pathways affected by the modulated RNAs. Our data show that some genes and molecular pathways known to be perturbed in glioblastoma are already disrupted in the apparently tumor-free peritumoral area, where it is conceivable that early tumor development occurs, predisposing cells to recurrence. Moreover, our results, differentiating STS from LTS, may help unravel the basis of this still elusive distinction.