IMMUNOTHERAPY WITH A POSTTRANSCRIPTIONALLY MODIFIED DNA VACCINE INDUCES COMPLETE PROTECTION AGAINST METASTATIC NEUROBLASTOMA

The successful induction of a T-cell–mediated tumor-protective immunity against poorly immunogenic malignancies remains a major challenge for cancer immunotherapy. The authors achieved this by immunization with a tyrosine hydroxylase (mTH)–based DNA vaccine, enhanced with the posttranscriptional regulatory acting RNA element (WPRE) in combination with an antibody-cytokine fusion protein (ch14.18–IL-2) that targets interleukin-2 (IL-2) to the tumor microenvironment. This DNA vaccine mTH-WPRE was carried by attenuated *Salmonella typhimurium* and applied by oral administration in a mouse model of neuroblastoma. Mice immunized with the vaccine, and which additionally received a boost with suboptimal doses of ch14.18–IL-2, were completely protected against hepatic neuroblastoma metastases. In contrast, all controls presented with disseminated metastases. Both T-cell and natural killer (NK) cell–dependent mechanisms were involved in the induction of a systemic tumor-protective immunity. Thus, up-regulation of interferon (IFN) expression in CD8 T cells occurred only in those animals that received the mTH-WPRE vaccine plus the ch14.18–IL-2 boost. Up-regulation of this cytokine was not observed in mice immunized with mTH-WPRE vaccine alone. A role for NK cells was indicated by the complete abrogation of systemic tumor-protective immunity in all animals that were depleted of NK cells in vivo. These data demonstrate that immunization with a posttranscriptionally enhanced DNA vaccine encoding the WPRE sequence, combined with a boost of the ch14.18–IL-2 fusion protein, completely protects against hepatic metastases in a murine model of neuroblastoma. This work represents a new approach in the development of vaccines against cancer. It also represents a possible strategy for prevention of metastatic neuroblastoma.

Pertl U, Wodrich H, Ruehlmann JM, et al.
Blood 2003;101:649-54

EGFR BLOCKADE WITH ZD1839 ("IRESSA") POTENTIATES THE ANTITUMOR EFFECTS OF SINGLE AND MULTIPLE FRACTIONS OF IONIZING RADIATION IN HUMAN A431 SQUAMOUS CELL CARCINOMA

Signaling pathways initiated by the epidermal growth factor receptor (EGFR) may play important roles in the response to ionizing radiation. In this study the consequences of inhibiting the EGFR were investigated *in vitro* and *in vivo*, using the selective EGFR-tyrosine kinase inhibitor, ZD1839 ("Iressa"). Treatment of A431 cells (human vulvar squamous cell carcinoma cells that overexpress EGFR) with ZD1839 *in vitro* reduced proliferation, increased apoptosis, and reduced clonogenic survival after radiation. Greater than additive effects of ZD1839 in combination with radiation on tumor growth delay were observed *in vivo* in athymic nude mice with established subcutaneous A431 xenografts after either a single 10 Gy fraction (enhancement ratio: 1.5) or multiple 4×2.5 Gy fractions (enhancement ratio: 4). ZD1839 reduced tumor vascularity, as well as levels of vascular endothelial growth factor (VEGF) protein and mRNA induced by stimulation with epidermal growth factor (EGF), suggesting a possible role of inhibition of angiogenesis in the effect. The authors conclude that inhibiting EGFR-mediated signal transduction cascades with ZD1839 potentiates the antitumor effect of single and multiple fractions of radiation. These data provide preclinical rationale for clinical trials of EGFR inhibitors including ZD1839 in combination with radiation.

Solomon B, Hagekyriakou J, Trivett MK, et al.
Int J Radiat Oncol Biol Phys 2003 55:713-23

RAPID AKT ACTIVATION BY NICOTINE AND A TOBACCO CARCINOGEN MODULATES THE PHENOTYPE OF NORMAL HUMAN AIRWAY EPITHELIAL CELLS

Lung cancer is an environmental cancer commonly associated with tobacco use. This paper describes that nicotine, the addictive component of tobacco induces activation of the serine threonine kinase Akt in human normal bronchial epithelial cells. The activation occurs at nanomolar doses within minutes after exposure to this compound. The activation of Akt depends on the binding of nicotine to nicotine acetylcholine receptors an subsequently the activation of the PI3K pathway. Activation of Akt is also induced by 4-(methylnitrosamino)-1-(3-pyridil)-1-butanone (NNK). Once activated by tobacco components, Akt increases phosphorylation of downstream substrates, increasing cellular survival to genotoxic agents and conferred some properties of transformed cells. The work also shows that Akt was activated *in vivo* in NNK-treated A/1 mice and also in human lung cancers from smokers. The authors propose a model where carcinogens promote tumorogenesis, not only by inducing DNA damage but also inhibiting apoptosis by activating the Akt pathway, facilitating the survival of cells with damaged DNA.

West KA, Brognard J, Clark AS, et al.
J. Clin Investigation 2003;111:81-90