YW2-17  HST-1/FGF-4 gene protects mice from lethal irradiation.

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The fibroblast growth factor-4 (HST-1/FGF-4) is a heparin-binding growth factor that influences on epithelial and many other cells through interaction with FGF receptors. It has been demonstrated that the HST-1/FGF-4 gene protects mice from lethal irradiation by preventing bone marrow damage and intestinal tract damage. However, the radioprotective mechanism is unknown. We found induction of endogenous Hst-1/Fgf-4 expression in intestine when mice are exposed to 9.0 Gy irradiation. Laser-captured microdissection (LCM) coupled with RT-PCR analysis revealed that expression of Hst-1/Fgf-4 was found in epithelial cell of the villi and crypt cells. Pretreatment of HST-1/FGF-4 caused an increase in the number of surviving crypt cells, and clearly suppresses the radiation-induced apoptosis of the crypt cells. Moreover, exogenous HST-1/FGF-4 enhances epithelial cell restitution and proliferation in an in vitro model. These data suggest that HST-1/FGF-4 is induced by irradiation injury and that HST-1/FGF-4 will find a therapeutic role in the prevention of intestinal cell toxicity following intensive chemotherapy and radiation therapy protocols and in allogenic cell transplantation.

YW2-18  Gene expression profiling of early- and late-relapse nonseminomatous germ cell tumor and primitive neuroectodermal tumor of the testis

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We studied the gene expression profiles of 17 nonseminomatous germ cell tumor of testis (NSGCT) s (10 yolk sac tumors, 3 embryonal carcinomas, and 4 teratomas) and 2 derivative, primitive neuroectodermal tumor (PNET) s obtained from patients with two clinical outcomes to elucidate the molecular mechanisms in the tumorigenesis and progression of these tumors. Tissue samples were obtained from the University of Indiana. One group of patients developed metastasis within two years (early-relapse, chemosensitive), while the other group developed metastasis two years or more (late-relapse, chemoresistant), after the initial successful treatment. Gene expression in both groups of patients was quantified using microarrays and real-time quantitative PCR. We demonstrated that gene expression profiles are correlated with histological types. Furthermore, we identified the gene set that could distinguish between early-relapse and late-relapse yolk sac tumors.

This is the first study attempting to understand the molecular profiles for the NSGCTs and drug response in early- and late-relapse tumors. Our results suggest that two molecularly distinct forms of NSGCTs exist and that the integration of expression profile data with clinical parameters could enhance the diagnosis and prognosis of NSGCTs.

YW3-01  Antisense oligodeoxynucleotide therapy targeting antiapoptotic genes for advanced prostate cancer

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Progression to androgen-independence remains the main obstacle to improving survival for patients with advanced prostate cancer. Here, I would like to summarize the findings we have recently demonstrated to establish novel therapeutic strategy for advanced prostate cancer using antisense oligodeoxynucleotide (ODN). We initially characterized changes in gene expression after androgen withdrawal in the androgen-dependent Shionogi and LNCaP tumor models using cDNA arrays. Based on these results, we focused on genes highly up-regulated after androgen ablation (i.e., bcl-2, bcl-xL, clusterin, IGFBP-2, IGFBP-3), which have antiapoptotic or mitogenic activities, and thereby confer a resistance to several stimuli inducing apoptotic cell death. We further demonstrated the efficacy of an antisense ODN strategy for prostate cancer through the inhibition of target gene expression, resulting in a delay in the progression to androgen-independence by enhancing apoptosis induced by androgen withdrawal, chemotherapy, radiation, and adenoviral-mediated p53 gene transfer. Based on these preclinical studies, we are currently performing the phase-I clinical studies using antisense ODN either alone or in combination with chemotherapeutic agents in patients with advanced prostate cancer.

YW3-02  Phase I Dose Escalation Clinical Trial of Adenovirus Vector Carrying Osteocalcin Promoter-Driven Herpes Simplex Virus Thymidine Kinase in Localized and Metastatic Hormone-Refractory Prostate Cancer

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Osteocalcin (OC), a major non-collagenous bone matrix protein, is expressed highly in both prostate cancer epithelial cells and surrounding stromal cells of hormone refractory prostate cancer patients. We constructed an adenovirus vector carrying osteocalcin promoter-driven herpes simplex virus thymidine kinase (Ad-OC-hsv-TK) to cotarget prostate cancer cells and their surrounding stromal cells. A phase I dose escalation clinical trial of the intralesional administration of Ad-OC-hsv-TK followed by oral valacyclovir was conducted at the University of Virginia in 11 men with localized recurrent and metastatic hormone-refractory prostate cancer (2 local recurrent, 5 osseous metastasis, and 4 lymph node metastasis) in order to determine the usefulness of this vector for the palliation of androgen-independent prostate cancer metastasis. This is the first clinical trial in which therapeutic adenoviruses are injected directly into prostate cancer lymph node and bone metastasis. We report the clinical and experimental results of this study, evaluate and correlate the biochemical markers in tissues, blood, and urine of patients treated with this form of adenoviral gene therapy with the clinical responses of the patients.