Influence of the Neural Microenvironment in Prostate Cancer

Introduction and Objective: Nerves exhibit inductive and trophic functions in development and adult tissues. They are important for wound repair and tissue homeostasis. Cancer cells induce neurogenesis and perineural invasion results in a survival advantage for cancer cells.
Materials and Methods: To address the functional significance of neural input to tumorigenesis, the major pelvic ganglion (MPG) of male NIH-Foxn1rnu nude rats was excised, sham operated, or injected with Botox or vehicle, and the anterior prostate glands were inoculated with VCaP-luc human prostate cancer cells (2×10^6) for 7 weeks. As a second model we used VCaP-luc orthotopically in nu-nu mice that underwent the same procedures except MPG dissection. Chemical denervation was used to eliminate the potential confounding factors of affecting blood vessels. Laser captured epithelium, stroma and tumor was used for gene array analysis. We next evaluated the gene expression profiles in laser-captured material obtained from prostate cancer patients with spinal cord injuries.
Results: Quantitative histologic image analysis demonstrated that bilateral denervation (Botox injection, MPG dissection or spinal cord injury) resulted in a significant reduction in tumor size, both in the rat and mouse experiments. Gene expression profiling analysis revealed that both chemical and physical denervation produced similar expression profiles that self-clustered in each compartment, confirming that both act through similar mechanisms. The gene profile of tumors shared similarities with tumors in patients with spinal cord injuries, confirming an effect through denervation. Normal, non-neoplastic epithelium exhibited variable atrophic histology, but alterations in gene expression are extensive with a total of 1231 unique genes differentially expressed at a high significance threshold (2237 gene probes, ANOVA $p<0.01$, $SD>0.2$, true positive rate, ~83%). Gene Ontology (GO) analysis of genes downregulated in denervated epithelium compared to intact prostates include translational elongation, ribosome, structural constituent of ribosome, translation, cytosolic small and large ribosomal subunit, RNA binding, ribonucleoprotein complex, and protein binding.
Conclusions: These studies suggest that nerves exert trophic effects on epithelium and prostate cancer cells and are paramount for cancer progression. The studies have lead to new therapeutic approaches to target the neural niche in cancer, including a human neoadjuvant clinical trial with botox.