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Prostate-Specific Antigen: Where we are and where we are going

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Prostate cancer has the highest incidence of any non-cutaneous malignancy in the western world and is the second leading cause of cancer related deaths in men. Prostate-Specific Antigen (PSA) is an androgen regulated serine protease of the tissue kallikrein family, and a well recognized biomarker for the early diagnosis and management of prostate cancer. However, PSA test is neither disease specific nor tissue specific and test results are >70% false positive and 35% false negative. Therefore, one of the major goal is to identify additional circulating biomarkers that will either alone or in combination with PSA test will significantly improve the sensitivity and specificity in the early diagnosis and in management of prostate cancer. At present, we are investigating the relevance of IL-8, TNF-α and sTNFR1 etc as potentially new biomarkers. Our preliminary results strongly suggest that serum levels of IL-8, TNF-α and sTNFR1 will provide powerful tools in differentiating between the benign and malignant tumors; which is the major disadvantage of currently available PSA test.

PSA has been hypothesized to have anti-tumorigenic and anti-angiogenic activities. We have shown that intact PSA has anti-angiogenic activity in vitro in the Matrigel tube formation assay based on tube formation by human umbilical vein endothelial cells (HUVEC). PSA is also known to regulate expression in prostate cancer cells of pro-angiogenic growth factors/cancer genes/proteins including VEGF, IL-8, EphA2, CYR61, Bcl2, Pim-1 oncogene, uPA, and up regulate expression of anti-angiogenic genes/proteins, including interferons and interferon related genes. Furthermore, exogenously administered PSA inhibited growth of PC-3M prostate tumor xenografts in nude mice. In preliminary studies, we have shown that PSA significantly decreased micro vessel density (MVD) in xenografts of human prostate cancer tissue harvested from animals treated with PSA; compared to animals treated with vehicle. These observations validate both the potential therapeutic importance of PSA and the utility of primary xenograft model for evaluation of anti-angiogenic therapeutics.

Impact of our research: The physiological role of PSA in prostate tissue microenvironment, in prostate tumor growth and progression, and in prostate cancer metastasis is not known. Attenuation of PSA levels with age, disease progression, or during androgen deprivation therapy, however, removes this important regulator of angiogenesis, and by extension results in tumor progression. Re-introduction of human PSA into the prostate tissue microenvironment may suppress tumor angiogenesis through either the inhibition of expression of pro-angiogenic genes or induction of expression of anti-angiogenic genes, or via inhibition of signaling mechanisms associated with angiogenesis that are independent of gene transcription. Validation of an anti-angiogenic effect of PSA on the human tissue vasculature in a pre-clinical model of primary xenografts of human prostate and prostate cancer tissue will provide compelling evidence that PSA has therapeutic potential against prostate cancer.

Biography

Kailash Chadha is the Associate Member and Associate Professor of Oncology in the Department of Molecular and Cellular Biology at Roswell Park Cancer Institute, and Department of Medicine, State University of New York at Buffalo, NY, USA. He got his Ph.D. degree in Virology from the University of Guelph, Guelph, Ontario, Canada. He joined Roswell Park Cancer Institute as Cancer Research Scientist in the Department of Molecular Cellular Biology. His research interests are in the area of cell and molecular biology of Herpes viruses, interferons and prostate cancer. He has published well over 125 publications, written several book chapters and currently holds four U.S. patents. He has been invited to participate in numerous national and international scientific meetings and has often chaired sessions on several international meetings. He is currently on the editorial board of six journals and member of several professional organizations including New York Academy of Sciences; AAAS, Society for Experimental Biology & Medicine; AACR; ISICR & SUBR. His research is being supported by National Cancer Institute, American Cancer Society, National Multiple Sclerosis Society, and EMD Serono Inc

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