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Activation of Wnt/beta-catenin promotes CRPCa progression

Prostate cancer begins with abnormal growth of epithelial cells which is caused by activation of growth factors or oncogenes or inactivation of tumor suppressor genes. However, the rapid cell proliferation alone is not sufficient to cause cancer transformation. These pre-cancerous cells generally need to acquire a second mutation or "hit" to acquire the ability to invade into the surrounding stromal tissue and form malignant PCa. It is now widely accepted that the process of invading through the basement membrane is a hallmark characteristic of prostate adenocarcinoma. Our previous studies have found that activation of Wnt/beta-Catenin signaling resulted in mouse prostatic intraepithelial neoplasia (mPIN). In the large probasin promoter directed SV40-Large T-antigen (LPB-Tag) expressing mouse prostate, mPIN forms with rare areas of adenocarcinoma. Combining expression of both Wnt/beta-Catenin signaling and Tag expression in the mouse prostate, we have studied the role Wnt/beta-Catenin signaling in the progression from mPIN to adenocarcinoma. Our results show that the prostates of mice expressing Tag alone or nuclear beta-Catenin alone developed mPIN while the activation of both Tag and the Wnt/beta-Catenin pathway resulted in invasive prostate adenocarcinoma. Also, Foxa2 a forkhead transcription factor was induced by active Wnt/beta-Catenin signaling and the expression of Foxa2 was associated with the invasive phenotype in the primary prostate cancer. Furthermore, we also assessed AR and AR signaling pathway in these LPB-Tag/D.A. beta-Catenin mice. Although beta-Catenin is a well known AR co-activator in vitro, our study provides strong in vivo evidences indicating that both AR protein and the AR pathway were down-regulated in the prostate of LPB-Tag/D.A. beta-Catenin mice. Histological analysis shows that prostate sections derived from the LPB-Tag/D.A. beta-Catenin mice display neuroendocrine differentiation (NED) but NE cancer does not develop. Together, our findings indicate that Wnt/beta-Catenin signaling plays an important role in the progression of mPIN to prostate adenocarcinoma with NE differentiation.

Biography

Xiuping Yu graduated from Nankai University and got her Ph.D. degree from Dalian Medical University, China. He was trained in Dr. Robert Matusik's laboratory at Vanderbilt in the area of molecular and cancer biology with particular expertise in the transcriptional regulation of prostatic genes and the use of genetically engineered mouse models as well as tissue recombination approach in PCa research. He is currently Assistant Professor of Biochemistry & Molecular Biology, LSU Health Sciences Center Shreveport. He research interest focuses on studying the mechanisms through which PCa become castration resistant and the development of neuroendocrine PCa.

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