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PREFACE

According to the American Cancer Society, an estimated 218,890 new cases of prostate cancer will be diagnosed in United States in 2007. Prostate cancer remains the second leading cause of cancer related deaths in men in the United States, lung cancer being responsible for most number of cancer deaths. Over the years, a tremendous amount of research effort has resulted in groundbreaking discoveries, which improved our understanding of this disease. These advances of the scientific community have identified molecular targets for rational drug design, which can potentially lead to improved clinical management of prostate cancer. Unfortunately, in spite of all available treatment options, the fact remains that prostate cancer reappears after initially regressing following therapeutic intervention. This stage of the cancer, referred to as Androgen Independent Prostate Cancer (AIPC), is untreatable and ultimately metastasizes to a number of distant organs, resulting in morbidity and mortality. The major sites of prostate cancer metastasis are bone, lung, lymph nodes and liver. The molecular events driving this progression and metastasis of prostate cancer is not yet fully understood. In this project, we studied the role of stathmin, a microtubule destabilizing protein, in the progression of prostate cancer. Stathmin is upregulated in a variety of human malignancies like leukemia, breast and ovarian cancer. Previous reports suggest that stathmin expression is elevated in poorly differentiated prostate cancer. We have shown that increased stathmin expression correlates with high Gleason pattern in human prostate cancer. We have also established that androgens and anti-androgen treatment can modulate stathmin phosphorylation – a mechanism that can potentially drive progression

to AIPC. Furthermore, we have also demonstrated a role for stathmin in epithelial cell homeostasis. Transforming growth factor-beta (TGFβ) is one of the most enigmatic molecules in the context of normal development and tumorigenesis, acting as growth inhibitor in normal cells and growth stimulator in cancer cells. We have shown that stathmin can modulate TGFβ signaling to induce epithelial to mesenchymal transition in prostate cancer cells – a mechanism that makes the cancer cells more invasive, eventually leading to metastasis. Hence, this project establishes the regulation of stathmin expression and activity as a novel mechanism for prostate cancer progression to a more aggressive phenotype.

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AR……...Androgen Receptor

AD……...Androgen Dependent

AI……...Androgen Independent

AIPC……...Androgen Independent Prostate Cancer

BPH…….Benign Prostatic Hyperplasia

CK……...Cytokeratin

CHX……..Cycloheximide

DHT……...Dihydrotestosterone

EMT……..Epithelial-to-mesenchymal Transition

HGPIN……..High-grade Prostatic Intraepithelial Neoplasia

HPE……..Human Prostate Epithelial (Cells)

LGPIN……...Low-grade Prostatic Intraepithelial Neoplasia

LUTS……..Lower Urinary Tract Symptoms

OHF…….Hydroxy-flutamide

PB…….Probasin

PCa……Prostate Cancer

PIN……..Prostatic Intraepithelial Neoplasia

PSA……...Prostate Specific Antigen

RTKs……...Receptor Tyrosine Kinases

TGFβ……...Transforming Growth Factor-beta

TMA…….Tissue Microarray