2. ABSTRACT OF THE THESIS

Tumor progression requires interplay among several cytokines, growth factors and enzymes, all contributing to an integrated sequence of events regulated in the tumor microenvironment. The process of tumor progression is characterized by various events including deregulated growth control, proliferation, adhesion, ECM degradation, angiogenesis and metastasis. Among men, prostate cancer is the most common cancer diagnosed, and the second leading cause of death from cancer in United States. Metastasis or migration of malignant cells from prostate tumor to the distant sites makes prostate cancer one of the deadly diseases. Therefore, understanding the molecular mechanism underlying prostate cancer metastasis will be helpful for the diagnosis and treatment of cancer.

Osteopontin (OPN) is a chemokine like phospho-glycosialoprotein known to express in a variety of tissues. Enhanced expression of OPN has been detected at the tumor sites as well as plasma and serum of patients with various types of cancer. Studies have shown that OPN acts as a crucial oncogenic molecule and its enhanced expression is not only associated with tumor progression, it also acts as a lead marker for various types of cancer. Research from various laboratories have demonstrated the multifaceted role of OPN in the broad array of physiological as well as pathophysiological processes such as tissue remodeling, bone resorption, wound healing, immunological responses, restenosis, atherosclerosis, and autoimmune diseases. However, the molecular mechanism by which OPN regulates tumor growth, metastasis and angiogenesis is not clearly understood. In this study, using multiple in vitro and in vivo models, we have demonstrated the molecular mechanism implicated in OPN-regulated prostate tumor growth, metastasis and angiogenesis.

We have shown that OPN regulates prostate tumor progression via cyclooxygenase-2 (COX-2)/prostaglandin E₂ (PGE₂)-mediated autocrine and paracrine pathways. OPN stimulates the activation of protein kinase C α (PKCα)/nuclear factor-inducing kinase (NIK)/nuclear factor-κB (NF-κB)-dependent signaling that induces COX-2 expression, which in turn regulates the PGE₂ production, matrix metalloproteinase-2 (MMP-2) activation, tumor cell motility, invasion and angiogenesis. Moreover, our data showed that celecoxib (a NSAID) or EP2 blocking antibody suppressed the OPN-induced xenograft tumor growth in vivo. Human prostate specimen analysis further supported our in vitro and in vivo findings suggesting that blockage of OPN
and/or COX-2 is a promising therapeutic approach for the inhibition of prostate tumor progression and angiogenesis.

Furthermore, we have demonstrated the in-depth molecular mechanism showing that PGE\(_2\) activates the epidermal growth factor receptor (EGFR) and \(\beta\)3 integrin through EP2 or EP4 receptor mediated pathways which leads to the AP-1 activation. PGE\(_2\) induces activating transcription factor-4 (ATF-4) activation and crosstalk between ATF-4 and AP-1 that regulates the enhanced expression of urokinase plasminogen activator (uPA) and vascular endothelial growth factor (VEGF), which eventually regulate prostate tumor cell motility. *In vivo* Matrigel angiogenesis assay showed that PGE\(_2\) induces neovascularization through EP2 or EP4 receptor mediated pathway. Our experimental data suggest, at least in part, that targeting PGE\(_2\) signaling pathway (i.e. blocking EP2/EP4 receptors) might be a rationale therapeutic approach for overcoming the side effects of COX-2 inhibitors and that could be a novel strategy for next generation of prostate cancer management.