ABSTRACT OF THE THESIS

Cancer or the malignancies of the cells has been considered as one of the most dreadly disease. The majority of the death caused by cancer is due to the distant migration of the cancer cells and the phenomenon is termed as tumor metastasis. Angiogenesis or neovascularization or formation of the new blood vessels from the existing one plays crucial role during tumor progression. Recent studies from various laboratories indicated that angiogenesis not only provide nutrients to the tumor cells but also help the tumor cells to metastasize to the distant parts of the body. Thus, angiogenesis is considered as the most important step not only for the tumor growth but also for the tumor metastasis and therefore, understanding the molecular mechanism underlying the regulation of angiogenesis may help to invent novel approaches for cancer therapy.

Osteopontin (OPN), the ECM associated calcified phosphosialoprotein has been considered as one of the major molecule which play crucial role in tumor metastasis. In this study using multiple in vitro and in vivo approaches we have demonstrated for the first time that OPN acts as an important angiogenic factor that augments the expression of vascular endothelial growth factor (VEGF) and regulates tumor angiogenesis in breast cancer model.

We have showed that both exogenous and tumor-derived OPN regulates VEGF expression at transcriptional and translational level. Moreover, we have identified, at least in part, the in-depth signaling pathway by which OPN promotes the αvβ3-c-Src-PI 3-kinase mediated NIK phosphorylation and NIK-IKKα/β-NF-κB dependent VEGF expression in human breast cancer cells. We have demonstrated a novel signaling pathway by which OPN induces the breast tumor kinase (Brk) phosphorylation and Brk dependent but NF-κB-dependent/independent activation of activating transcription factor 4 (ATF-4) and how all of these events ultimately regulate VEGF expression. Moreover, our data showed that OPN-induced VEGF regulates in vitro tumor as well as endothelial cell motility and in vivo angiogenesis via autocrine and paracrine mechanism. Furthermore, we have showed that how OPN controls VEGF dependent tumor-endothelial interaction via VEGF receptor neuropilin-1(NRP-1)-KDR dependent juxtacrine pathway.

Our in vivo study showed that OPN regulates VEGF-NRP-1 dependent breast tumor growth and angiogenesis in mouse xenograft breast orthotopic model. Moreover, our data showed that intratumoral injection of OPN specific siRNA (OPNi) significantly inhibited breast tumor growth and angiogenesis in mice. Interestingly, we have observed reduced breast tumor growth in OPN-knockout mice as compared to wild type one and this study further indicated that both tumor as well as host-derived OPN plays crucial role in VEGF dependent breast tumor growth and angiogenesis. Furthermore, we have observed the important role of OPN in external carcinogen pristane-induced breast tumor growth in mice. We have also detected significantly elevated
expression of OPN in human breast carcinoma of higher grades, which further correlated with the enhanced activation of NF-κB, ATF-4, AP-1, increased expression of VEGF, Brk, NRP-1, MMP-2&-9, MT1-MMP and uPA and higher tumor angiogenesis. In this study, we have demonstrated the important insight into the role of OPN in genesis of angiogenic switch. Our results further warrant the molecular mechanism shown in the mouse model underlies the human pathology and a clear understanding of such mechanism(s) may facilitate the development of OPN-based therapeutic approach for next generation of cancer management.