Title of the thesis:
Identification Of Prognostic Markers Of Human Breast Cancer Towards Metastasis In Eastern India Population : A Special Focus To Immune Regulatory Molecules

ABSTRACT

We have screened primary breast tumor samples and autologous healthy tissues for expression of chemokine ligand CXCL13 and its receptor CXCR5 and correlated with clinicopathological parameters. Co-expression of CXCL13-CXCR5 is found to be positively associated with metastasis to lymph nodes. Moreover, CXCL13 induces EMT of breast cancer cells and activates MMP9, while RANKL is taking part in CXCL13-CXCR5-mediated signaling pathway, upstream of both PI3Kp110α and Src.

Further, transcription regulation of cxcl13 and cxcr5 has been studied. Significantly raised CXCL13 expression and increased cxcl13 promoter activity is observed in RelA-overexpressed breast cancer cells. Additionally, we have identified two functional RelA binding sites within the cxcl13 promoter region. Interestingly, Nrf2 has been found to regulate cxcl13 transcription negatively and a significantly decreased CXCL13 mRNA and protein expression is observed in breast cancer cells induced with RelA-Nrf2 co-overexpression. RelA also regulates the transcription of cxcr5, while, Nrf2 did not show any effect. We have observed significant increase in mRNA level and surface expression of CXCR5 in RelA-induced breast cancer cells. Further, promoter region of cxcr5 encompasses a CpG island and methylation within the island inhibits cxcr5 transcription.

M2 macrophage has gained immense importance in recent years for the understanding of breast cancer metastasis. Among the different immune cell populations within the breast tumor microenvironment, intra-tumoral M2 macrophage percentage is found to be positively associated with the level of CXCL13 within the primary tumor. Our in vitro analyses indicate that breast cancer cell line-conditioned medium is able to induce human monocytes to express significantly higher CXCL13 and increased M2-specific markers, CD206 and CD163. Additionally, M2 macrophage percentage is sensitive to expression of Th2-attracting chemokines, CCL17 and/or CCL22. Th2-marker CD294 was found significantly higher in primary tumor samples expressing elevated CCL17 and/or CCL22.

In conclusion, co-expression of CXCR5 and CXCL13 could be considered as a poorer prognosis marker for breast cancer metastasis in patients from eastern India and may be used as a potential target for future therapeutics. CCL17 and CCL22 expression within the primary breast tumor could also be considered as a marker for poorer prognosis as it is positively associated with intra-tumoral M2 macrophage percentage.
“Man needs his difficulties because they are necessary to enjoy success.”

Dr. A. P. J. Abdul Kalam