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Role of genetic and epigenetic signals in breast cancer stem cell expansion and induction of EMT

Fayaz Malik, Hasan Korkaya, Ali Quraishi and Max Wicha

University of Michigan Comprehensive Cancer Center Ann Arbor, USA

It has been widely recognized that the cancer stem cells (CSCs) mediate number of processes such as metastasis in tumor progression and therapeutic resistance in advance tumors. In addition to number of oncogenes and tumor suppressors, epigenetic alterations may also play role in CSC regulation. Furthermore multistep genetic and epigenetic alterations may lead to malignant transformation of normal epithelium. In this study, we demonstrated that down regulation of two major tumor suppressors, PTEN and TP53 results in malignant transformation of normal mammary epithelial cells by activating IL-6 and TGF- β mediated autocrine feedback loops. These feedback loops in turn expand the CSC population and induce epithelial mesenchymal transition (EMT) phenotype as demonstrated by CSC and EMT specific markers.

Although either PTEN or TP53 down regulation was able to induce limited EMT phenotype and CSC expansion, malignant transformation is achieved only by down regulation of both genes which showed greater activity in stimulating stem cell related pathways, Wnt/b-Catenin, Stat3 and NF- κ B. In addition, we found that IL-6 and TGF- β productions were increased by more than hundred fold in cells with down regulation of both PTEN and TP53. Stem cell factor Lin28 has been shown to regulate NF- κ B and IL-6 production, thus we tested the ability of Lin28 to induce similar changes. Our preliminary studies suggested that Lin28 overexpression in MCF10A cells substantially increased the number CSCs and induced EMT phenotype similar to the PTEN and TP53 down regulation. We are currently dissecting the signaling cascades involving PTEN, p53 and Lin28 which may play role in malignant transformation as well as tumor progression.

Biography

Fayaz Malik completed his PhD from the Indian Institute of Integrative Medicine and is currently doing his postdoctoral studies at the University of Michigan Comprehensive Cancer Center. He has been involved in cancer research for the past six years and has published more than a dozen papers in reputable journals.