Involvement of signal transduction mechanism in STAT1 mediated epigenetic regulation of T helper cell differentiation during breast cancer

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Abstract

Epigenetic mechanisms are essential for normal development and maintenance of tissue-specific gene expression patterns in mammals. Global changes in the epigenetic landscape are a hallmark of malignancy. It has already been well documented that Signal Transducer and Activator of Transcription 1 (STAT1) plays a crucial role in the T cell differentiation. Some mutations or lack of STAT1 results into severe immunodeficiency and malignancy. In the current research, we examined the contribution of signal transduction mechanism through STAT1 that contribute to the epigenetic regulation of $CD4^+$T helper (T_H) cell differentiation during breast cancer which is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year and also being the second most common cause of death from cancer among women in the world. Amongst different types of breast cancer Invasive Ductal Carcinoma (IDC) is the most frequent type of breast cancer, accounting for 80% of all diagnosis. In the present study $CD4^+T_H$ cells were isolated from Peripheral Mononuclear Cells (PBMCs) of normal subjects and IDC patients. After depletion and overexpression of STAT1 separately in T_H cells of normal subjects and IDC patients, the cells were polarized into different subsets of T_H cells. Amongst the different subsets of T_H cells, T_H1 cells showed high levels of STAT1 and IFN-γ cytokine levels. Upon Knocking out of STAT1, IFN-γ levels decreased however upregulating IL-17A, IL-10 and IL-4 levels, the %enrichment of H3K27me3, HDAC3 & γH2A.X increased and that of H3K4me3 & H3K14Ac decreased, p53 and BRCA1 were downregulated with c-Myc and NOTCH1 being upregulated. In STAT1 over-expressed cells, though IL-10, IL-4, IL17A expression were downregulated, IFN-γ was upregulated, the %enrichment of H3K27me3, HDAC3 & γH2A.X were reduced and %enrichment of H3K4me3 & H3K14Ac were increased, p53 and BRCA1 expression increased with a decrease in c-Myc and NOTCH1 expression. Thus, our study has revealed the involvement of certain signal transduction mechanism and certain epigenetic regulators associated with STAT1 for evoking protective immunity during IDC. Thus, STAT1 mediated epigenetic regulation of T helper cell differentiation linked to malignancies may offer us an appealing avenue of targeted therapeutic intervention for breast cancer.

Biography of presenting author

Dr. Koustav Sarkar has completed his PhD at the age of 28 years from Chittaranjan National Cancer Institute/Jadavpur University, Kolkata, India. Currently, he is the Research Assistant Professor in department of Biotechnology, SRM Institute of Science and Technology, Chennai, India. He presented papers in more than 50 national and international conferences. Dr. Sarkar has been involved in research over the last twenty years (including a Ph.D. and three Post-Docs) and made several important contributions to the development of advanced science and technology. He was involved in understanding the molecular mechanisms of the development of human immune responses in health & disease. Dr. Sarkar has already published 46 high-impact scientific publications in internationally reputed journals. He was also co-author of four book chapters. During PhD, Dr. Sarkar has developed a process for isolating glycoprotein(s) from neem leaf, which has immunomodulatory and cancer preventive functions. One patent (Patent Number: 259434; Grant Date: 12-Mar-2014) has been granted for this invention. He found out that the neem leaf glycoprotein helped to generate carcinoembryonic antigen specific anti-tumor immune responses utilizing macrophage & dendritic cell mediated antigen presentation to T and B cells and the induction of type 1 protective immunity. To study the intricate molecular mechanisms involved in the type 1 protective immunity, Dr. Sarkar moved to USA. Research from his US laboratory was essential in revealing for the first time a novel nuclear function for a well-known cytoskeleton structure associated protein, Wiskott Aldrich Syndrome Protein (WASp) in the transcriptional regulation of T helper cell 1 (Th1)-differentiation through its effect on epigenetic modifications at the T-BET gene-promoter locus. Since that time, Dr. Sarkar has been actively involved in further understanding how different types of epigenetic mechanisms are involved in T helper cell differentiation during breast cancer.

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