Meetings International SciTechnol

Gurusamy Mariappan et al., J Pharm Sci Emerg Drugs 2018, Volume: 6
DOI: 10.4172/2380-9477-C4-014

Stem cell target: An effective therpeutic stratergy in breast cancer

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Cancer is a leading cause of death worldwide, accounting for 14 million deaths. Globally, nearly 1 in 6 deaths is due to cancer. There are three main strategies for conventional cancer therapy: surgical resection, chemotherapy, and radiotherapy. The surgery and radiation therapy imposes several limitations so that chemotherapy is the best choice. But chemotherapy also fails due to drug resistance and tumor relapse, secondary cancer due to strong implications of cancer stem cells. However, an effective therapeutic strategy to overcome this resistance is yet to be identified. We have recently discovered the DNA methyltranferases, especially DNMT1, play a critical role in MaSCs and CSCs self-renewal and targeted deletion of this gene impaired mammary tumor formation by inhibiting CSCs formation. In this study, using MMTV-Neu-Tg mouse mammary tumor model, we found that both luminal progenitor and basal stem cells susceptible to genetic and epigenetic modifications, which lead to activation of un-activated Neu-Tg into transformed tumor forming phenotype. Combination of 5-Azacytidine, a DNMT inhibitor, and butyrate, a HDAC inhibitor, markedly reduces CSCs and consequently increases the overall survival of the animals. RNA-seq analysis of the CSCs treated with 5-AzaC+ butyrate provides evidence that combined inhibition of DNMTs and HDACs reduces CSCs pool in the mammary gland by blocking growth promoting signaling molecules like RAD51AP1 and SPC25. RAD51AP1 and SPC25, which are known to play a key role in DNA damage repair is significantly over expressed in breast tumor tissues. Further, these two genes are over expressed in Tamoxifen and Taxol resistance human breast cancer cell lines. Functional inactivation of these genes in breast cancer cells facilitates chemotherapy-induced apoptosis and reduces tumor growth. Overall our studies provide strong evidence that breast CSCs (both basal stem cell and luminal progenitor cells) are susceptible for genetic and epigenetic modifications and associated with resistance to chemo- and radiotherapy. Thus, combination of DNMT and HDAC inhibitors can serve as an effective therapeutic strategy in breast cancer treatment.

Biography

Gurusamy Mariappan has completed his PhD from University of North Bengal, West Bengal India and postdoctoral studies from Cancer Research Center from Augusta University USA. He is the Professor cum Research Director of St.Mary's College of Pharmacy Secunderabad, Telangana India. He has published more than 35 papers in reputed journals. He is the recipient of overseas fellowship from Department of Biotechnology, Government of India. He is also a fellow in Institution of Chemist India and life Member of Association of Chemistry Teachers and Indian Association of Cancer Research.

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