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Role of DNA methyltransferases in regulation of breast cancer stem cells

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In recent years, impressive technical advancements have been made in the isolation and validation of the mammary stem cells (MaSCs) and cancer stem cells (CSCs). However, the signaling pathways that regulate stem cell self-renewal are largely unknown. Further, CSCs are believed to contribute to resistance to chemotherapy and radiation therapy. However, an effective therapeutic strategy to overcome this resistance is yet to be identified. Using MMTV-Neu-Tg mouse mammary tumor model, we found that both luminal progenitor and basal stem cells are susceptible to genetic and epigenetic modifications, which in turn reprogram normal MaSCs into cancer propagating CSCs. Combination of 5-Azacytidine, a DNMT inhibitor, and butyrate, a HDAC inhibitor, markedly reduces CSCs and consequently increases the overall survival of the animal. 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 and kinetochore assembly, are significantly over-expressed in breast tumor tissues and associated with decreased overall patients' survival. In conclusion, our studies provide strong evidence that breast CSCs (both basal stem cells 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 to block mammary tumor growth and to overcome drug resistance by inhibiting CSCs.

Biography

Muthusamy Thangaraju has completed his PhD from the University of Madras, India and Post-doctoral studies from the McGill University, Montreal, Canada, Mayo Clinic, Rochester, MN, and National Cancer Institute (NCI), Fredrick, MD. He is an Associate Professor in the department of Biochemistry and Molecular Biology at the Georgia Regents University, Augusta, GA. He has published more than 65 manuscripts in well reputed journals and is a recipient of various NIH and DOD research grants and has been serving as a member in various NIH and DoD study sections.

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