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FoxM1 inhibition: A novel therapeutic avenue to treat breast cancers

Manjeet Rao

University of Texas Health Science Center, USA

Defect in DNA damage response serves as a major factor predisposing normal cells to acquire oncogenic mutations. However, after tumor develops, cancer cells manage their survival by repairing DNA damage resulting from unchecked DNA replication. Moreover, the ability of cancer cells to repair chemotherapy-induced DNA damage also serves as one of the mechanisms for therapy resistance. Therefore, successful targeting of factors/pathways that are capable of inducing DNA damage and suppressing DNA repair responses of cancer cells will have promising therapeutic outcomes. We recently discovered that imipramine blue (IB), a novel analogue of anti-depressant imipramine that we recently synthesized, induces DNA damage and inhibits the ability of breast cancer cells to repair DNA. Using an innovative ex-vivo model of tumor explants from breast cancer patients, we demonstrate that IB inhibits breast cancer growth without affecting normal mammary epithelial cell proliferation. Notably, our studies revealed that systemic delivery of IB using nanoparticle-based drug delivery approach suppressed breast cancer growth and metastasis without inducing any toxicity in pre-clinical mouse models. Furthermore, our in vitro studies show that IB may improve the efficacy of doxorubicin and paclitaxel, a chemotherapeutic drug combination that is routinely used to treat TNBC patients. Importantly, our drug-interaction results suggest that IB may directly bind to and inhibit the activity of proto-oncogene FoxM1 and subsequently alter FoxM1-associated signaling that play critical roles in DNA repair and are known to mediate taxol resistance. We believe that our study will set the stage for a new paradigm of treating breast cancers using IB therapeutic. Our preliminary studies showing inhibition of breast cancer growth in orthotopic mouse model and explants from breast cancer patients by IB without targeting normal mammary epithelial cells suggest that IB may serve as a novel therapeutic with negligible toxicity. Since FoxM1 has been proposed to be a bonafide therapeutic target for several cancers including non-breast cancers, identification of a compound like IB that inhibits FoxM1 and FoxM1-dependnet mechanisms has immense translational potential for treating many aggressive cancers.

Biography

Manjeet Rao has completed his PhD from University of Delhi and Postdoctoral studies from MD Anderson Cancer Center, Houston, TX, USA. He is an Associate Professor at Greehey Children's Cancer Research Institue, University of Texas Health Science Center, San Antonio. He has published more than 38 papers in reputed journals including cell, PNAS, blood, leukemia, oncogene and clinical cancer research.

raom@uthscsa.edu

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