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Activated mTOR pathway in estrogen receptor positive human breast tumors is predictive of better treatment outcome

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Abstract

The status of estrogen receptor (ER) in breast cancer is the cornerstone of endocrine therapy. Selective ER modulators (SERM) such as tamoxifen are the first line of endocrine treatment of breast cancer with proven efficacy in metastatic breast cancer and chemoprevention. Albeit two isoforms of ER are known - ERα and ERβ, the breast tumors are characterized based on the status of ERα. Despite the expression of ERα some patients develop tamoxifen resistance and 50% present de novo tamoxifen resistance. The mechanism by which these tumors progress from hormone dependence to hormone independence remains elusive, however earlier reports have demonstrated that increased activity of growth factors such as epidermal growth factor (EGF) and insulin like growth factors (IGF) bestow estrogen-independent growth of ERα positive breast cancer cells thus impeding the effectiveness of SERMs. The PI3K/Akt/mTOR signaling axis regulates cell growth, proliferation and transformation. Hormone independent growth of ERα positive breast tumor cells is in part due to the increased activation of the PI3K/Akt/mTOR signaling pathway. The consequent activation of various kinases in these pathways may activate ERα in a ligand independent manner directly and/or indirectly through modulation of co-activator activity. Phosphorylation of ERα on multiple residues regulates its activity .The role of phosphorylation of these residues in breast tumors is not fully known, however in breast cancer cell lines they can regulate transcription, nuclear localization, dimerization and DNA binding. Our research group is interested in investigating relevance of phosphorylation of these residues in breast tumors *in vivo* in predicting overall survival (OS) and relapse free survival (RFS). Earlier, it was demonstrated that a combination of multiple phosphorylated residues on ERα was a better predictor of OS and RFS. This is based on a phosphorylation score, called P7 score, which represents the presence of up to seven phosphorylated-ERα sites detected in a tumor. On multivariate analysis the P7 score is significantly associated with OS from breast cancer death and RFS in ERα positive breast cancer patients who were later treated with tamoxifen. The P7 score represents the balance of those phospho-ERα sites associate with good versus poor clinical outcome. Mammalian target of rapamycin (mTOR) is a central hub of signaling pathways impacting cell growth, proliferation, metabolism and protein synthesis. Since mTOR activation is implicated in resistant to endocrine therapy in breast cancer we investigated whether activation of mTOR pathway is associated with OS and RFS. Therefore, we evaluated the relationship of activated mTOR signaling and the ERα phosphorylation score, as a measure of the balance of ligand dependent and independent ERα signaling, using cases of human breast cancers, where the patient was later treated with tamoxifen. We observed that activated mTOR pathway predicts better treatment outcome. These data suggest that in breast tumors where there is intact estrogen regulated signaling, mTOR is regulated by estrogen and therefore associated with an increased likelihood of responsiveness to endocrine therapy.

Biography

Anuraag Shrivastav completed his PhD in 2002 from the Banaras Hindu University, India. He received postdoctoral fellowship from Canadian Institutes of Health Research and obtained postdoctoral training at the department of Pathology and Laboratory Medicine and Saskatchewan Cancer Agency, University of Saskatchewan, Canada. Dr. Shrivastav is a faculty member at the University of Winnipeg and adjunct member at the University of Manitoba and CancerCare Manitoba. He has published over 40 peer-reviewed articles in the International journal of repute. His laboratory is engaged in studying cellular signaling mechanisms that are intricately linked to homeostasis that control cell proliferation, survival and death in cancer cells. Currently, his research group is actively pursuing scientific research to identify novel markers for CRC screening and early detection and prognostic markers for breast cancer.