Thesis Title: Analysis of TNF-α regulated metabolic reprogramming in ER/PR +ve and – ve breast cancer cells

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Abstract:

Breast cancer is a heterogeneous disease that shows a higher degree of complexity. Breast cancer tumor microenvironment is complex and consists of different cell population and inflammatory cytokines and chemokines that drive tumorigenic potential of these cells. Breast cancer subtypes have distinguished characteristics and hence a well-designed approach is necessary to achieve better treatment responses. ER/PR +ve and ER/PR -ve breast cancer cells have different molecular patterns and metastatic and invasion potentials that have laid foundations for therapeutics. ER/PR -ve or TNBC have limited therapeutic targets and shows high immune invasion and recurrence rates. Inflammation and metabolism are two major determinants in the TME that drive the tumor cell survival and dictate changes underlying resistance to therapies. TNF-induced NF-κB pathway regulate multiple cellular processes in the cancer cells. TNF-α plays a critical role in breast cancer cell proliferation, correlates with higher tumor grade and metastasis. However, the inflammation mediated metabolic adaption of different breast cancer cell types in not yet understood. Mitochondria has emerged a platform for immune-metabolic changes thus act as critical platform integrating inflammation in TME due to various cell type for metabolic adaption in tumor cells which may differentially effect tumor progression in different breast cancer subtypes. Inflammation induced mitochondrial adaptation in different breast cancer cell types and breast cancer cells survival is not well understood. Here we demonstrated that TNF-α modulates expression of mitochondrial proteins in ER/PR +ve and ER/PR -ve breast cancer cells. TNF-α modulates metabolism differentially in ER/PR +ve and ER/PR -ve breast cancer cells by modulating the levels of critical assembly factors and subunits involved in mitochondrial respiratory chain super complexes. TNF-α modulated metabolic reprogramming and shows accumulation of metabolites like pyruvate, aspartate and succinate that favours survival and proliferation of more aggressive ER/PR -ve breast cancer cells. Further, large scale database of breast cancer patient showed TNF-α negatively correlates with major subunits of mitochondrial complexes in Basal subtype compared to luminal breast cancer patients. The study here strongly suggests that TNF-α induced metabolic pathways and mitochondrial protein expression in ER/PR +ve and ER/PR -

ve breast cancer cells induced cell migration and clonogenicity and are novel targets for therapeutics to prevent progression in aggressive breast cancers. Further, changes in mitochondrial proteins and mitochondrial complex activities contribute to generation of ROS which is a major driver for metastasis in breast cancer cells. The study identified LYRM7, an assembly factor for mitochondrial complex III that modulates breast cancer invasion and migration under inflammatory conditions. TNF-induced NF-κB regulate the expression of LYRM7 in MDA-MB-231 breast cancer cells. The study further identifies TNF-α induced LYRM7 in regulating the breast cancer cell migration and invasion potentials by modulating mitochondrial OXPHOS capacity. The expression of LYRM7 decreased in TNBC patients as compared to other subtypes. Infliximab, a monoclonal antibody against TNF-α showed reduced LYRM7 gene expression as compared to control in breast cancer mice model. Thus, the study indicates that TNF-α induced NF-κB is a critical regulator of LYRM7, a major factor for modulating mitochondrial functions under inflammatory conditions, which determines growth and survival of breast cancer cells. Infliximab that reduces TNF-α in the breast cancer mice model showed reduced tumor growth and metastasis to lungs specifically. TNF-α induced NF-κB can regulate the expression of autotaxin which play a role in clonogenicity of breast cancer cells. This work provides an increased understanding of how to regulate the ATX-LPA-inflammatory cycle and prevent it from becoming maladaptive and pro-metastatic. This concept could be developed as a novel treatment for improving the outcomes for breast cancer patients by using infliximab to decrease the effects of TNF-α together with ATX-LPA inhibitors. The study suggest that TNF-induced pathway can be targeted using Infliximab and other developing biologics or developing combinatorial therapy targeting the OXPHOS and metabolic pathway acting synergistically in presence inflammatory milieu of breast cancers.