2. Aims and Objectives

2.1 Rational of Hypothesis

Evidence suggests that inflammation plays a critical role in the activation of multiple pathways that are responsible for development and growth of breast cancer. The inflammatory state created by the presence of cytokines in the TME is known to drive different phases of tumor development and progression. TNF-α, a proinflammatory cytokine is high in tumors from different origin and contribute to the inflammatory state in TME. The role of TNF-α in regulating the mitochondrial proteins and functions in different subtypes of breast cancer and determining their metastatic potentials is yet to be explored. The current study aims to understand the role of TNF-α regulated metabolic reprogramming in human breast cancer cells by modulating the expression of mitochondrial proteins. Further TNF-α induced differential regulation of mitochondrial OXPHOS complex assembly and activity and their role in tumorigenic potential of breast cancer subtypes had also been investigated.

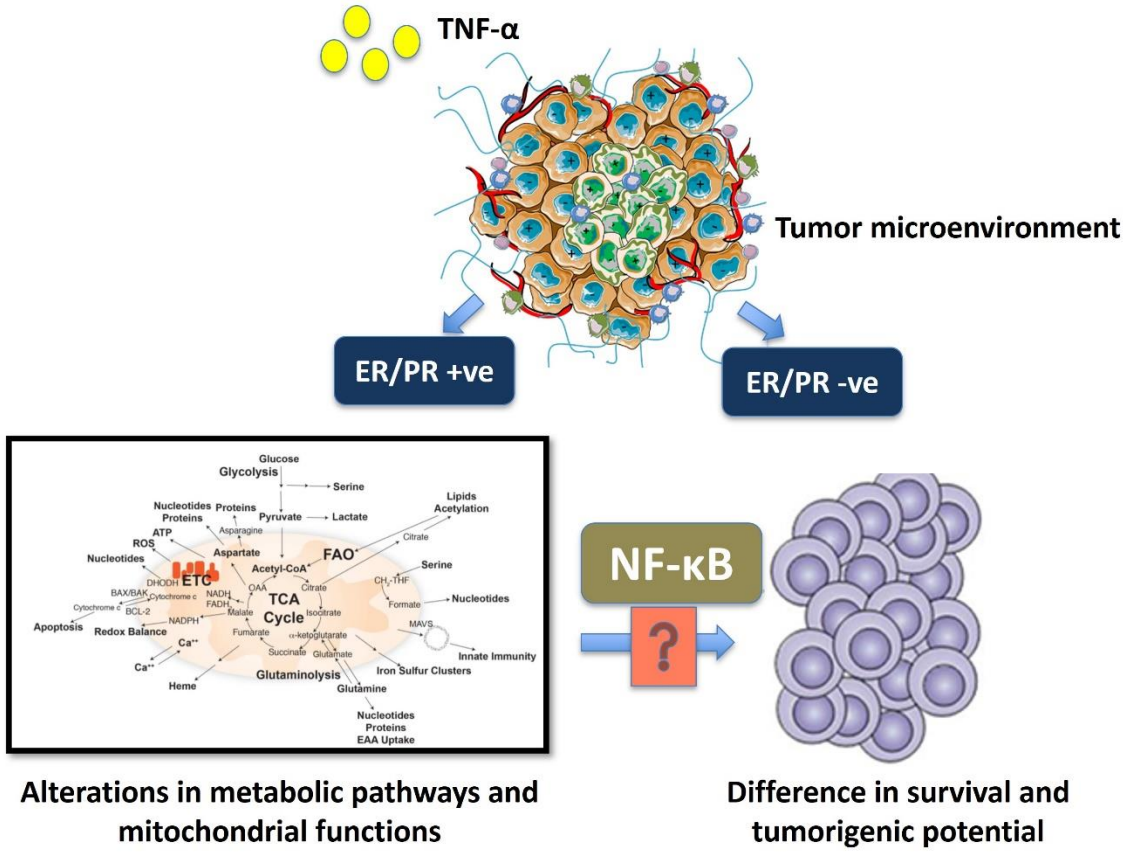

Figure 5: Schematic representation of hypothesis of the study

2.2 Objectives:

Objective 1: Study the role of TNF-α -regulated oxidative phosphorylation and aerobic glycolysis in ER (+ve) and ER (-ve) breast cancer cells.

Objective 2: Analysis of mitochondrial proteome and mitochondrial respiratory complexes assembly in ER (+ve) and ER (-ve) breast cancer cells in presence and absence of TNF-α.

Objective 3: Functional characterization of differentially abundant proteins (TNF-α treated vs Untreated), their role in mitochondrial functions and effect on tumorigenicity in ER/PR +ve/-ve cells.

Hypothesis:

The emerging evidence strongly suggests that cytokine in the solid tumor including breast cancer show distinct pattern of cytokine where TNF-α predominates in TME of solid tumors including breast cancer. TNF-α regulates NF-κB, key transcriptional signaling, which may differentially regulate OXPHOS capacity of the different breast cancer cell types: specifically, ER/PR +ve (MCF-7) and triple negative (MDA-MB-231). TNF-α may differentially regulate the mitochondrial proteome by modulating key transcriptional factor NF-κB which may regulate the expression of mitochondrial proteins encoded by nuclear DNA and proteins involved in metabolic adaption of the breast cancer cells and key proteins which may regulate OXPHOS assembly and activity hence OXPHOS adaption in different breast cancer cell types. Further TNF-α induced NF-κB may regulate expression of critical enzymes such as Autotaxin. TNF-NF-κB and ATX-LPA are both inflammatory axis that can overlap to enhance breast cancer metastasis in tumor microenvironment.