Chapter Three:
Aims and Objectives

3.1 Rationale and Hypothesis

Chronic inflammation associated with TME of solid tumors such as breast cancer plays an important role during different stages of tumor development. Intratumoral cytokines are the key modulators of inflammatory response and promotes the overall growth of tumors by evading cell death signaling and immune activation. An increased level of TNF-α have been reported in various solid tumors such as breast, pancreatic, renal and hepatocellular carcinoma. The specific mechanisms of association of inflammatory response with tumor development and its role in cancer cell survival and metabolic reprogramming are not well understood.

In addition to its primary role in ATP generation, mitochondria are emerging as a molecular platform for the assembly of immune adaptor protein complexes such as MAVS and STING, which regulates activation of type-I IFN and NF-κB pathways during viral infections. The mitochondria-localized immune adaptor proteins are widely expressed in non-immune cells however their role in regulation of mitochondrial function and metabolic adaption during tumor progression is not well understood.

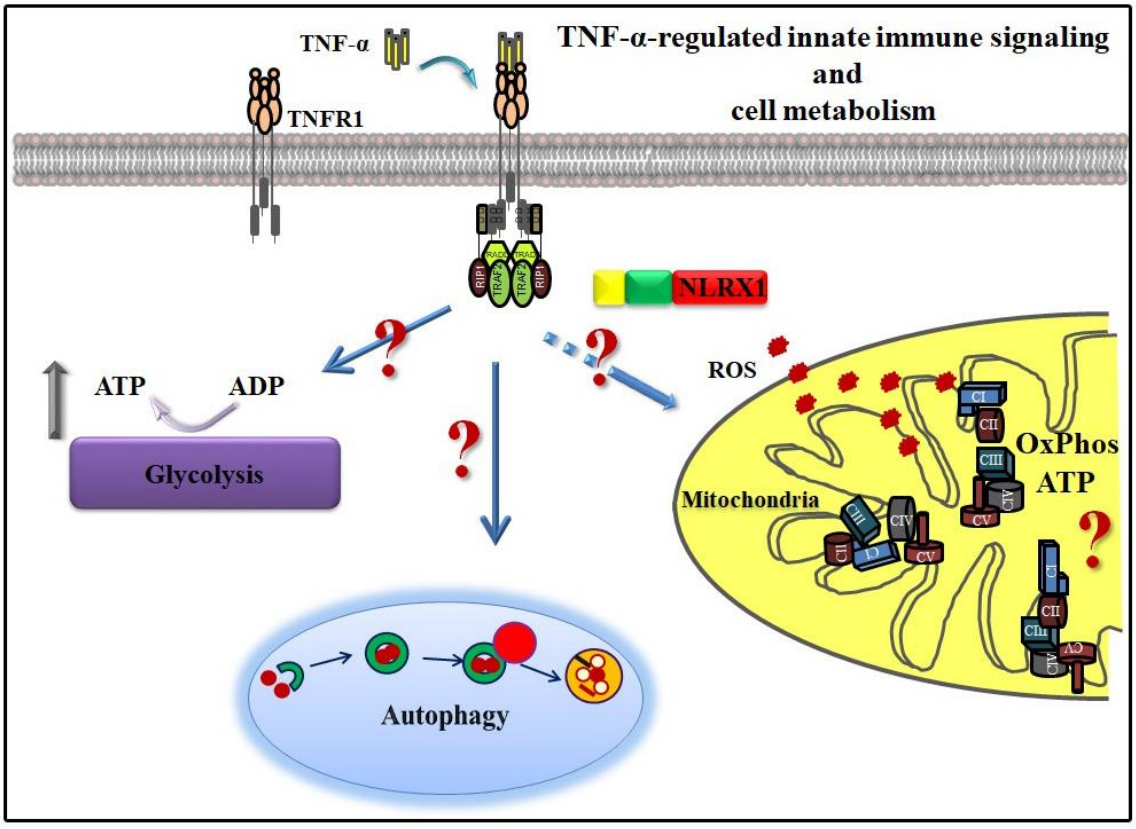

Figure 3.1: *NLRX1 may modulate the crosstalk between TNF-α-regulated innate immune response (cell death and autophagy) and mitochondrial metabolism in cancer cells.*

NLRX1, a member of NLR family receptor proteins, localizes to mitochondria and is a negative regulator of innate immune signaling. However, the submitochondrial localization of NLRX1 and its implication in regulation of mitochondrial functions and cell death is not clear. Further, role of NLRX1 in preserving mitochondrial homeostasis to regulate the tumorigenic potential of cancer cells during inflammatory stress condition is not well understood *(Figure 3.1)****. Hence, the following objectives were proposed:***

3.2 Objectives of the study:

1. **Study the role of NLRX1 in regulation of TNF-α induced cell death.**
2. **Role of NLRX1 in TNF-α induced ROS generation and metabolism.**
3. **Role of NLRX1 in TNF-α induced autophagy and its crosstalk with cancer cell metabolism.**

These objectives have been divided into three major chapters of this Ph.D. thesis:

Chapter 1 demonstrates the role of NLRX1 in sensitizing TNF-α induced cell death and regulating mitochondrial metabolism of breast cancer cells. This study has been published as manuscript entitled "*NLRX1 acts as tumor suppressor by regulating TNF-alpha induced apoptosis and metabolism in cancer cells*" in *BBA: Mol Cell Research (2015). doi: 10.1016/j.bbamcr.2015.01.016*

Chapter 2 reveals the mechanism through which NLRX1 may regulate mitochondrial function and hence metabolic reprogramming of breast cancer cells in the presence of TNF-α. This study has been published as manuscript entitled "*NLRX1 resides in mitochondrial RNA granules and regulates mitochondrial RNA processing and bioenergetic adaptation*" in *BBA: Mol Cell Research (2018). doi: 10.1016/j.bbamcr.2018.06.008*

Chapter 3 demonstrates a functional role of NLRX1-regulated mitochondrial function in controlling TNF-α-induced autophagy flux to maintain the metastatic potential of invasive breast cancer cells. This study has been communicated as manuscript entitled "*NLRX1 regulates TNF-α-induced mitochondria-lysosomal crosstalk to maintain the tumorigenic potential of breast cancer cells*".