3. RATIONALE

Recent reports of TLRs expression on cancer cells suggest their contribution in the development and progression of the cancer. TLR expression has been reported in various kinds of cancers including gastric, colorectal, breast and lung cancer. Literature suggests that TLRs are expressed in HNSCC. Adapted tumor micro-environment and various kinds of therapies are the main reasons of stress inducing the release of DAMPs. These DAMPs can bind to the TLRs and activate the downstream signaling cascade. Downstream kinases of the pathway-IRAK-1 and IRAK-4, play a crucial role in TLRs signaling. Their phosphorylated form indicates an activated TLR signaling. Their expression and phosphorylation have been linked to the development and progression of tumors like TNBC, PDAC and CRC.

Cancer cells can benefit from the activated TLR signaling. Aberrant MAPK/NF-κB/IRF activation through TLRs signaling leads to the generation of inflammatory mediators that strengthens the tumor microenvironment. It has a potential to elevate the pro-oncogenic properties like increased cell proliferation, survival, cancer stem cells (CSCs) formation, metastasis and epithelial to mesenchymal transition (EMT) of cells in the tumor microenvironment. Such signaling may also contribute to the development of resistance to the conventional chemo-drugs, that are used as front-line therapies. Their role and contribution in HNSCC have remained largely unexplored.

In this study, we propose to investigate the role of TLR signaling on the oncogenesis of HNSCC. In such a state, the TLR signaling may serve as biomarker of disease progression or therapeutic resistance as well. It can also have an impact on therapeutic responses. If such phenomenon holds true than inhibiting TLR signaling could be an attractive therapeutic approach for HNSCC **(Figure 3.1)**.

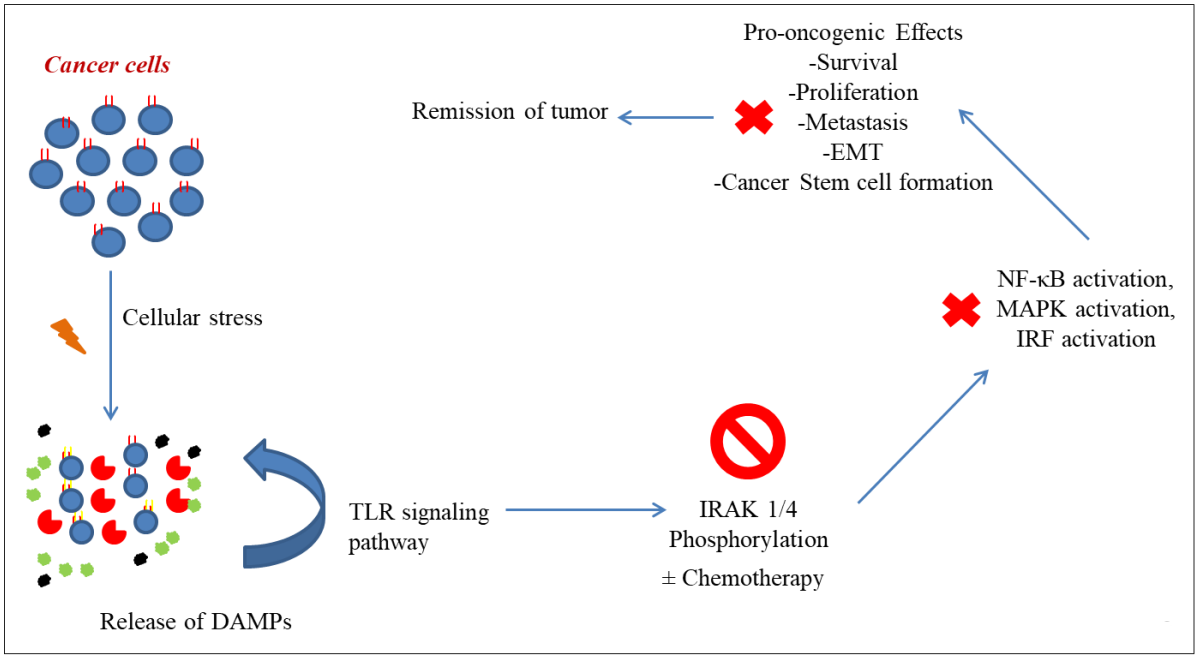

Figure 3.1: Probable role of TLR signaling in HNSCC progression

AIM

To understand the role of TLR signaling in progression of HNSCC and evaluate it as therapeutic target.

OBJECTIVES

1. Expression profiling of TLRs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 on HNSCC cell line
2. Evaluation of constitutive TLR signaling in HNSCC cell line
3. Evaluation of the impact of TLR signaling on the oncogenic properties of HNSCC cell line
4. Evaluation of the role of TLR signaling in chemo-resistant HNSCC
5. Evaluation of therapeutic potential of TLR inhibitor as combination therapy with conventional chemo-drugs using HNSCC cell line