Summary

The main theme of this thesis was to unravel the role of transcription factor AIRE in cancer and TB infection. Additionally, we have also made an effort to build a database possessing therapeutically relevant information regarding autophagy.

AIRE drives the negative selection of self-reactive T cells in the thymus thereby prevents from autoimmune disorders. Recently, its function in modulating cancer progression has been discovered. However, the mechanistic insights are missing. AIRE being regulated by sex hormones estrogen and androgens made us wonder its role in sex hormone related cancers. It is known to promote apoptosis in breast cancer cells. However, its role in prostate cancer was not investigated. Early stage prostate cancers are dependent on androgens for their growth and survival and androgen withdrawal causes them to regress. Progressive prostate cancers eventually acquire androgen independence rendering anti-androgen therapy ineffective. However, the factors leading to this have not been adequately addressed. In chapter 3, we have shown that AIRE modulates the prostate tumor microenvironment by transcriptionally activating IL-6 malignancy gene in androgen-independent cells. Additionally, we have shown that AIRE prevents the cancer cells from anticancer drug-induced cell death and enhances their invasiveness. Moreover, AIRE by modulating the cytokine milieu skews the tumor-associated macrophage polarization towards M2 phenotype with increased CD206 and CD163 expression. Subcutaneous mouse model of prostate cancer revealed $AIRE^{+/+}$ mice forming a palpable tumor and presents lymphadenopathy, however, only a small benign tumor is observed in $AIRE^{-/-}$ mice and lymph nodes appear normal in size. In conclusion, our findings suggest AIRE as a probable factor in promoting prostate cancer progression.

M. tuberculosis is a causative organism responsible for the deadly disease TB which comprises one of the major global health issues. Most importantly, it shows sexual inequality by being more prevalent in males than females worldwide. One possible reason could be the hormonal effects as the sentinel cells harbor the receptors for the sex steroid hormones. However, signaling mechanisms have not been dissected out. In chapter 4, we have shown that in males AIRE known to be regulated by androgen

leads to increase in susceptibility to TB. Whereas, in females probably AIRE function is being suppressed by estrogen so it does not lead to increase in the bacillary burden as compared to the $AIRE^{-/-}$ female mice.

Despite in depth research into the process of autophagy and its role in pathophysiological processes, the resources available to use it for therapeutic purposes are currently lacking. In chapter 5 we have developed a freely available resource, Autophagy Small Molecule Database (AutophagySMDB; http://www.autophagysmdb.org/) of small molecules and their cognate protein targets that modulate autophagy. Presently, AutophagySMDB enlists ~9000 small molecules which regulate 64 target proteins. AutophagySMDB is an exhaustive, cross-platform, manually curated database, where either the cognate targets for small molecule or small molecules for a target can be searched. This database is provided with different search options like text search, advanced search and structure search. We have also incorporated various tools like tree tool, cataloging tools, and clustering tools for advanced analysis. Along with the search options and tools provided, this database helps to choose small molecules based on various properties and to identify common or unique scaffolds for designing novel drugs or to improve current ones.