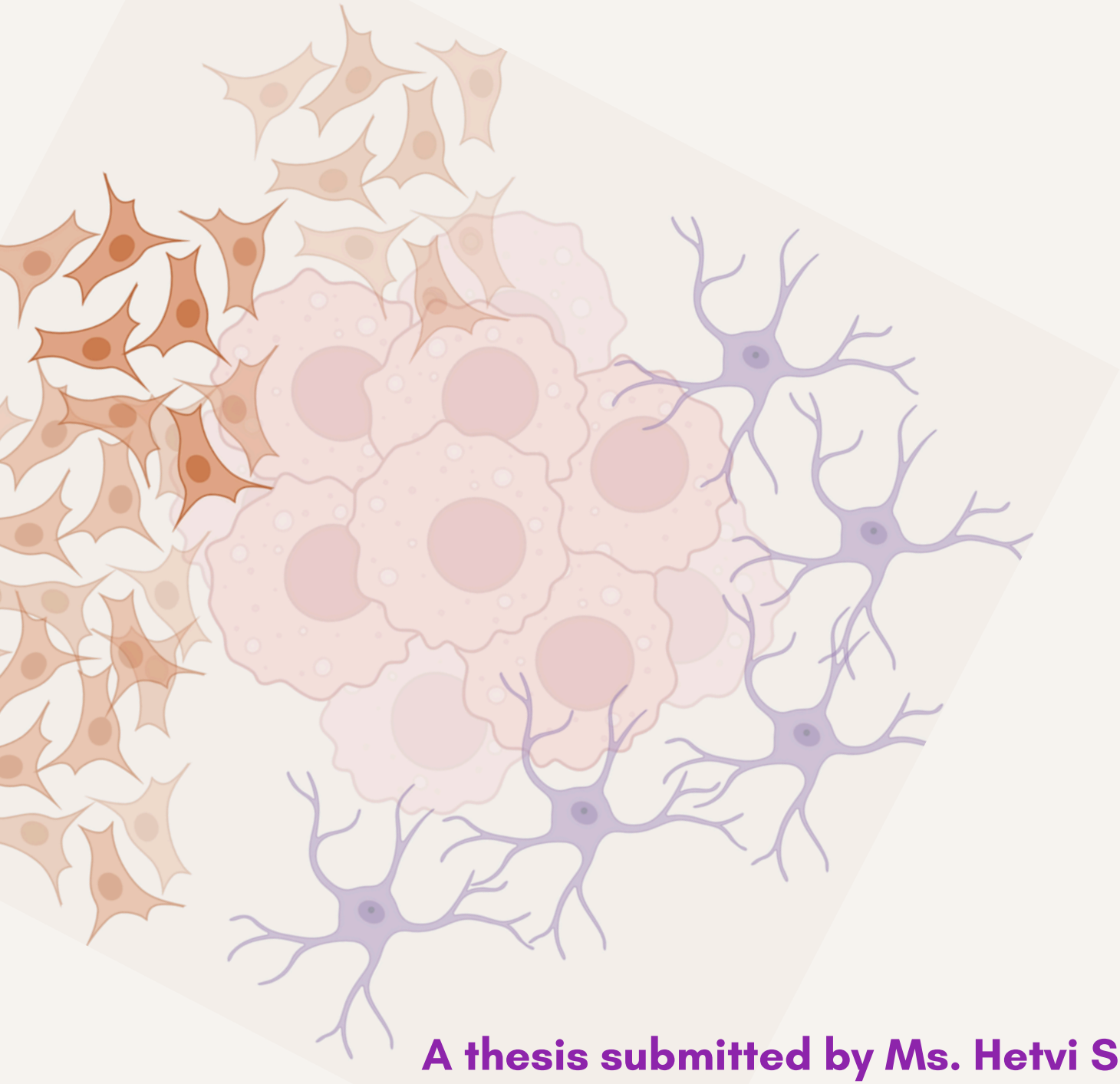
# Mechanistic Insights into the Role of Kisspeptin-1 in Cancer Progression and Metastasis : *in vitro* and *in silico* Approach



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# *Summary of Findings*

This study has systematically examined the role of human *KISS1* gene and its biologically active peptide Kisspeptin-10 in cancer progression in different cancer types, such as Triple Negative Breast Cancer, Glioblastoma, and Ovarian Cancer. In addition, Chapter 1 of the current dissertation used bioinformatic tool-based structural studies that inferred that KISS1 is an intrinsically disordered protein with a higher content of random coil, thus conferring structural adaptability on KISS1 that could allow for the interaction of the protein with multiple biologically active proteins. Secondly, this study established an association of the human KISS1 gene with respective transcription factors. SP1, MYCN, CDX2, FLI1, GATA2, and HDAC2 transcription factors are associated with KISS1. Following the identification of the transcription factors, protein-DNA docking and 150 ns molecular dynamics simulation studies confirmed the dynamic stability of KISS1 transcription factor complexes.

In Chapter 2, functional validation studies on TNBC cell lines, i.e., MDA-MB-231 and MDA-MB-468, results established the dose-dependent cytotoxic effects of Kisspeptin-10 on TNBC cells and their role in the suppression of cell migration and invasion. In addition, upregulation of epithelial cell markers such as E-cadherin and pro-apoptotic proteins such as BAX and Caspase-3, along with the suppression of mesenchymal cell markers such as Vimentin and ZEB1, and pro-survival protein BCL2, have established the regulation of KISS1 on EMT, apoptosis, and oncogenic signaling pathways. The results of the study also highlighted the role of Kisspeptin-10 on the overall survival of breast cancer patients. The Kaplan-Meier survival analysis results indicated that the patients who have an upregulated KISS1 transcript have better survival outcomes.

As discussed in Chapter 3, Kisspeptin-10 treatment in U87MG glioblastoma cells demonstrated considerable inhibition of invasion and alteration of the EMT protein markers. Analysis of differentially regulated genes from public databases led to the identification of core networks of glioblastoma progression regulation, and Kisspeptin-10 altered key transcription factors, adhesion proteins, apoptosis regulators, and signaling modifiers. Analysis of the miRNA profile indicated the regulation of the glioblastoma phenotype by Kisspeptin-10 via miR-345, miR-200c, and miR-577.

In Chapter 4, it was shown that the anti-invasive and anti-EMT capacities were similar in SKOV-3 ovarian cancer cells. Kisspeptin-10 reduced migratory and invasive potential, modulated transcription factors such as SP1, GATA2, CDX2, and ZEB1, and also signaling molecules like PLCB1, PKA, PKR, and CJUN. The overexpression of miR-200, miR-345, and miR-577 assisted in transcriptional and post-transcriptional gene expression. The regulatory motifs for KISS1 suggested potential involvement in telomerase-related pathways.

These studies collectively suggest that KISS1/Kisspeptin acts as a metastasis suppressor system that integrates transcriptional control, EMT regulation, apoptosis induction, signaling pathway regulation, and metabolic reprogramming. The present study thus purportedly bridged structural bioinformatics with its functional validation across a range of aggressive cancer entities with implications for KISS1 as a multi-level regulatory hub.

# CONCLUSION

This study provides clear evidence that exogenous Kisspeptin-10 regulates metastasis and progression through multiple interconnected biological pathways. Across triple-negative breast cancer, glioblastoma, and ovarian cancer, Kisspeptin treatment was associated with modulation of transcription factors, intracellular signaling molecules epithelial–mesenchymal transition markers and apoptosis markers. These coordinated effects suggest that Kisspeptin functions as a regulatory supporter that influences gene expression, signaling stability, and phenotypic behavior in aggressive cancer cells.

This research strengthens our understanding of the *KISS1/KISS1R* axis as a multi-level modulatory system. By highlighting its association with transcriptional regulation, apoptotic pathways, signaling mediators, and potential telomerase-linked regulation, the study identifies Kisspeptin-related networks as promising biomarkers and supportive therapeutic targets. The findings provide a foundation for future translational research and combinatorial treatment strategies, particularly in metastasis-related cancers.

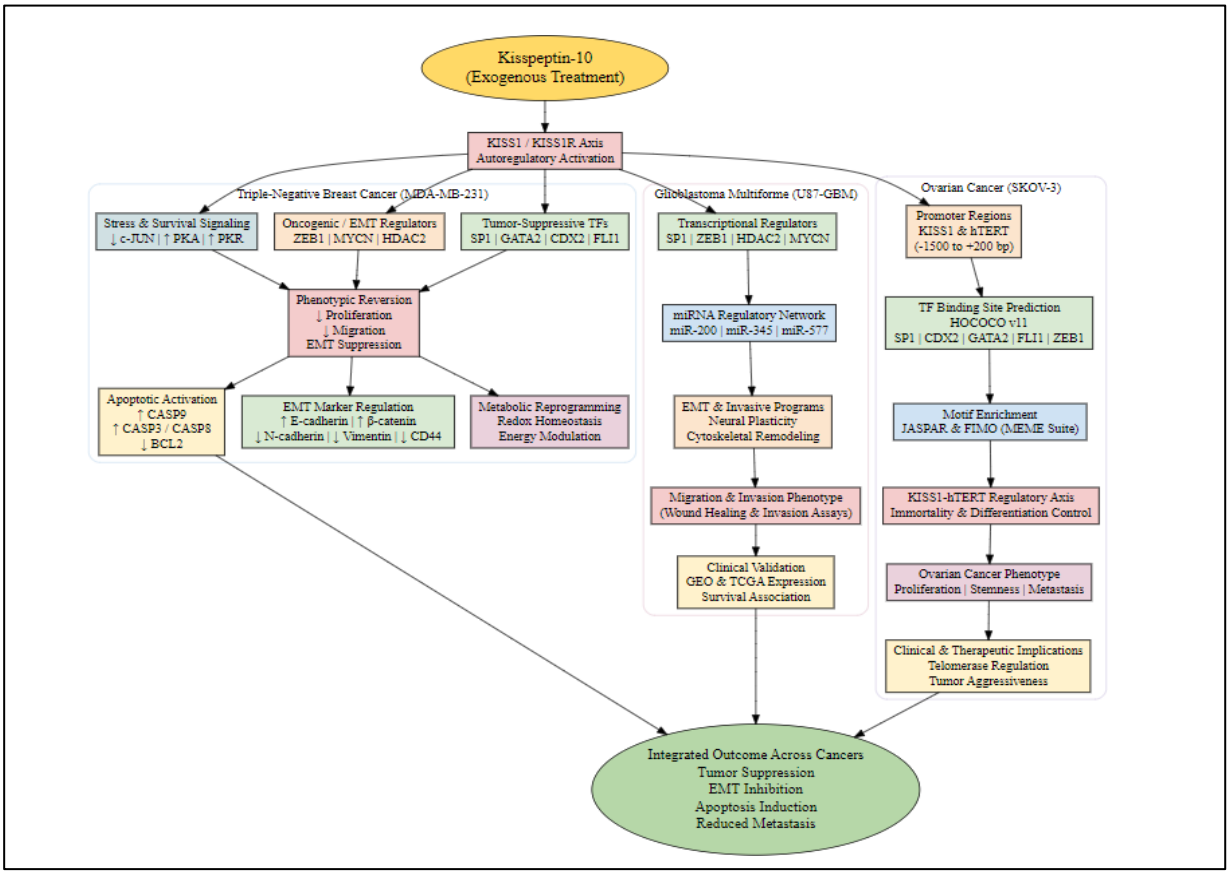


***Figure 6:*** *Overall conclusion image depicting the multi-model role of Kisspeptin in Triple-Negative Breast Cancer, Glioblastoma and Ovarian Cancer*

# Future Prospects

The mechanistic framework through which the KISS1/Kisspeptin axis participates in transcriptional regulation, modulation of epithelial-to-mesenchymal transition, apoptotic reprogramming, integration of signaling cascades, metabolic remodeling, and microRNA-mediated post-transcriptional regulation in triple-negative breast cancer, glioblastoma, and ovarian carcinoma is elucidated in this present investigation. This study offers a multidimensional understanding of KISS1/Kisspeptin's functional context and presents several avenues to advance mechanistic understanding.

**1. Development of KISS1-Centric Prognostic and Predictive Biomarkers**

Such consistent findings between high levels of KISS1 expression and positive outcomes in terms of breast cancer cohorts emphasize the importance of this biomarker. Further studies should aim to evaluate the potential of KISS1, together with other cis-regulators like SP1, ZEB1, BAX, and Vimentin, as a composite biomarker for stratifying metastasis risk. Measurement of levels of KISS1 transcripts and/or its protein products in tumor tissues, tumor cells, and possibly even extracellular vesicles has the potential to identify high-risk individuals and aid precision medicine strategies.

2. **Experimental Validation of Transcriptional Regulatory Hierarchies**

The *in-silico* identification of various transcription factors, such as SP1, MYCN, CDX2, FLI1, GATA2, and HDAC2, as potential transcriptional regulators that influence KISS1 promoter activity requires validation. A series of chromatin immunoprecipitation assays with both qPCR and sequencing would confirm DNA-protein interactions, while promoter reporter gene assays would investigate regulated transcriptional function, thus enhancing our understanding of a hierarchical regulatory model.

**3. Therapeutic Exploitation of miRNA-Mediated Regulatory Circuits**

The modulation of miR-200, miR-345, and miR-577 supports the possibility that the KISS1 metastasis suppressive functions are achieved through post-transcriptional reprogramming. In addition, the specific application of miRNA-based therapeutic reagents would allow for the studying the metastatic phenotypes to enhance the KISS1 anti-tumor effects.

**4. Combinational Therapeutic Effect**

In view of the anti-proliferative and anti-invasive activities of Kisspeptin-10, assessment of combination therapies using established other chemotherapeutic agents may reveal a synergistic interaction. The assessment of combination indices and dose-reduction indices could improve the therapeutic efficacy while reducing the systemic toxicity.

**5. Validation of the finding on Preclinical models or Patient-Samples**

To transcend the limitations of the 2D culture models, in the future, 3D spheroid cultures, organoids, and orthotopic xenograft models should be included. Also, an extensive evaluation of KISS1 and its associated regulatory axis in well-characterized patient cohorts is a necessity for clinical translation. transcriptomic and immunohistochemical profiling across molecular subtypes of TNBC, glioblastoma, and ovarian carcinoma should be correlated with clinicopathological parameters and longitudinal survival outcomes. This would validate the robustness and generalizability of the KISS1 regulatory signature.