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Inflammatory Breast Cancer: Role of the CEBPD-FBXW7 Signaling Pathway

Lay Summary

Inflammatory breast cancer (IBC) is an uncommon and highly aggressive form of breast cancer (classified by NIH as Rare Disease), accounting for 2-5% of all breast cancer (BC) diagnoses but approximately 10% of BC deaths. Women often have metastatic disease at the time of diagnosis and no disease-specific therapeutic option exists. Despite this clinical reality, IBC is significantly understudied compared to all other BC subtypes. IBC presents usually as a "no lump" disease with dispersed invasive histology, extensive lymphangiogenesis, and presence of cancer cell clusters, termed emboli, within the lymphovascular spaces. One distinct molecular feature of IBC is the upregulation and ubiquitous expression of cell-cell adhesion molecules, which is typically a marker of good prognosis in non-IBC breast cancers. There is no disease-specific therapeutic option at present, and IBC patients are treated with aggressive systemic therapy. There is an urgent need to identify the molecular changes responsible for the pathogenesis of IBC to enable better outcomes for IBC patients through specific targeted therapies.

The transcription factor CCAAT/enhancer binding protein delta (CEBPD) is expressed in normal breast epithelial cells. Yet, many of the known CEBPD target genes are implicated in the pathology of IBC, which prompted us to investigate the potential role of CEBPD in IBC cell biology. Analysis of patient tissues and cell lines demonstrated that CEBPD is expressed in IBC, including emboli structures. Using gene-silencing approaches in IBC cell lines, we found that CEBPD supports expression of genes associated with inflammation, self renewal (stemness), and proliferation. Functional assays showed that CEBPD promoted cell invasiveness in culture and also emboli formation in suspension culture, which was associated with expression of cell-cell adhesion molecules. Based on these results, which identify CEBPD as a possible driver of malignant features in IBC cells, we propose that pharmacological downregulation of CEBPD could be of therapeutic benefit. We explored the effect of inhibitors of histone deaceylases (HDACi), which are in clinical trials for several types of cancer. We found that HDACi inhibited CEBPD expression in IBC cell lines in vitro and in vivo, diminished cell survival in culture, and inhibited primary tumor growth in a xenograft mouse model. With ongoing studies we are in the process of narrowing down the specific HDAC involved in promoting CEBPD expression and IBC cell malignancy. Taken together, our studies have identified CEBPD as a new player in IBC, which promotes several malignant pathways in IBC, and as a target of clinically approved HDAC inhibitors, which downregulate CEBPD along with malignant features of IBC cells.

This grant from Metavivor has jump-started a new research direction of this laboratory. The findings were presented at several national and international conferences, have provided the basis for the next generation grant applications, and have also spurred new collaborative efforts. Current and future efforts will address the specific role of CEBPD in the effect of HDAC inhibition, and the potential prognostic/predictive value of CEBPD expression in cancer tissues. Furthermore, we will use pre-clinical models of metastatic breast cancer to assess the potential synergy of HDAC inhibition with chemotherapies and radiation, which are currently standard of care for IBC patients. Given that HDACi are relatively well tolerated, these approaches may significantly advance the options for IBC patients and perhaps also non-IBC metastatic breast cancer patients.