Targeting Cancer Stem Cells to Treat Metastasis

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Despite the initial effectiveness of current treatment regimens, many breast cancer patients die because they develop either metastasis or resistance to chemotherapy. Triple Negative Breast Cancers (TNBCs) are an aggressive breast cancer subtype that is particularly prone to develop metastasis and is associated with a high mortality rate due to the lack of effective therapies and the emergence of chemotherapy-resistant tumors following treatment with conventional therapies. The dearth of effective anti-metastatic therapies for TNBCs calls for an improved understanding of the molecular mechanisms underlying the progression of this disease to metastasis, and the emergence of residual tumors post-chemotherapy.

The high therapeutic failure of TNBCs has been attributed to the existence of breast cancer stem cells (CSCs), a subset of tumor cells that exhibits an intrinsic resistance to chemotherapy, and is thus more capable of surviving treatment to regenerate the tumor. Moreover, we found that tumor cells undergoing an epithelial-mesenchymal transition (EMT)—a process typically associated with the increased ability of cancer cells to detach from the primary tumor and metastasize—also acquire stem cell attributes rendering them resilient to drug treatments and more capable of establishing metastases in mice.

In this proposal, we aim to understand the molecules and mechanisms that control EMT and how these may lead to the acquisition of stem cell attributes and contribute to metastasis. In addition, we propose that exploiting this knowledge will either help prevent or control the incidence of metastases and/or the emergence of drug resistance. Towards this goal, we have identified a molecule called FOXC2 as a key regulator of EMT, CSC properties and metastatic ability. Importantly, whereas FOXC2 is absent from most normal adult tissues, its levels are significantly elevated in TNBCs, strongly advocating FOXC2 as a promising therapeutic target for selectively targeting CSCs and metastasis. Moreover, the introduction of FOXC2 into non-metastatic cancer cells predisposes them to undergo EMT leading to the acquisition of CSC properties and an increased ability to metastasize. Importantly, we have found that blocking the activity of FOXC2, using genetic means, can reverse EMT-associated changes and cause breast cancer cells to lose the CSC properties critical for metastasis. With the above considerations in mind, we aim to develop strategies that interfere with the abnormal FOXC2 functions in TNBC cells, without affecting normal cells. However, FOXC2 belongs to a class of molecules, known as transcription factors, which are not readily amenable to drug development. Nevertheless, the activity of transcription factors is regulated by enzymes, termed protein kinases, which are often therapeutically targetable. Indeed, we have identified a targetable kinase that positively regulates FOXC2 levels and activity. Our initial data, using an established drug that inhibits this kinase, show a dramatic decrease in FOXC2 levels in treated cells, accompanied by a marked reduction in stem cell properties. We will use this highly selective protein kinase inhibitor in a range of cellular assays to determine its effects on EMT as well as in pre-clinical mouse models of TNBC metastasis to determine whether this kinase inhibitor can treat and/or prevent metastasis. We will complement our studies using sophisticated methodologies to deplete the expression of the kinase that regulates FOXC2 to confirm the molecular basis of the observed effects and the specificity of the drug. We will also examine whether combinations of the said drug with current standard-of-care chemotherapies can efficiently curtail TNBC metastasis and measurably improve long-term survival. These studies will provide a proof-of-principle for inhibiting the kinase that regulates FOXC2 as a viable therapeutic strategy to target metastatic TNBC cells. Our long-term goal is to develop specific therapies against FOXC2-expressing CSCs to improve the survival of TNBC patients and prevent or eradicate metastatic disease.