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Regulation of the cancer stem cell phenotype by TGFBR1 and TGFBI in breast cancer

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Many tumors follow a plastic hierarchical organization in which a subset of cells, the so-called cancer stem cells (CSCs), are at the apex. In these tumors, including breast, CSCs are responsible for tumor maintenance, metastasis and resistance to therapies.
The identification and isolation of CSCs is still a challenge due to the lack of universal markers, which poses a problem in understanding how homogeneous is the CSC pool. One of the aims of my thesis was to study the possible overlap between different subset of CSCs in breast cancer. By using two different isolation strategies, I identified two CSCs subpopulations with distinct capacity to initiate tumors in the primary or the secondary site in the murine MMTV-PyMT breast cancer model. In addition, I aimed at understanding how these two populations of cells were regulated. Due to its pleiotropic role, TGF-β has been described as a pro or anti-tumorigenic factor; however, it remains one of the main drivers of the epithelial-to-mesenchymal transition (EMT), a process which has been described to enhance cell invasion and metastasis. My results show that blocking TGF-β signaling through its receptor TGFBR1 impairs metastasis formation but shifts the balance between the two CSCs populations, and triggers the expansion of tumor-initiating cells.
CSC plasticity is a result of a crosstalk between cancer cells and signals coming from the microenvironment. The extracellular matrix is an important element of the CSC niche, as it regulates CSCs maintenance and expansion. The matricellular protein TGFBI plays a role during development and it is involved in the pathogenesis of several diseases, including cancer. It has a context-dependent function, and depending on the tumor type it can act as a tumor suppressor or a tumor promoter. Therefore, and given the important role that the ECM play in regulating CSCs, I next aimed at studying the role of TGFBI in modulating CSCs and the tumor microenvironment in breast cancer. Interestingly, my results show that depletion of *Tgfbi* in MMTV-PyMT tumors normalizes the vasculature and reduces hypoxia. As a result of these microenvironmental changes, *Tgfbi* loss lead to a dramatic decrease in CSC content and lung metastasis. Accordingly, *in silico* analyses revealed that *TGFBI* predicts poor prognosis in breast cancer patients. Additionally, human breast tumors containing higher level of TGFBI are more hypoxic and have increased EMT features.
Taken together, these findings suggest that TGFBI may be used as a prognostic factor in breast cancer and open potential new opportunities for combinatorial therapies.

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