Breast Cancer RESEARCH

VIEWPOINT

Basal-like breast cancers: the phenotypic disparity between the cancer-initiating cells and tumor histology

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Abstract

Recent evidence suggests that a rare-cell population with a stem cell phenotype maintains breast tumors. Therefore, to devise breast cancer therapies that are more effective, we need to understand the unique biology of these cancer stem cells. Currently, very little is known about the origin of cancer stem cells and their relationship to the tumor phenotype. A recent study from Smalley's group demonstrates that targeting an inactivating Brca1 mutation to the luminal progenitors could yield basal-like breast cancers. This observation suggests that the inherent plasticity of the primitive cells can be hijacked by the tumorigenic processes to produce tumors with an unpredictable phenotype.

In the mid-19th century, pathologists observed that some malignant tumors have features that are similar to those of the embryonic tissues (extensive proliferation and differentiation). This led pathologists to suggest that activation of quiescent, undifferentiated embryonic cells may be the root cause of cancer [1,2]. However, it was not until 1961 that Till and McCulloch [3] were able to provide the definitive proof that adult tissues are maintained by stem cells. Later, Bonnet and Dick [4] were able to show that, similarly to the normal adult tissues, malignant tumors can be initiated and maintained by a rare-cell population with stem cell properties (cancer stem cells). These observations suggest that a lack of knowledge about the unique biology of these cancer stem cells is the reason for the failure of the current cancer therapies. Moreover, they suggest that understanding the mechanisms that regulate the biology and function of the normal primitive cells will provide a framework to determine how alterations to these mechanisms can confer a cancer stem cell phenotype on these rare-cell populations.

Recent research efforts have led to the isolation and molecular characterization of the normal human and mouse breast stem cells and progenitors [5-8]. These studies revealed that breast stem cells are estrogen receptor-negative (ER^-) and therefore were thought to be the origin of the ER^- basal-like breast tumors [9]. Currently, however, the nature of the cancer-initiating cells remains elusive. Cancer-initiating cells are referred to the normal cells in the adult tissues, including the stem cells and progenitors as well as the differentiated cells that can acquire enough mutations to transform into cancer stem cells. Therefore, cancer stem cells arise from cancer-initiating cells and are responsible for tumor recurrence (that is, proliferation and self-renewal potentials) and the tumor heterogeneity (that is, multi-lineage differentiation potential).

To ascertain the nature of the cancer-initiating cells, Molyneux and colleagues [10] used a mouse model of breast cancer in which inactivating *Brca1* mutation in *p53* heterozygote mutant animals causes basal-like breast carcinoma. To identify the cancer-initiating cell population, the authors induced an inactivating *Brca1* mutation under the expression of Cre enzyme either in the ER^- luminal progenitors using beta-lactoglobulin promoter (*Blg*-Cre*Brca1*$^{f/f}$*p53*$^{+/-}$) or in the stem cells and basal cells using the cytokeratin 14 promoter (K14-Cre*Brca1*$^{f/f}$*p53*$^{+/-}$). Interestingly, the authors found that inactivation of *Brca1* gene in the luminal progenitors, and not in the basal and stem cells, produced tumors that closely resembled the human *BRCA1* mutant (basal-like) breast tumors as determined by immunohistopathological studies. Despite this, the molecular characterization of 18 *Blg*-Cre*Brca1*$^{f/f}$*p53*$^{+/-}$ and 3 K14-Cre*Brca1*$^{f/f}$*p53*$^{+/-}$ tumors revealed that 16 out of the 21 tumors closely resembled the normal ER^- luminal cells. However, when human breast cancer subtype classifier gene sets (PAM50 and Hu306) were used as predictors [11,12] to classify

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Blg-Cre*Brca1*$^{f/f}$*p53*$^{+/-}$ and the K14-Cre*Brca1*$^{f/f}$*p53*$^{+/-}$ tumors, the authors found that all tumors associated with the sporadic basal-like breast cancers. This observation was confirmed when the same mouse tumors were classified using the gene expression profile of a panel of 53 grade-3 human breast cancers [13] and the NKI295 tumor gene expression data set [14]. Interestingly, when comparing the histological features of the secondary and tertiary transplanted tumors, the authors found evidence of clonal selection. This observation suggests that ER$^-$ luminal progenitors, when harboring a *Brca1* loss, can act as cancer-initiating cells, some of which can acquire a cancer stem cell phenotype and produce basal-like tumors. This finding is interesting since Lim and colleagues [15] reported the expansion of the luminal progenitors in the *BRCA1* mutation carriers.

The data described by Molyneux and colleagues [10] explore the relationship between the cancer-initiating cells, cancer stem cells, and the tumor phenotype. Their data suggest that luminal progenitors, and not the breast stem cells, are the more likely sources of the cancer-initiating cells that can lead to the generation of basal-like tumors. This conclusion implicates the plasticity of the cancer-initiating cells as the most likely determinant of the tumor type, which may be different than the cancer-initiating cell phenotype.

Knowledge about the origin of cancer-initiating cells will enable the development of novel cancer preventative approaches. Such therapeutic measures will depend on the elucidation of the molecular mechanisms that regulate the proliferation, differentiation, and self-renewal capacities of the normal stem and progenitors cells. For example, it would be interesting to determine the precise role of *Brca1* in the normal biology and functions of the ER$^-$ luminal progenitors and how its inactivation can cause these cells to develop basal-like cancers. Such knowledge can lead to the development of therapies not based on the *Brca1* gene itself but on the affected signaling pathways. In addition, characterization of the basal-like cancer-initiating cells can lead to the identification of new diagnostic markers that will enable the detection of the breast tumors at a premalignant stage.

Abbreviations

Blg, beta-lactoglobulin; ER$^-$, estrogen receptor-negative.

Competing interests

The author declares that he has no competing interests.

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