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Commentary

Cancer stem cell gene profile getting closer to the clinic to enhance precise treatment

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The identification of cancer stem cells (CSCs) has been received with great fanfare. Intuitively, the identification of CSCs was a promise to develop new treatments to eradicate cancer. The intuition of CSCs being targets to prevent cancer resurgence was changed to evidence resulting in a distinct branch of cancer biology.

CSCs share molecular and functional similarities with normal stem cells [1]. Thus, like normal stem cells in non-malignant tissues, the CSCs have been shown overwhelmingly to be responsible for tumor formation [1]. This has led to search for small molecules to target CSCs, mostly focusing on genes that are involved in self-renewal of stem cells, e.g., Notch 1 and BMI [2,3]. The early issues in the field of CSCs were based on the identify of specific markers for organ-specific CSCs. Indeed several laboratories have reported on varying markers. These markers have not sustained due to the lack of robust reproducibility. This has led to investigators to define CSCs in the context of the specific study. This has allowed the field to progress rather than the area of CSCs remaining in the background.

Another issue with the field of CSCs is the acceptance that the those working in the area need to remember that the CSCs are a subset of cancer cells and they are not normal stem cells, despite the similarities with respect to the affected genes. Since the non-CSCs are transformed cells, it is expected this population will also express some of the stem cells genes. In this regard, the non-CSCs will show some overlapping properties with stem cells. In support of the latter, it should be noted that cancer is defined as normal cells that have adapted stem cell properties, hence the difficults in defining CSCs. This key fact formed the basis for studies by Pece et al. who identified a 20 gene profile linked to stem cells [4].

The authors used the appropriate approach by keeping their analyses unbiased. They first used an in silico method to interrogate published databases of breast cancer using the genes belonging to the profile of normal mammary stem cells. This allowed them to narrow the gene set of normal human mammary stem cells to a cluster of 329 that the investigators found to be highly expressed in a subgroup of patients. Upon reclustering, the authors were able to divide breast cancers into those that with stem cell like and non-stem cell like properties. Interestingly, the population with high expression of stem cell-like profile showed worse prognosis. This argued that the stem cell-like genes would be in the cells that could display CSC properties associated with chemoresistance and perhaps ability to become dormant for later resurgence [5,6]. More importantly, a recent small report showed that if breast cancer patients have circulating CSC-like cells their prognosis was worse [7]. These latter studies are now supported by the large prospective studies employed by Pece et al. The authors further narrowed their search to 20 genes that represented a cluster highly expressed in the CSCs versus those without stem cell property.

The 20 genes were validated using three independent datasets and showed across the three analyses that the 20 genes were associated with poor prognosis. The investigators further validated the 20 genes by RT-PCR with transcripts from paraffin sections. Another interesting result is the independence of the 20 genes to other clinical factors such as invasion to the vascular system. Such independence is expected because the 20 gene set would not change due to self-renewal of the genes in the CSCs. In fact, it is possible that the number of cells expression this 20 gene set could increase since other subset of non-CSCs could take on the property of stem cells. This area of the studies may require further investigation because although the independence of the 20 genes, although intrinsically regulated, could be influenced by the complex microenvironment such as the bone marrow. The extrinsic niche is likely to change the signature of the cancer cells. The authors as well as other investigators, going forward, will have to consider that the non-CSCs, given the appropriate niche are likely to dedifferentiate to CSCs and this would lead to poor prognosis. Another issue is if there is a subset of non-CSCs that might be more susceptible to dedifferentiate to CSCs. Nonetheless, the findings by Pece et al. begun the 'journey' to have a stem cell gene signature profile to be incorporated in patient treatment.

Disclosure

The author declared no conflicts of interest.

References

[1] Patel SA, et al. Delineation of breast cancer cell hierarchy identifies the subset responsible for dormancy. Sci Rep 2012;2:906. https://doi.org/10.1038/srep00906.
[2] Li L, et al. Notch signaling pathway networks in cancer metastasis: a new target for cancer therapy. Med Oncol 2017;34:180. https://doi.org/10.1007/s12032-017-1039-6.
[3] M JR, S V. BMI1 and PTEN are key determinants of breast cancer therapy: A plausible therapeutic target in breast cancer. Gene 2018;678:302–11. https://doi.org/10.1016/j.gene.2018.08.022.

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https://doi.org/10.1016/j.ebiom.2019.03.036

[4] Pece S, et al. Identification and clinical validation of a multigene assay that interrogates the biology of cancer stem cells and predicts metastasis in breast cancer: a retrospective consecutive study. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.02.036.
[5] Bliss SA, et al. Mesenchymal stem cell-derived exosomes stimulate cycling quiescence and early breast cancer dormancy in bone marrow. Cancer Res 2016;76:5832–44. https://doi.org/10.1158/0008-5472.Can-16-1092.
[6] McGrath J, Panzica L, Ransom R, Withers HG, Gelman IH. Identification of genes regulating breast cancer dormancy in 3D bone endosteal niche cultures. Mol Cancer Res 2019. https://doi.org/10.1158/1541-7786.Mcr-18-0956.
[7] Bliss SA, et al. Evaluation of a developmental hierarchy for breast cancer cells to assess risk-based patient selection for targeted treatment. Sci Rep 2018;8:367. https://doi.org/10.1038/s41598-017-18834-5.