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# The importance of immature cancer cells in predicting patient outcome

The word “cure” for breast or any other type of cancer might be unfair to a patient since this will give the individual a false sense of comfort. The misuse of `cure’ is evident in breast cancer (BC) as these cells may be dormant (sleeping phase) in the bone marrow (BM) for decades with the potential to resurge into metastatic cancer years later. The dormant BC cells behave as cancer stem cells (CSCs), which are immature cells that resist current treatments. This is often a result of the dormant cancer cells’ slow rate of dividing. This property is an issue for current drugs since most of the cancer drugs require rapidly dividing cells to be effective. Another problem is that dormant breast cancer cells can use the other stem cells in the BM to protect themselves from the immune system. This occurs by specialized stem cells, known as mesenchymal stem cells (MSCs). The MSCs protect dormant cancer cells by keeping the immune response at a distance but allow those involved in suppressing the immune cells closer. This situation poses a serious dilemma for the fast growing field of immune therapy.

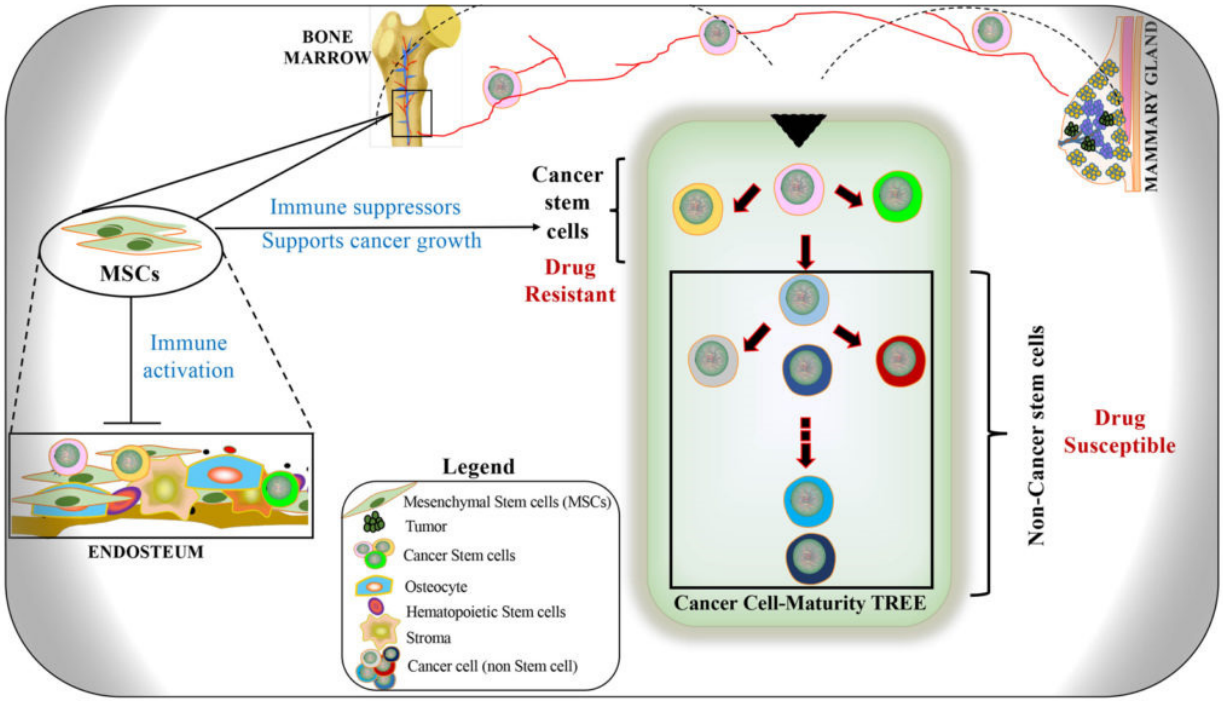


Fig. 1. The cancer cell maturation tree in the context of behaior. Shown are Cancer stem cells (CSCs) from the primary and secondary sites (bone marrow). The CSCs are resistant to current treatments and are functionally immature. CSCs can form other subset of cancer cells, known as the mature or non-cancer stem cells. Together, this leads to heterogeneity of the cancer. Due to the heterogeneity of the tumor, decreased tumor burden is mostly due to the drugs targeting the non-cancer stem cells but saving the CSCs. MSCs within the bone marrow niche acts as an immune suppressor to protect and support the CSCs from the immune system. The MSCs prevent the activation of immune cells thus keeping CSCs in a sleeping phase until they find a suitable form of stress to wake them into dividing cells, causing cancer relapse.

To fully understand the clinical issues discussed above, we used gene profiling methods to determine how cancer cells are related to each other in a hierarchal map. This was done by carefully examining the genes that encode membrane proteins and then using those to develop a hierarchy (similar to a family tree) in which the CSCs are placed at the top and the non-CSCs were further sub-divided and placed within the branches and on the trunk of the `tree'.

Once we established the tree, we then selected blood from BC patients to determine where their circulating cancer cells belonged within the 'tree'. We then waited up to two years to see the outcome of the patients. Although the sample size was relatively small, we concluded that if, after treatment, the CSCs or cells that are similar to them continue to be in the blood, the prognosis is poor. Specifically, the patient would relapse within a short period because the immature CSCs are the subset that can initiate tumors.

The question is what can be done if the oncologist found circulating CSCs or those within the immature type? Based on the studies, we propose that available drugs could be repurposed to induce the differentiation of the CSCs to make them susceptible to the current drugs. This might require lower levels of the drugs to be used in a maintenance manner to prolong the time of remission.

This discussion began with dormancy in the BM. Indeed, we reported a hierarchy (tree) that can be applied to understand how BC cell subsets interact with the BM resident cells to allow the BC cells to adapt dormany (Fig. 1). This will help scientists identify methods to reverse dormancy and eliminate the cancer cells. We do not propose reversing the dormancy when a patient is in remission but to incorporate additional methods during treatment because dormancy can occur at any time, including decades before diagnosis. During treatment, the drug may induce factors and small vesicles to be released from the resident bone marrow cells. These factors can then assist the cancer cells to survive. Cancer cells use these released factors as means of communication, dictating to resident bone marrow cells that they need help to survive. The research would lead to personalized method to treat the patient effectively. The intent is to have fewer surviving cancer cells and perhaps with the survivors living a long and healthy life.

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## Publication

Evaluation of a developmental hierarchy for breast cancer cells to assess risk-based patient selection for targeted treatment.
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