Cancer Stem Cells: What are they and what is their clinical relevance?

By Michael Keeling

With the evolution of medicine, many diseases have become treatable and potentially curable. Cancer is such a disease that despite advancements in medicine, is still difficult to treat. In 2015 cancer was the second leading cause of death globally and accounted for 8.8 million deaths (1). Why, despite the increased molecular understanding of cancer, are the death tolls of the disease still high? To address this question, it is important to first define what cancer is.

Cancer is a generic term that encompasses a large group of diseases characterized by the growth of abnormal cells that can invade other parts of the body and/or spread to other organ systems (1). Almost any tissue in the body has the potential to become oncogenic, another term for cancerous. Each type of cancer arising in different anatomical locations has multiple molecular subtypes, and is considered a unique disease. Given that cancer encompasses a large group of diseases, each disease requires specific management strategies (1). Recently, it has been accepted that there is a small and rare population of tumor cells responsible for metastasis and tumor relapse; cancer stem cells (CSCs).

What are CSCs?

Cancer stem cells (CSCs) or tumor initiating cells (TICs) are cancerous cells that have stem cell-like properties such as **self-renewal**, **differentiation** and **unlimited proliferation** ability. **Self-renewal** refers to the ability of the cell to undergo cellular division and maintain an undifferentiated state. **Differentiation** refers to the ability of cells to transform into a specialized cell to perform a more specific function, such as a red blood cell or a muscle cell. **Unlimited proliferation** refers to the ability for countless cell divisions. Given these attributes, it's no surprise a single CSC has the ability to drive new tumor formation and metastasis.

How do CSCs affect cancer patients?

Currently, cancer patients have various treatment options depending on the form of cancer they have. These treatment options can include chemotherapeutics, radiation therapy, molecular targeted and immunotherapies, and more recently precision medicine. The vast majority of these therapies aim to kill cancer cells through apoptosis (primary form of cell death). CSCs are inherently resistant to apoptosis, which is an issue given conventional anti-cancer treatments induce apoptosis. One reason why CSCs are resistant to apoptosis is they have an abundance of a variety of ABC transporters. Most ABC transporters are specialized channel proteins that function as drug efflux pumps which recognize various chemical substrates, and remove them from the cell. With the variety of ABC transporters, CSCs are primed for drug resistance.

What does drug resistance mean for cancer patients?

For cancer patients, drug resistance means that despite receiving treatment their disease can progress to an untreatable stage. Think about a bacterial infection, you go to the doctor and receive some antibiotics. After taking antibiotics for three or four days the symptoms are relieved and you decide not to take the remaining prescribed four days' worth of antibiotics. The consequence is that you leave residual antibiotic resistant bacteria which remain and potentially prolong your illness due to their antibiotic resistance. Similarly, a patient who receives current anti-cancer therapies has their tumor size reduced initially by eradicating the bulk of the tumor (differentiated cells), but the drug-resistant CSCs remain. The unaffected CSCs can propagate and re-build the tumor, leaving the patient with a more aggressive and drug resistant tumor (Figure 1).

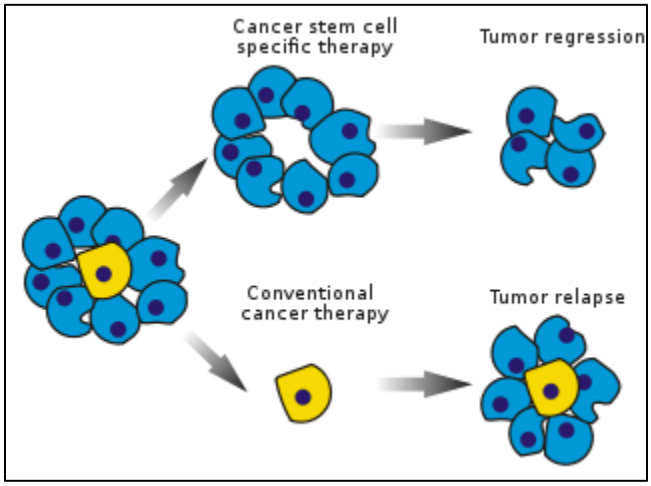

Figure 1: Differentiated cells (Blue) and CSC (Yellow). Tumor that receives conventional cancer therapies will result in the leftover of drug resistant tumor cells, which can include both cancer stem cells (CSC) and drug resistant differentiated cells. The unaffected CSC will begin to re-establish the tumor (tumor relapse), which now has acquired drug resistance. Cancer stem cell specific therapies aim to remove this specialized population of cells, resulting in the tumors hindered ability to re-establish itself. Coupled, both conventional and CSC therapies could work synergistically to result in tumor dormancy. Picture adapted from *Cancer stem cell. (2017, January 31). Retrieved February 17, 2017, from https://en.wikipedia.org/wiki/Cancer_stem_cell*

Fortunately, researchers and clinicians are shifting their focus on developing ways to target and eliminate this specialized population within a tumor.

One such research lab working on solving this issue is the Carraway/Sweeney lab located at the U.C. Davis Sacramento campus, which is where I am actively doing research. Currently, the lab has demonstrated 5-(N,N-hexamethylene) amiloride (HMA), a derivative of the FDA-approved blood pressure regulator amiloride, has been shown to be effective in killing drug resistant breast cancer cells independent of molecular type and proliferative status. HMA acts

through a novel reactive oxygen and lysosomal dependent programmed necrotic mechanism (2). Programmed necrosis refers to a wide variety of pathways that trigger cell death in a way that is distinct from apoptosis. The Carraway/Sweeney labs findings are important because they demonstrated HMA's toxicity towards drug resistant tumor cells, even though current treatments show diminished toxicity towards. This is one example of a group of pioneers thinking outside the box to deal with CSCs and drug resistant tumor populations.

This is a very exciting time for cancer biologists and oncologists alike. With the vast amount of information being gathered about cancer, and the discovery of the CSC, the future will bring some radical changes in cancer treatment.

References

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