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Breast Cancer Stem Cells & Cancer Stem Cells and Their Treatments

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Breast cancer is a deadly disease that affects women around the world. Although there have been many advancements in technology for breast cancer treatment, drug resistance and the regeneration of tumors through breast cancer stem cells have increased the danger of this disease. Breast cancer tumors are made of many diverse cell types that have different proliferation potentials. Like other cancers, breast cancer is thought to rise from multiple series of mutations that occur based on internal and external environmental factors. The genetic mutations lead to proto-oncogenes activating into oncogenes as well as the inactivation of tumor suppressor genes. In the case of breast cancer, the cancer cells are found in the mammary epithelium within the breast, which contains many adult stem cells. The mammary gland within the breast develops mostly during puberty. This gland is associated with adult breast stem cells that help with development and plasticity. This links the concept of breast stem cells to that of breast cancer stem cells and if they play a role in breast cancer. The evidence of cancer stem cells in many different types of cancer, and in this case, breast cancer, will help with the advanced understanding and treating cancer (Charafe-Jauffret et al., 2018) (Al-Hajj et al., 2003) (Butti et al., 2019) (Morrison et al., 2008).

Introduction

Many women around the world are diagnosed with breast cancer every day. While there has been a decline in death rates due to prevention, early diagnosis, and medical developments such as chemotherapy and radiation, the disease is still resistant to many treatments. Drug resistance is caused by the small number of cancer stem cells within the tumor (Butti et al., 2019). Cancer stem cells act in ways that are similar to both stem cells and cancer cells. The cancer stem cells have properties that enhance their growth rate. They can self-renew, avoid apoptosis, divide asymmetrically, and have both metastatic and tumorigenicity causing potential (Lawson et al., 2009). Although it is stated that cancer stem cells are similar to stem cells, it is important to understand they are not derived from stem cells, they are interpreted by certain functions. Specifically, breast cancer stem cells have been identified in the field of breast cancer. Since breast cancer is one of the leading causes of the death of women, this discovery piqued the interest of many. Cancer stem cells were first found in acute myeloid leukemia, but this is not

a tumor cancer. In a 2003 study by Al-Hajj et al., the differentiation of nontumorigenic cells from those that are tumorigenic in solid breast cancer tumors was done using surface markers in mice. The cell surface markers in the breast cancer cells were CD44, CD24, and B38.1. Using flow cytometry, it was found that CD44 and CD24 adhesion molecules were the best route in studying this topic. They found that certain types of cancer cells that were injected into the mice had tumorigenic potential, while others did not. This means that the cell populations within the types of breast cancer contain a small and distinct group of tumorigenic cells while the larger portion of the tumor contains the nontumorigenic cells. Most notable is that the $CD44^{+}CD24^{-/low}$ $Lineage^{-}$ tumorigenic cells go through similar self-renewal and differentiation pathways that normal stem cells do. The cells of $CD44^{+}CD24^{-/low}$ $Lineage^{-}$ were not only able to cause tumorigenic cells, but also cause many diverse nontumorigenic cells that formed the majority of the tumors. This method of separation of different cell types could potentially lead to the ability of identifying specific pathways that cause tumorigenic potential (Al-Hajj et al., 2003). Along with $CD44^{+}CD24^{-/low}$ cells, aldehyde dehydrogenase ($ALDH1^{high}$), $CD133^{+}$, and ganglioside 2^{+} ($GD2^{+}$) are markers of cancer stem cells and normal stem cells. Many pathways are also important to how breast cancer stem cells maintain their characteristics. Breast cancer stem cells can also preform vasculogenic mimicry to induce the formation of new blood vessels for their continued growth and health. The tumor needs oxygen and nutrients to help maintain the growing tumor (Butti et al., 2019).

Recent Progress

There have been several steps forward in treating and understanding of breast cancer based on cancer stem cells since they were discovered. Recently, signaling pathways were studied because of their importance in embryonic development and stem cell maintenance. The signaling pathways that are important to stem cells and their characteristics can cause mutations and accidental activation of cancer cells when they are dysfunctional. These pathways can help with the targeted treatment of cancer (Butti et al., 2019).

The Notch Pathway: The Notch is a transmembrane signaling receptor that is involved in stem cell fate, along with cell differentiation and other things. The activation of Notch in breast cancer is expressed around 50% of the time. In severe cases of breast cancer, JAG1, Notch1, and Notch4 (signaling components) are very common. It was found that when enriched cancer stem cell populations are compared to non-stem cells, the activation of Notch is higher (Butti et al.). Notch1 and Notch4 are important subtypes that have different functions when they are activated and deactivated. Notch4 overexpression can induce metastases in the epithelial breast tissue (Aaliyari-Serej et al., 2020).

The Wnt Pathway: Wnt is a glycoprotein that serves as a ligand within the cell. Evidence shows that Wnt signaling plays an important part in the cancer stem cells' self-renewal and cell differentiation. An increase in Wnt3a signaling is present in many different subtypes of breast cancer. microRNAs can regulate the signaling of this pathway. Specifically, excess expression of miR-374a enhances Wnt driven Epithelial-mesenchymal transition (EMT) and metastasis of breast cancer. Also, when miR-600 is silenced, non-canonical Wnt signaling is activated and ultimately breast cancer stem cell self-renewal is enhanced along with tumorigenicity (Butti et al., 2019).

Other signaling pathways play specific roles within breast cancer and breast cancer stem cells. With each study, more knowledge is gained in how the pathways can communicate with cells as well as the body and other

pathways. Many pathways can help maintain and support cancer stem cells. Cancer stem cells are important factors in the reoccurrence of cancer and resistance to treatment. (Butti et al., 2019). Regulation at different points and by different methods could lead to the targeting and effective treating cancer stem cells (Duan et al., 2021).

Another discovery has been made is that the cancer stem cell niche is a vital part in the processes of self-renewal and cell differentiation. This niche can produce new cancer stem cells from non-cancer stem cells through signals from the microenvironment and stem gene activation. These new cancer stem cells will then result in cancer cells and can turn more non-cancer stem cells into cancer stem cells. The method that targets the hypoxic microenvironment of cancer stem cells with a nanoparticle system of sodium alginate and docusate sodium to encapsulate methylene blue helps in trying to understand this process. When this system was stimulated by light, the nanoparticle system with methylene blue dramatically reduced the formation of not only primary, but secondary mammospheres as well as aldehyde dehydrogenase-positive cells. This result points to the idea that this type of therapy could be important for targeting cancer stem cells (Duan et al., 2021).

Discussion

Cancer stem cells has been proven to be a challenge in the overall treatment and remission of breast cancer in women. The pathways and niches of breast cancer stem cells are the most complex and important places to target when trying treatment. Specifically, breast cancer stem cells show resistance to both chemotherapy and radiotherapy. Certain types of these therapies increase the number of $CD44^{+}CD24^{-/low}$ cells within tumors. Along with therapy resistance, drug resistance is also apparent. The signaling pathways associated with cell differentiation and self-renewal only help with resistance (Velasco-Velázquez et al., 2012). Targeting these cancer stem cells seems easy, but many pathways that are enhancing the strength and proliferation of cancer stem cells also help promote normal, healthy stem cells. For example, the Wnt pathway is very important in adult stem cells. Accurately and effectively targeting this pathway should be done very delicately. By targeting the Wnt pathway in cancer stem cells, there would need to be careful consideration of the role of Wnt pathways in tissue repair and homeostasis within the body. This could also lead to effects on embryonic development. Targeting the Wnt pathway could lead to the loss of epithelial tissue and issues with bone formation and density (Kim et al., 2014). The line between what could help with cancer stem cells and hurt healthy stem cells is very thin. The complications between eradicating a harmful cancerous mass while maintaining healthy and needed cells is something we will have to continue researching. On the other hand, targeting the niche environment can help reduce mammospheres that form from breast cancer stem cells. Targeting this area only affects the cancer stem cells in the tumor, which will stop the spread of the tumor. Without the cancer stem cells, the progression is halted.

While there are many possible approaches to the treatment and remission of breast cancer stem cells, as well as cancer stem cells in other cancers, there is no treatment that is able to cure the disease. The enhanced abilities of cancer stem cells help cancer and tumor spread while being immune to the human immune system. Because cancer is caused by multiple mutations, each cancerous cell has the potential to be one of many variants. Defining and separating the tumorigenic from non-tumorigenic cells has to be done through experiments and cannot be done just by looking at a sample. The main question that remains unanswered and is still being researched is: what is the best way to treat cancer stem cells?

More studies need to be done on how drugs can target these cancer stem cells and how the treatments affect the healthy cells throughout the body. Overall, the targeting and treating of cancer stem cells is a challenging obstacle for many researchers and a deadly issue in the lives of cancer patients.

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