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MULTIDRUG RESISTANCE IN CANCER STEM CELLS: A STATE OF THE ART REVIEW

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Abstract

The expression of ATP-binding cassette (ABC) transporters is the key mechanism of defense of stem cells. These transporters function in the body as the guardians of the population of stem cells. Unfortunately, these very same ABC efflux pumps provide cancer stem cells in tumors with protection, protecting them from chemotherapy's adverse effects. There are currently a range of strategies under study to bypass the role of these transporters in cancer stem cells. These strategies include the production of competitive and allosteric modulators, inhibitor delivery mediated by nanoparticle, targeted transcriptional control of ABC transporters, inhibition mediated by miRNA, and targeting of ABC transporter modulating signaling pathways. This paper will examine the role of ABC transporters in cancer stem cells and will also address strategies aimed at overcoming drug resistance induced by these unique transporters. For a long time, chemotherapy has been the method of choice for the treatment of metastatic tumors, yet cancer cells also develop an almost unusual capacity to withstand the effects of chemotherapeutic agents on cancer.

Keywords: *ABC, Cells, Cancer, Transporters, Stem.*

I. INTRODUCTION

This tendency of cancer cells to become immune to many structurally unrelated drugs at the same time that do not have a common mechanism of action is known as multidrug resistance and can seriously affect the effectiveness of chemotherapy for cancer. In the cancer cell itself, cellular mechanisms of drug resistance occur due to either genetic or epigenetic changes that can affect the drug's sensitivity[1]. This may involve pumping out of the drug by ABC transporters (ABCB1/P-glycoprotein, ABCC1, ABCG2, etc.) in the clinical setting, sequestering drugs into vesicles and eventual extrusion by exocytosis, and decreased drug intake, such as water-soluble drugs that are piggybacked on transporters and carriers used to carry nutrients into the cell[2].

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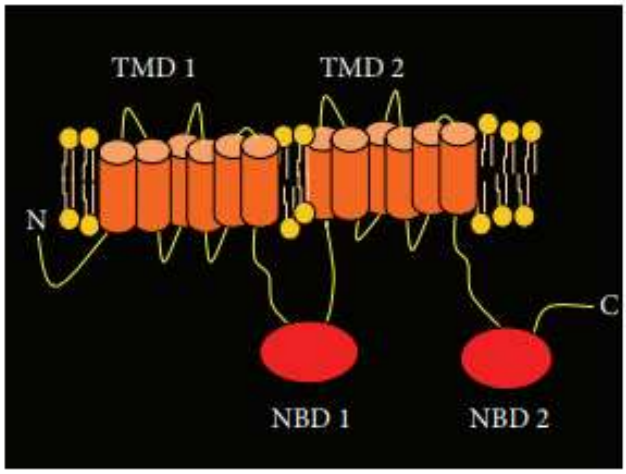

Figure 1: Depicts the ABC transporter[3].

The activation of detoxifying pathways, such as the cytochrome P-450 pathway and the cellular glutathione system, and mechanisms to repair drug-induced cancer cell damage and disruption of apoptotic signaling pathways, are other mechanisms that enable cells to become immune to drug-induced apoptotic cell death in cancer cells[4]. More than one of these mechanisms of multidrug resistance may be present in cancer cell populations subjected to chemotherapy; this phenomenon is referred to as multifactorial drug resistance[5].

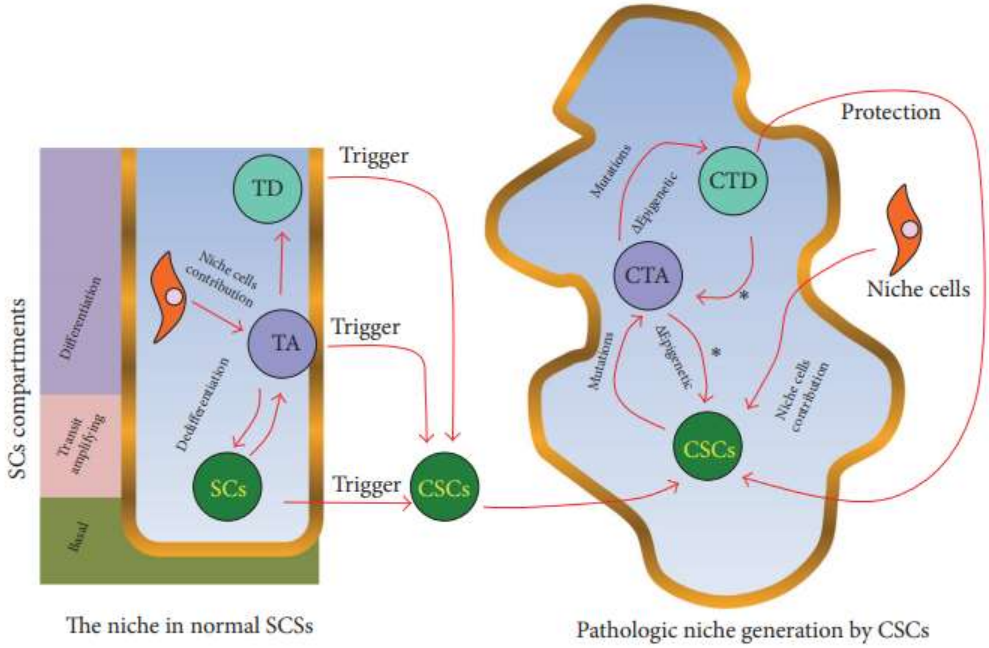

Figure 2: Illustrates the origin of Cancer Stem Cells[6].

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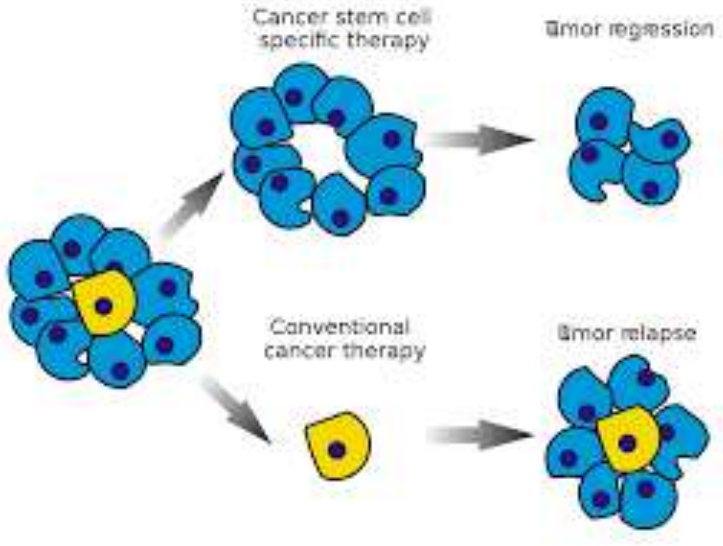

Figure 3: Illustrates the cancer stem cells[7].

II. DISCUSSION

Cells susceptible to chemotherapy are killed during treatment and, in general, a few cells remain in the tumor and become drug-resistant; these resistant cells multiply and the tumor eventually becomes unresponsive to treatment. Our outlook on carcinogenesis and chemotherapy has drastically changed with the unanticipated detection of cancer stem cells in solid tumors[8]. The implications of this discovery are far-reaching and would suggest that a self-renewing population of cancer stem cells is present in tumors for all intents and purposes. More notably, unlike other cells, these cancer stem cell (CSC) populations are "inherently" immune to chemotherapy. This suggests that after chemotherapy, surviving cancer stem cells will spread and eventually give rise to tumors.

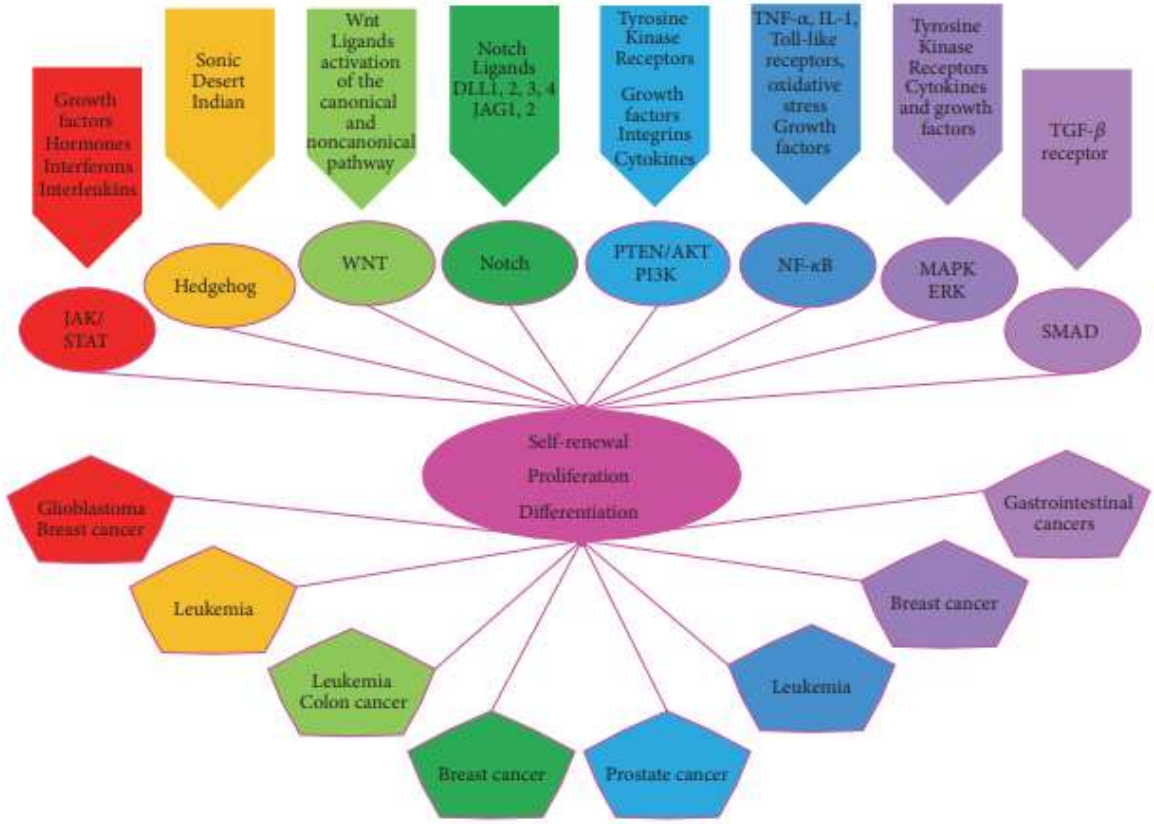

Figure 4: Illustrates general signaling pathways between Stem Cells[8].

The cancer stem cell (CSC) model discusses the process by which cancers that are established can propagate. The CSC theory proposes that the "exclusive" property of a defined population of cancer cells (known as cancer stem cells) is to drive the growth and propagation of a tumor. CSCs may also give rise to offspring that have a restricted capacity to differentiate. However, some of the control mechanisms present in normal stem cells where proliferation is tightly regulated and the genomic integrity of the cells is maintained are often missing in tumorigenic stem cells. If it is believed that the doctrine that tumors contain stem cells is right, then we might probably view the accumulation of mutations in these stem cells as the fundamental "multistep" carcinogenesis process. Figure 1 depicts the ABC transporter. Figure 2 illustrates the origin of Cancer Stem Cells. Figure 3 illustrates the cancer stem cells. Figure 4 illustrates general signaling pathways between Stem Cells.

III. CONCLUSION

A greater understanding of the pathways involved in the resistance of stem cells to chemotherapy is crucial. If the mechanism is understood, it may lead to new therapeutic targets being identified and existing anticancer strategies being strengthened. ABC transporters are one element that is responsible for chemo resistance in CSCs. It is evident from multiple studies that targeting ABC transporters in CSCs can lead to a better outcome for patients, provided that these stem cells are the only cells in the tumor capable of giving rise to a new tumor, according to the cancer stem cell hypothesis. In the field of cancer drug resistance, the stem cell model of drug resistance is an

important move forward because it gives us an opportunity to understand how cancers that display an obvious complete clinical response to chemotherapy can rebound within months or even years afterwards. However, it is important to identify stem cells by their long-term self-renewal ability and not just by the presence of a side population in order to elucidate and build on this model. The simple fact that cancer stem cells can now be detected, purified and propagated can allow us to develop new strategies in the future to enhance targeted cancer therapeutics and thus improve patient outcomes.

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