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A FOCUS ON FAILURE OF DRUG THERAPY FOR TARGETING CANCER STEM CELL: A REVIEW

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ABSTRACT

Medical oncology and innovation in pharmaceutical industry, targeted therapy provides physicians and patients with more options to improve clinical outcomes as evidenced by improvement in overall survival (OS), progression-free survival (PFS), and response rate (RR), among other end points. Effective anti-cancer treatments have been able to eliminate macroscopic tumors both at primary sites and at common distal sites. There has been a consensus that, to improve the results of targeted therapy, challenging drug resistance problems needs to be solved through better understanding the mechanisms. Nevertheless, even if they showed an impressive response to treatment initially, the majority of cancer patients relapsed because small cohorts of tumor cells can survive in cryptic anatomic loci and exhibit up to 90% resistance to one or more therapeutic agents for months or year(s). As such, drug resistance has been a major hurdle for classic anti-cancer medicines, and it still is a great challenge facing the emerged array of targeted therapies. In this article, we provide a comprehensive overview regarding cancer stem cell targeted therapy resistance.This review aims to focus on Concept of growth of cancer stem cell and describe the Failure to avoid drug resistance when targeting cancer cell as well as modifications inducing cancer cell resistance to chemotherapy.

KEYWORDS: oncology, targeted therapy, cancer stem cell, cancer cell resistance.

INTRODUCTION

Extensive cancer research in the past few decades has identified the existence of a rare subpopulation of stem cells in the grove of cancer cells. These cells are known as the cancer stem cells marked by the presence of surface biomarkers, multi-drug resistance pumps and deregulated self-renewal pathways (SRPs). They have a crucial role in provoking cancer cells leading to tumor genesis and its progressive metastasis. The field of CSC is evolving rapidly. CSCs have the ability to self-renew, dedifferentiate, form tumors, and are resistant to chemo, immune, and radiotherapy. So the Cancer stem cells are main culprit of failure to treat cancer. In order to cure cancer along with other cells types in cancer, cancer stem cells need to be targeted in the tumor bed.[1] Conventional cancer treatment of chemotherapy and radiotherapy can target only the bulk of sensitive tumor cells, which are in rapidly dividing phase. This therapeutic intervention induces many tumor cells to undergo apoptosis and die, whereas the CSCs survive this process by remaining in G0 phase and give rise to 'second-line tumors' with acquired resistance.[2] The investigation and development of the cancer stem cell (CSC) model has received much focus during these years. These cells also express different surface markers that can be used for their identification and to design therapeutic drug against them.[2] However, in most of the cases, these markers are also expressed by normal adult stem cells that make it hard to differentiate and target CSC only. Current cancer research is focused toward targeting these CSCs and it has become essential to develop novel therapeutic approaches to prevent cancer recurrence and emergence of drug resistance. During and after the treatment period CSCs maintain their self renewal and differentiation capacities by activating the embryonic signaling pathways.[3] The Hh, Notch, Wnt and BMI1 maintains the proper functionality in normal stem cells but a deregulated behavior in these pathways, owing to some alterations in the genes encoding the signaling molecules is observed in CSCs and also have been found in human tumor samples clearly stating their role in tumor development and maintenance.[4] As normal stem cells and CSCs share similarities in the signaling pathways, it would be extremely important while designing drugs to understand the complex biology of these pathways to destroy the CSCs and selectively sparing the normal stem cells.[2,5] Present review focused on targeting strategies of CSCs and their failure in Cancer treatment could possibly be an encouraging direction for future cancer therapy.

Concept of growth of cancer stem cell

CSC hypothesis is most widely accepted theory regarding cancer generation. It states that there are

different tumorigenic phenotypes inside a tumor mass.[6] One of these cell phenotypes is capable of generating new tumors if transplanted to a host and it is able to self-generate and regenerate the rest of the tumor cells.[7] CSC are able to grow in vitro under special circumstances under which other cancer cells tend to die or are unable to spread. Cells undergo a series of genetic changes until they transform into cancer cells, more than just generating stem cell characteristics.[8] Signaling pathways such as Hedgehog, Notch, Wnt and others, have roles in development and progression of tumors and are critical for the generation, differentiation and drug-resistance of CSC.[9] Cell niche are basic units of tissue physiology, where stem/cancer stem cells are found, regulate cell fate. Within the human body, stem cell niches maintain adult stem cells in a quiescent state. From the embryonic development, various niche factors act on embryonic stem cells to alter gene expression, and induce their proliferation or differentiation for the development of the fetus, but after tissue injury, the surrounding micro-environment actively signals to stem cells to either promote self-renewal or differentiation to form new tissues.[10]

The self-renewal of CSC guarantees their long-term survival. During progression, cancer cells may accumulate additional mutations through the self-renewal process. The ability of self-renewal in CSC is not fixed, where in some conditions; it can actually be enhanced, weakened, acquired, or even lost. Notably, several factors and key signalling pathways have been implicated in the regulation of GCSC self-renewal.[11]

The cancer stem cell hypothesis posits that cancer stem cells are a minority population of self-renewing cancer cells that fuel tumor growth and remain in patients after conventional therapy has been completed. The hypothesis predicts that effective tumor eradication will require obtaining agents that can target cancer stem cells while sparing normal stem cells. Experimental evidence in human AML suggests that, compared with the bulk population of leukemic blasts, the leukemia stem cells are relatively resistant to conventional chemotherapeutic agents. Although it has been speculated in solid tumors that conventional agents kill the non-tumorigenic cancer cells while sparing the cancer stem cells, this has not been proven. There are other models of drug resistance consistent with the existence of cancer stem cells that could explain relapse, including the classic view of mutation and selection.

Failure to avoid resistance for targeting cancer cell

Conventional cancer therapies have three main strategies like surgical resection, chemotherapy, and radiotherapy. Surgical resection is still the most effective method to treat certain tumors.[12] However, it has limitations: resection cannot cure metastatic cancer completely, and it restricted in hematopoietic cancer therapy. Resection may also influence physical function since excision may remove some normal tissues, causing sequel. CSCs are known to be resistant to chemotherapy and radiotherapy.[13] Failure to completely eliminate CSCs with these approaches leads to disease recurrence. Cancer stem cell theory has created a new prospect for cancer therapy: targeting CSCs. Therefore, CSC-targeted therapy should be an important part of cancer therapy.

- **Approaches for cancer stem cell therapy**

Study suggest, four CSC-targeted approaches used for cancer therapy. These include increasing sensitization of CSCs to conventional drugs, promoting CSC differentiation, targeting and blocking relevant CSC signaling pathway components, and destroying CSC niches.[14] Increasing the sensitivity of CSCs to conventional drugs and radiotherapy is a valid approach to eradicate CSCs and prevent tumor recurrence. CSCs also have properties similar to normal stem cells, including insensitivity to conventional chemotherapy and radiotherapy, making them difficult to eliminate completely. Therefore, increasing sensitivity of CSCs to conventional therapy is crucial for improving therapeutic effects.[15] The researchers reviewed several proposals that attempted to explain CSCs' resistance to conventional therapy. These include activation and overexpression of drug transporter proteins, stem cell pathway activation, accelerated cellular metabolism, altered expression of detoxifying enzymes, impaired autophagy, more efficient DNA repair, resistance to apoptotic and senescence pathways, and interactions between CSCs and their microenvironments[16] Targeting cellular transporters and membrane receptors was successful in some instances; combination therapies that target CSCs, for example, were effective in basal cell carcinoma, but less so for other cancers. Small molecules that act against components of the extracellular matrix may be able to prevent CSCs from manipulating the microenvironment.[17] More recent studies have isolated tumor-initiating cells with CSC-like properties in a number of solid malignancies, beginning with the isolation of CD44+, CD24−/low breast cancer initiating cells[18] These cells are thought to exhibit stem cell-like properties because they are capable of reconstituting the heterogeneity of the originating tumor.

CSC maintenance to combat cancer

In recent years, study of CSC-specific surface markers, characteristics, signaling pathways, and niches provided evidence at the gene and protein levels to support the theory of CSC-targeted therapy.[19] Strategies such as RNA interference-mediated down-regulation of gene expression, including anti-apoptotic genes, epithelial cell adhesion molecule (EpCAM), which is expressed in normal epithelial progenitor cells[20] TGF-β family cytokines, is likely to be a major contributing factor in the etiology of some cancers and study of these will make CSC eradication possible in the future.

Targeting EMT pathways and CSC maintenance

It is a promising therapeutic strategy. Several studies have successfully shown that pharmacological agents can

modulate the differentiation state of a tumor. Moreover, CSCs can be eliminated or functionally antagonized by inducing their differentiation. Thus, 'differentiation-inducing' agents such as salinomycin or HDAC inhibitors may have therapeutic value.[21]

Targeting the TGF-b and Wntpathways: TGF-β family cytokines are mediators of embryonic development and tissue homeostasis in the adult[22] (Heldin et al., 2009). TGF-β itself is a regulator of many types of physiological and pathophysiological EMT.[23] Type I and type II TGF-β receptors (TβRI and RII) are dual specificity kinases, exhibiting both serine/threonine and tyrosine kinase activities. Targeting the TGF-b provides additional means to eliminating CSCs.[24] These pathways can strongly activate anti apoptotic signaling, such as those mediated by PI3K and nuclear factor-kB. Thus, PI3K or Akt inhibition to block EMT and the emergence of CSCs may prove useful.

Micro RNAs in mediating EMT and CSC maintenance

A role for microRNAs in TGF-β signaling has recently been appreciated. Initially, Smad proteins can directly regulate microRNA processing by binding to the DROSHA complex, which has been shown for mir-21[25] (Davis et al., 2008). MicroRNAs can regulate TGF-β-induced apoptotic and growth suppressive functionality. For instance, TGF-β can activate Akt in glomerular mesangial cells by inducing expression of mir-216a and mir-217, which target the PI3K negative-regulator PTEN[26] (Figure 3a; Kato et al., 2009). The E2F1-regulated microRNA mir-17-92, which has established oncogenic properties[27] (He et al., 2005), and mir-106b-25 can block TGF-β-mediated growth arrest in gastric cancers by targeting p21/CIP1 and the proapoptotic protein BIM[28] (Figure 3a; Petrocca et al., 2008). it is fully appreciated, therapeutic delivery of microRNAs may represent yet an additional strategy to potentially disrupt this axis of evil in the war on cancer.

Difficulty for Implementation of new therapies against cancer stem cell

The moving target nature of cancer stem cells may present a challenge in the clinic. To achieve effective implementation of new therapies, physicians will require methods of determining the type (or types) of cancer stem cells present in a given patient's tumor. As per, workshop was convened by the AACR to discuss the rapidly emerging cancer stem cell model for tumor development and progression.[29] At this, Work involving 150 CML patient peripheral blood and bone marrow samples is encouraging in that patients in blast crisis all exhibited an expansion of the granulocyte-macrophage progenitor population, which included the fraction displaying stem cell properties. The work shop concluded that tumors sharing a similar pathology may also share common features in their cancer stem cell populations, which would facilitate diagnosis and the application of appropriate treatments. This point, however, needs to be borne out by further study. It is important that agents directed against cancer stem cells discriminate between cancer stem cells and normal stem cells. This will require identification of realistic drug targets unique to cancer stem cells.[29] The identification of such targets and the development of anticancer agents will require a fuller understanding of normal stem cell biology as well as the genetics and epigenetics of tumor progression. There is some indication that such an approach can be successful.

CONCLUSION

The technical advances will be required in most vertebrate systems where stem cells from a variety of tissues can be imaged and genetically modified and improve our ability of stem cells with single cell resolution. It will also be important to more systematically test mechanisms that are proposed to regulate stem cell maintenance using genetics: are proposed mechanisms really necessary for stem cell maintenance under physiological conditions in vivo and can niche cells be identified by conditionally deleting potential maintenance factors from specific cell types that reside nearby the stem cells for the treatment of Cancer. Until these demanding goals are achieved, chemotherapy will remain somewhat speculative. By better understanding the physiological mechanisms that regulate stem cell maintenance new strategies can be developed to promote tissue regeneration after injury, to maintain stem cell activity during aging, and to sensitize cancer stem cells to therapy. Clearly, fundamental scientific and medical questions reside within the niche. With that, It's important to define specific CSC markers to "precisely annihilate" CSCs. It is a need to determine the mechanisms governing CSC resistance to conventional therapy. Conventional anti-cancer therapies may transform the CSC microenvironment, disturbing anticancer homeostatic mechanisms. Combination therapies including drugs that target CSCs specifically may be the best approach, particularly for highly aggressive tumors with poor prognosis. Investigation of cancer stem cells offers the possibility of generating novel targets that could overcome issues of drug resistance, improve therapeutic efficacy, and make cancer treatment more successful and perhaps even curative while obviating systemic toxicity. Furthermore, cancer genome monitoring and microRNA profiling are being actively translated from bench to bedside in oncology, to hopefully help therapeutic selection and adjustment.

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