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Mini-review

Targeting autophagy in cancer stem cells as an anticancer therapy

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ABSTRACT

Cancer stem cells (CSCs), which comprise a small proportion of total cancer cells, have special capacities for self-renewal, differentiation and tumor formation. Currently, CSCs are regarded as the major cause of the failure in anticancer therapy, such as chemoresistance and/or radioresistance, tumor recurrence and metastasis. Autophagy, a process of cellular self-digestion and response to stress, has a role in tumor formation and progression, and it may play a dual role in CSCs-related resistance to anticancer therapy. Most researchers believe that autophagy contributes to stemness maintenance of CSCs and is responsible for the failure of anticancer therapy. Unexpectedly, several studies have also suggested that loss of stemness in CSCs could be mediated by autophagy. Here, we review the recent advances in CSCs and autophagy, especially analyze the complex relationship between them, and hope to apply this new knowledge to the strategies for anticancer therapy.

Introduction

In recent decades, cancer has become a major public health problem due to its high incidence rate and mortality rate [1]. Multiple strategies, such as surgery, chemotherapy, radiotherapy, targeted therapy, and a combination of these therapies, have been used to treat human cancers. Because the patients with advanced cancers cannot undergo operations, chemotherapy and/or radiotherapy are commonly used as alternative or supplemental treatments and play significant roles in anticancer therapy. However, the failure of these two anticancer therapies occurs frequently in clinical cases. Chemoresistance and/or radioresistance, tumor recurrence and metastasis are regarded as the major reasons. Cancer stem cells (CSCs), which comprise a small proportion of total cancer cells, have the capacity for self-renewal, differentiation and tumor formation. An increasing body of evidence has shown that CSCs are the roots of tumor formation [2] and recurrence [3]. Thus, elucidating the mechanisms underlying CSC survival and stemness maintenance of CSCs is important for targeting CSCs to improve the efficiency of anticancer therapy.

Autophagy, a process of resolving and recycling proteins and damaged cellular organs, has been shown to protect cells from nutritional deficiency and prevent cell death. There are three major types of autophagy, macroautophagy, microautophagy and chaperone-mediated autophagy (CMA). In this review, we focus on macroautophagy (hereafter referred to as autophagy). Multiple studies have closely linked autophagy to many disease processes, especially cancers [4]. Recently, researchers noted that elevated autophagic flux in CSCs could maintain metabolic homeostasis and cell viability, which promoted CSCs to resist to microenvironmental stresses, such as hypoxia, starvation or anticancer treatment. Thus, many researchers-believe that autophagy plays a significant role in the resistance to CSCs-related anticancer therapy [5]. Here, we review the recent advances in CSCs and autophagy, discussing the mechanisms underlying CSC survival and stemness maintenance of CSCs, and the role of autophagy in stemness maintenance of CSCs, and also assessing the implications of autophagy and CSCs in anticancer therapy to offer new strategies for preventing the resistance to anticancer therapy.

Abbreviations: 5-FU, 5-fluorouracil; ABC, transporter; ATP, binding cassette transporters; $ABCC_3$, ATP Binding Cassette Subfamily C Member 3; $ABCG_2$, ABC transporter $gene_2$; ALDH, aldehyde dehydrogenase; AML, acute myeloid leukemia; ATG7, autophagy-related protein 7; ATP, adenosine triphosphate; BCC, basal cell carcinoma; cis-DDP, cis-dichloro-diamine platinum; CMA, chaperone-mediated autophagy; CRC, colorectal cancer; CSCs, cancer stem cells; DDR, DNA damage response; DDL4, Delta-Like Ligand 4; DNMT1, DNA methyltransferase 1; ECSCs, esophageal cancer stem cells; EMT, epithelial–mesenchymal transition; ESA, epithelial-specific antigen; FDA, Food and Drug Administration; GSCs, glioblastoma stem cells; HIFs, hypoxia-inducible factors; Jak2, Janus-activated kinase; LC3B, light chain 3B; miRNA, microRNA; NOD/SCID mice, non-obese diabetic mice with severe combined immunodeficiency disease; NSCs, neural stem cells; OPN, Osteopontin; OS, osteosarcoma; PS-PDT, Photosan-II (PS-II)-mediated photodynamic therapy; ROS, reactive oxygen species; SP, side population; TNBC, triple negative breast cancer; TGF, transforming growth factor; UC, urothelial carcinoma.

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CSCs with biological characteristics of cancer

CSCs were first proposed in 1983 [6] to explain why only a proportion of cells within tumors have the capacity for self-renewal, differentiation into multiple cell types and tumor formation in vivo or in vitro. In 1997, Jone Dick and his group first isolated CSCs in acute myeloid leukemia (AML) cells, which were subpopulations of AML cells with the specific surface marker CD34 but without the CD38 marker. The authors established that the $CD34^{+}/CD38^{-}$cells could form tumors in non-obese diabetic mice with severe combined immunodeficiency disease (NOD/SCID mice) that were histologically similar to the donor [7]. Later, in a growing number of solid tumors, such as human cortical glial tumors [8], breast cancer [9], colon cancer [10], pancreatic cancer [11], ovarian cancer [12], prostate cancer [13], and melanoma [14], subpopulations of cells with similar characteristics were identified.

CSCs in the resistance to anticancer therapy

Generally, the resistance to anticancer therapy, such as chemotherapy, radiotherapy, and targeted therapy, is a major challenge for cancer treatment and a constraint for patients' prognosis. Currently, traditional anticancer treatments are aimed at killing normal cancer cells but not CSCs. Recent studies have shown that CSCs can survive in anticancer therapy [15]. $CD44^{+}/CD24^{-}$/epithelial-specific antigen $(ESA)^{+}$ cells have the capacity for self-renewal. They can reconstitute the parental cell line and preferentially survive in chemotherapy [16]. Similarly, researchers found that in pancreatic adenocarcinoma cell lines, a subpopulation of slow-cycling cells with stem cell marker expression survived in following chemotherapy [17]. These results indicate that CSCs are a major cause of resistance to anticancer therapy. During anticancer therapy, it is crucial to target CSCs (Fig. 1). Efforts should be made to investigate the mechanisms of CSC resistance to anticancer therapy. The current literatures indicate that there are five major mechanisms.

Adenosine triphosphate (ATP)-binding cassette transporters (ABC transporters)

ABC transporters are membrane transport proteins that require ATP hydrolysis for energy to transport various substrates across cellular membranes [18], resulting in the development of resistance to multiple drugs, such as antibiotics and anticancer agents. Compared with common cancer cells, CSCs have more efficient ABC transporters. They can pump out chemotherapeutic agents and play an important role in CSCs-related drug resistance. For example, downregulation of ABC transporter $gene_2$ ($ABCG_2$), which encodes an ABC transporter protein, in glioblastoma CSCs may increase the efficacy of chemotherapeutic agents for glioblastoma [19]. Another study showed that ABCG2 was also highly upregulated in cancer stem-like side population (SP) cells from head and neck squamous cell carcinoma. This leaded to multidrug resistance [20]. ABC subfamily C member 3 ($ABCC_3$) is another member of the superfamily of ABC transporters. Knockdown of $ABCC_3$ gene could significantly sensitize CSCs to chemotherapeutic drugs in breast cancer. Furthermore, $ABCC_3$ knockdown cells also showed a decrease in the expression of stemness genes and the $CD44^{high}/CD24^{low}$ breast cancer stem-like subpopulation [21]. Therefore, downregulating ABC transporters could target CSCs and possibly improve anticancer therapies.

Aldehyde dehydrogenase (ALDH) activity

ALDHs are enzymes that catalyze the dehydrogenation of aldehydes. Researchers found that cells with high ALDH levels have increased chemoresistance. John Hilton demonstrated that the L1210 leukemia cell line with high ALDH activity was resistant to cyclophosphamide. Furthermore, studies showed that ALDH could maintain the stemness of ALDH-positive CSCs. As early as 1984, Christophe Ginestier reported that in breast cancers, high ALDH activity was associated with the tumorigenic cell fraction, self-renewal and tumor generation. Furthermore, human mammary epithelial cancer cells with increased ALDH activity have stem/

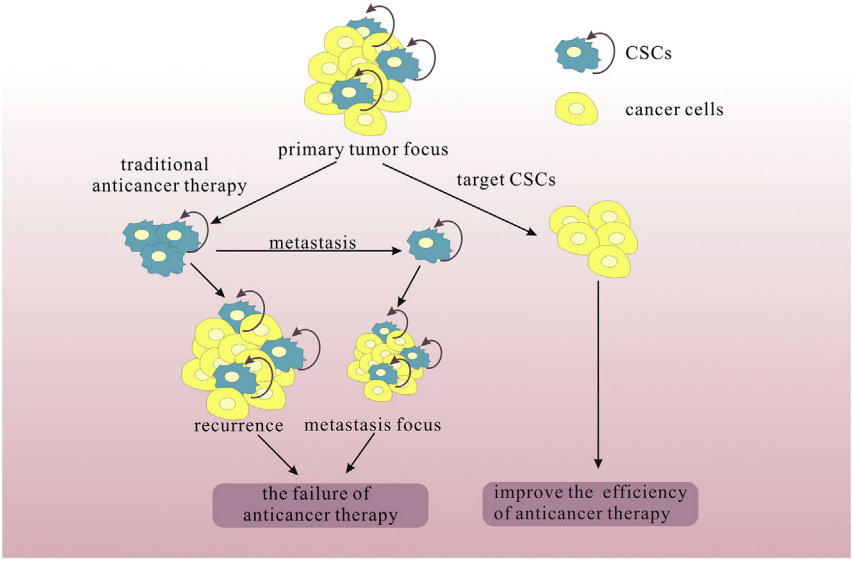

Fig. 1. CSCs and their behaviors in anticancer therapy. In primary tumor focus, only CSCs have the ability to generate a tumor based on their self-renewal properties and proliferative potential. Most traditional anticancer therapies are aimed at killing normal cancer cells but not CSCs. CSCs are considered as the roots of tumor formation, recurrence and metastasis. Therefore, it is important to develop specific therapies targeting CSCs to improve the efficiency of anticancer therapy.