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Mini-review

Combination of chemotherapy and cancer stem cell targeting agents: Preclinical and clinical studies

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ABSTRACT

The cancer stem cell model claims that the initiation, maintenance, and growth of a tumor are driven by a small population of cancer cells termed cancer stem cells. Cancer stem cells possess a variety of phenotypes associated with therapeutic resistance and often cause recurrence of the diseases. Several strategies have been investigated to target cancer stem cells in a variety of cancers, such as blocking one or more self-renewal signaling pathways, reducing the expression of drug efflux and ATP-binding cassette efflux transporters, modulating epigenetic aberrations, and promoting cancer stem cell differentiation. A number of cell and animal studies strongly support the potential benefits of combining chemotherapeutic drugs with cancer stem cell targeting agents. Clinical trials are still underway to address the pharmacokinetics, safety, and efficacy of combination treatment. This mini-review provides an updated discussion of these preclinical and clinical studies.

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Introduction

The cancer stem cell model proposes that the initiation, maintenance, and growth of a tumor are driven by a small population of cancer cells named cancer stem cells (CSCs) [1,2]. These CSCs undergo continuous self-renewal and differentiate into heterogeneous cancer cells, yielding new tumors recapitulating the parental tumors [1,2]. For instance, breast, pancreatic, head and neck, lung, ovarian, glioma cancers have been shown to contain subpopulations of cells that exhibit stem-like characteristics [3–8]. Accumulating evidence suggests that CSCs may be largely responsible for the emergence of tumor resistance to conventional chemotherapy [8–10] and radiotherapy [10–13].

CSCs possess a variety of features associated with therapeutic resistance, including dysregulated self-renewal signaling pathways (Wnt/β-catenin, Notch, and Sonic Hedgehog), elevated drug efflux mechanisms (e.g., high expression of drug efflux transporters), epigenetic aberrations (e.g., abnormal gene methylation), and limited differentiation capacity, and other altered pathways (e.g., NF-κB, mTOR, c-Met) [1,9,14,15]. These CSCs often survive the treatments, causing recurrence of the diseases.

Therefore, it has become increasingly important to examine the efficacy of agents that selectively target CSCs in combination with traditional chemotherapy. Several strategies have been explored so far to target CSCs in a variety of cancers, such as blocking one or more self-renewal signaling pathways to inhibit self-renewal, reducing drug efflux and ATP-binding cassette (ABC) efflux transporter expression to improve chemosensitivity, modulating epigenetic aberrations, and promoting CSC differentiation (Fig. 1). A number of cell, animal, and human studies have employed some of these strategies. They are discussed in the following sections.

Cell and animal studies

Blocking self-renewal pathways

Dysregulation of Wnt/β-catenin, Notch, and Sonic Hedgehog (SHH) signaling pathways are implicated in promoting CSC self-renewal of various cancers [16–18]. Binding of Wnt proteins to Frizzled receptors triggers cellular accumulation of β-catenin, which then translocates into the nucleus to assist the transcription factors T cell factor/lymphoid enhancer factor (TCF/LEF) to activate Wnt downstream genes, such as c-Myc and cyclin D1 [2,19–22]. The Notch proteins (transmembrane receptors), upon ligand binding, are cleaved by a protease of the ADAM (a disintegrin and

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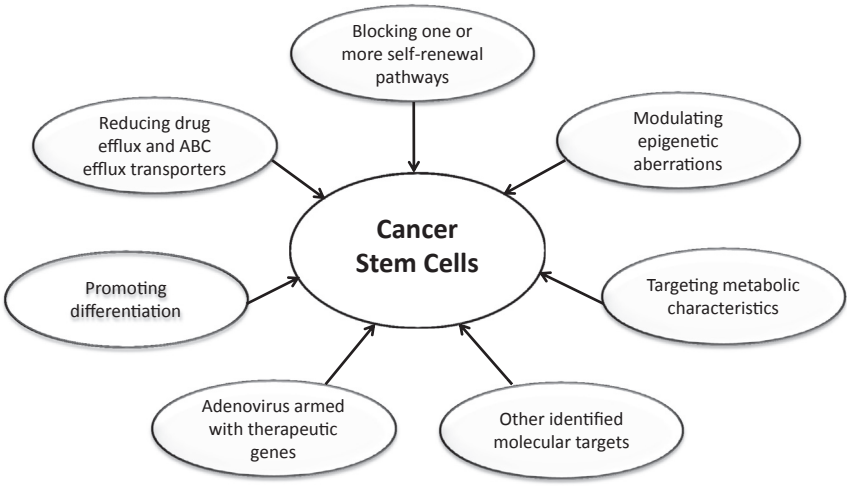

Fig. 1. Approaches of targeting cancer stem cells.

metalloprotease) family and γ-secretase [23]. The intracellular domain of Notch proteins is then released and translocates into the nucleus, where it acts as a transcription co-activator of recombination signal sequence-binding protein Jκ (RBP-Jκ) to activate Notch downstream genes [24,25]. In the SHH pathway, SHH ligand binds to the transmembrane receptor Patched (PTCH), releasing Smoothened (SMO). SMO then initializes activation of transcription factors GLI that leads to expression of an array of stemness genes [2,18]. Blocking one or more of these self-renewal pathways may be an effective strategy to inhibit or eliminate CSCs.

A Wnt signaling antagonist, secreted frizzled-related protein 4 (sFRP4), was examined for its effect in chemo-sensitizing the glioma cell line U138MG to chemotherapeutic drugs [26]. The sFRP4 treatment alone decreased neurosphere formation and induced neuronal differentiation through inhibiting Wnt/β-catanin pathway [26]. Furthermore, sFRP4 was able to sensitize glioma cells and CSCs to doxorubicin or cisplatin, increase apoptosis, decrease proliferation, and down-regulate the glioma CSC marker CD133 [26].

Chloroquine, an antimalarial agent, was identified to preferentially target CSC-like population ($EPCAM^+CD44^+CD24^+$) in primary human pancreatic ductal adenocarcinoma (PDA), one of the deadliest carcinomas due to early metastasis and strong chemoresistance [27,28]. Chloroquine blocked the SHH-induced chemotaxis by decreasing SMO protein levels and downstream activation of SHH pathway, including the reduction in PTCH and GLI [28]. This was further supported by the results of a GLI1-luciferase reporter assay [28]. Combination treatment with gemcitabine was effective in eliminating established tumors and improved overall survival of PDA patient-derived xenografts [28]. Approximately 50% of the tumors disappeared and did not relapse during long-term follow-up up to 230 days [28].

Withaferin A, a bioactive compound isolated from the plant *Withania somnifera*, has been a part of Indian traditional medicine for centuries [29]. Treatment of nude mice bearing orthotopic ovarian tumors (generated by injecting human ovarian cancer cells A2780) with a combination of Withaferin A and cisplatin resulted in a 70–80% reduction in tumor growth and complete elimination of metastasis [29]. Histochemical and Western blot analysis of the tumors revealed that withaferin (2 mg/kg), alone or in combination with cisplatin, resulted in downregulation of Notch1 and its downstream genes (Hes1 and Hey1) as well as significant elimination of cells expressing CSC markers including CD44, CD24, CD34, CD117 and Oct4 [29].

Epigallocatechin gallate (EGCG), a major catechin found in green tea, was reported to inhibit Notch1 signaling by reducing Notch1 transcription and its downstream proteins, Hey1 and Hes1 in head and neck squamous cell carcinoma (HNSCC) cells [30]. EGCG suppressed the sphere formation of HNSCC cells and attenuated the expression of CSC markers, such as Oct 4, Sox2, Nanog and CD44 [30]. Combination of EGCG and cisplatin inhibited tumor formation and induced apoptosis in a HNSCC xenograft model [30].

Reducing drug efflux and/or drug efflux proteins

Many ATP-binding cassette (ABC) efflux transporters are highly expressed in CSCs, contributing to chemoresistance by actively extruding chemotherapeutic drugs [31]. Thus, combining chemotherapy with an agent that can reduce drug efflux may be a viable strategy.

As discussed above, EGCG can inhibit Notch1 pathway in HNSCC cells [30]. In the same study, EGCG was found to enhance the chemosensitivity of HNSCC CSCs to cisplatin by down-regulating expression of ABC subfamily C member 2 (ABCC2) and ABC subfamily G member 2 (ABCG2) genes [30].

Glioma stem-like cells obtained from the neurosphere culture of human glioblastoma cell line U87 had an increased expression of drug-resistance protein P-glycoprotein (P-gp) and were highly resistant to camustine and temozolomide (two commonly used chemotherapeutic drugs to treat gliomas) [32]. EGCG was shown to down-regulate P-gp, reduce the efficiency of neurosphere formation and migration of U87 CSCs, and enhance the sensitivity of U87 cells to temozolomide [32].

Afatinib, a tyrosine kinase inhibitor targeting EGFR, HER2, and HER4, was found to effectively eradicate side population cells with CSC characteristics in patient-derived leukemia cells by down-regulating ABCG2 mRNA [31]. Afatinib enhanced the antitumor effect of a conventional chemotherapeutic drug, topotecan, *in vitro* and *in vivo* when used in combination [31].

Hypoxia-inducible factor 1 (HIF-1), which mediates efflux of chemotherapy from cancer cells, has been implicated in chemoresistance of breast CSCs [33]. Treatment of triple-negative breast cancer cell lines, including MDA-MB-231, SUM149 and SUM159, with paclitaxel or gemcitabine can induce HIF expression and transcriptional activity, resulting in an enrichment of breast CSCs among the survived cells [33]. Co-administration of a HIF inhibitor (digoxin or acriflavine) with paclitaxel or gemcitabine overcame

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