Cancer Letters 385 (2017) 87–96

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

At the crossroads of cancer stem cells and targeted therapy resistance

Anbang Wang [a], Le Qu [b, **], Linhui Wang [a, *]

[a] Department of Urology, Changzheng Hospital, Second Military Medical University, Shanghai, 200003, China
[b] Department of Urology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, 210002, China

ARTICLE INFO

Article history:
Received 17 August 2016
Received in revised form
24 October 2016
Accepted 25 October 2016

Keywords:
Targeted therapy
Cancer stem cells
Targeted therapy resistance
Combinational therapy
Anti-CSC therapy

ABSTRACT

Small-molecule targeted therapy (TT) has brought great hopes to patients with advanced malignancies. However, most patients suffer from tumor progression and relapse due to drug resistance. Recently, considerable efforts trying to elucidate the underlying mechanisms have focused on the contribution of cancer stem cells (CSCs) to the targeted therapy resistance (TTR). In this article, we provide an overview of the currently available literature on the rising roles of CSCs in TTR, as well as therapeutic opportunities of combining TT and anti-CSC therapy in the treatment of advanced malignancies.

Introduction

In the 21st century, small-molecule targeted therapy (TT) has been widely used in clinical practice and significantly improved the survival of patients with tumors [1]. However, some patients are inherently refractory to TT, and other patients often invariably end up with drug resistance and tumor progression, especially in solid tumors (usually within 6–18 months) [2–4]. Recently, substantial efforts to elucidate the molecular basis mediating targeted therapy resistance (TTR) have provided insight into multiple mechanisms [5–8], such as secondary mutations, and compensatory activation of alternative pathways. For instance, approximately 50–70% of non-small cell lung cancer (NSCLC) patients with resistance to epidermal growth factor receptor inhibitors (EGFRi) exhibited genetic changes, including EGFR secondary mutation and c-MET amplification [9,10]. Accordingly, targeting specific mutation may serve as second-line treatment for these resistant NSCLC patients. However, TTR is largely attributed to epigenetic modifications in several types of cancer, for which no effective and specific treatment is available at present.

In spite of effective killing target gene-dependent tumor cells, TT are unable to eliminate all tumor cells due to high intratumor heterogeneity [11]. Cancer stem cells (CSCs), exhibiting extended self-renewal potential and tumor-initiating ability, play non-negligible roles in tumor heterogeneity [12–14]. CSCs have been reported in various cancer types, including acute myeloid leukemia [15], brain [16], breast [17], colon [18], pancreas [19], liver [20] and prostate tumors [21]. More importantly, increasing evidence indicates that CSCs being enriched or activated by targeted drugs are responsible for tumor recurrence and TTR [22–25].

Recently, several studies suggest that high expression of CSC markers or stemness genes is significantly correlated with poor TT response. Researchers found that EGFRi-resistant NSCLC exhibited high expression of ALDH1 and Oct-4 [25–27]. Another study demonstrated that CD44 upregulation in metastatic clear cell renal cell carcinoma (ccRCC) patients was associated with poor response to sunitinib treatment [28], and residual tumor cells were positive for CD44 in metastatic ccRCCs after sunitinib treatment. Besides, $CD44^{+}/CXCR4^{+}$ cells were increased significantly in peri-necrotic areas after sunitinib treatment, indicating their poor response to sunitinib [29]. A most recent study proposed that $CD44^{+}/CD24^{-}$ phenotype could be served as a predictive factor for poor response to trastuzumab in HER2-positive breast cancer patients [30]. These studies not only reveal the possibility of predicting TT response by assessing the expression of CSC signatures, but also provide a possible strategy of overcoming resistance to TT by targeting CSC population.

In this review, we systematically review the interdependent relationship between CSCs and TTR and summarize combinational strategies to overcome TTR. Besides, we discuss the current

* Corresponding author. Fax: +86 021 81885732.
** Corresponding author. Fax: +86 025 860025.
E-mail addresses: septsoul@hotmail.com (L. Qu), wanglinhuicz@163.com (L. Wang).

http://dx.doi.org/10.1016/j.canlet.2016.10.039
0304-3835/

obstacles among targeting CSC population in clinical applications. Finally, we will share our views about future directions in anti-CSC therapies, hoping that anti-CSC therapies will curb the emergence of TTR.

How CSCs are activated upon targeted therapy

TT may induce both heritable changes, especially epigenetic modifications, and local tumor microenvironment alteration to activate CSC.

Epigenetic modifications

Epigenetics was originally defined by C. H. Waddington. It currently refers to a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence [31]. Epigenetic modifications can be grouped into three main categories: DNA methylation, histone modification and nucleosome positioning, which regulate various biological processes fundamental to tumorigenesis and tumor progression. It has been reported that epigenetic modifications in embryonic stem cells and adult stem cells exert crucial roles in gene regulation [32]. Notably, epigenetic modifications also play vital roles in CSCs [33].

By suppressing the predominant pathway of tumor cells, TT evokes considerable changes of epigenomics. For instance, tyrosine kinase inhibitor (TKI) treatment was reported to reduce DNA methylation of CD70 promoter in chronic myelogenous leukemia (CML). As a result, the upregulated expression of CD70 activated the Wnt/β-catenin pathway, resulting in the expansion of CSCs [34]. Similarly, lung cancer cells survived from high-concentration exposure of EGFRi exhibited hypermethylation of miRNA-200 promoter and reduced expression of miRNA-200, resulting in enhanced CSC properties, especially with aldehyde dehydrogenase isoform 1 overexpression. Notably, these TTR conferred by TT can be abrogated by histone deacetylase inhibitor (HDACi) [26]. Another study reported that erlotinib relieved EGFR-dependent repression of FOXO6 and thus upregulated SOX2 expression in EGFR mutant lung cancer patients. Indeed, the inhibition of SOX2 sensitized tumor cells to erlotinib and reduced the frequency of acquired resistance [35]. Altogether, these data prompt that TT contributes to the activation of CSCs by modulating epigenomics.

Tumor microenvironment

Like normal stem cells, CSCs are also maintained by the tumor microenvironment niche [36,37]. Mesenchymal cells in the niche could activate intracellular pathways and maintain CSC quiescence by secreting cytokines [38]. In colorectal cancer, the activation of Wnt signal in CSCs requires the stimulation of stromal cell-derived hepatocyte growth factor (HGF). Likewise, tumor-associated macrophages promoted CSC-like properties via TGF-beta1 induced epithelial-mesenchymal transition in hepatocellular carcinoma [39].

Extracellular matrix (ECM) is a critical component of CSC niche, promoting CSC maintenance and therapeutic resistance [40]. For instance, it has been reported that the ECM protein laminin was localized to the perivascular glioblastoma niche and enabled glioblastoma stem cell growth [41,42]. In a recent study, researchers found that laminin-332 increased hepatic CSC proportion and led to sorafenib resistance [43]. As the receptor of laminin proteins, several integrins including β3, α6, β1 also play critical roles in CSC stemness maintenance and drug resistance [44]. For example, β1 integrin mediated an alternative survival pathway in breast cancer cells resistant to lapatinib [45]. The expression of α2, α5 and β1 integrin subunits was increased in tumor biopsies from lung cancer patients refractory to erlotinib and gefitinib, while RNAi-mediated silencing of integrin β1 restored erlotinib sensitivity and reduced activation of Src and Akt signaling pathways [46]. The unliganded state of integrin αvβ3 could activate the TBK1 and NF-κB pathway by recruiting KRAS and RalB to plasma membrane, which is responsible for driving a tumor-initiating cell phenotype and erlotinib resistance [25]. Studies have revealed that treatment could potentially alter tumor microenvironment [47,48], thus contributing to the activation of CSCs via niche signals.

Hypoxia often appears in tumor bulks owing to rapid cell proliferation and aberrant blood vessel formation. As a cellular response to hypoxia, hypoxia-induced factors (HIFs) promote tumor cell survival by affecting angiogenesis and metabolism. It has been suggested that HIFs played a crucial role in CSC survival upon hypoxia and metabolic stress, such as glioma stem cell [49] and lung tumor CSC [50]. Although antiangiogenic TT intended to starve cancer cells, residual CSCs may survive by virtue of activating the hypoxia-associated pathway [51]. In addition, antiangiogenic TT promoted invasion and metastatic potential of tumor cells, accelerating the progression of RCC, and breast cancer and pancreatic neuroendocrine carcinoma in mice models [29,52,53]. Further studies demonstrated that this phenomenon may be caused by hypoxia-induced enrichment and activation of CSCs [23]. All these findings demonstrated that TT could promote CSCs propagation by altering the tumor microenvironment. Therefore, targeting the tumor microenvironment may provide a therapeutic opportunity to improve the efficacy of TT.

Why are CSCs refractory to targeted-therapy?

CSCs are believed to be highly resistant to conventional chemotherapies and radiotherapies. In the following contexts, we will illustrate possible mechanisms underlying CSCs-mediated TTR (Fig. 1).

Angiogenesis-independent growth

Although antiangiogenesis agents are effective to suppress tumor growth in theory, the standard therapies have displayed a limited survival benefit in clinical practice. Researchers found that neo-angiogenesis was dispensable for the growth and invasion of perivascular brain CSCs which were insensitive to angiogenesis inhibitors [54], supporting that the growth of CSCs was angiogenesis-independent [55]. This specific phenotype possibly maintained in a dormant state under normal oxygen conditions but reactivated to repopulate tumor cells when hypoxia occurred owing to angiogenic inhibitor treatment. Besides, growing evidence suggests that tumor cells themselves may mimic vasculogenesis via a process named vasculogenic mimicry [56]. In melanoma, CSCs were found to be responsible for vasculogenic mimicry [57], whereas angiogenesis inhibitors did not affect the tubular formation related to vasculogenic mimicry in melanoma cell [58]. Further investigations are required to explain the relationship between CSCs and angiogenesis, which may provide new approaches for elimination of the TTR tumor cells.

Survival ability

A crucial factor that determines the efficacy of TT is the balance between apoptosis and survival. CSCs show more powerful pro-survival and anti-apoptosis abilities compared with non-CSCs. Resistance to imatinib in CML CSCs involved the enhanced survival ability mediated by AKT/PKB pathway and Bcl-2 expression. In colon CSCs, resistance to anti-angiogenesis therapy was dependent on the activation of p38MAPK-MAPKAPK2-Hsp27 pathway [59].