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Review

A role for cancer stem cells in therapy resistance: Cellular and molecular mechanisms

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ABSTRACT

Similar to normal tissue, many tumors have a hierarchical organization where tumorigenic cancer stem cells (CSCs) differentiate into non-tumorigenic progenies. A host of studies have demonstrated that although CSCs and their non-tumorigenic progenies within the same clone can share common genotype, they display different epigenetic profiles that results in changes of multiple signaling pathways. Many of these pathways confer cell adaptation to the microenvironmental stresses including inflammation, hypoxia, low pH, shortage in nutrients and anti-cancer therapies. Treatment strategies based on combination of conventional therapies targeting bulk tumor cells and CSC-specific pathway inhibition bear a promise to improve cancer cure compared to monotherapies. In this review we describe the mechanisms of CSC-related therapy resistance including drug efflux by ABC transporters, activation of aldehyde dehydrogenase and developmental pathways, enhanced DNA damage response, autophagy and microenvironmental conditions, and discuss possible therapeutic strategies for improving cancer treatment.

Abbreviations: ABCG2, ATP-binding cassette G2; ALDH, aldehyde dehydrogenase; ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; APL, acute promyelocytic leukemia; ATM, ataxia telangiectasia mutated protein kinase; ATR, ataxia telangiectasia and rad-3-related protein kinase; ATRA, all-trans retinoic acid; BCRP, breast cancer resistance protein; BSO, buthionine sulfoximine; CAF, cancer associated fibroblasts; CCL2, chemokine (C-C motif) ligand 2; CD, cluster of differentiation; CHK1/2, checkpoint protein kinase 1 and 2; CSC, cancer stem cell; CXCL12, chemokine (C-X-C motif) ligand 12; CXCR4, (C-X-C) chemokine receptor type 4; DLL4, delta-like 4 ligand; DNA-PK, DNA-dependent protein kinase; DSB, double strand break; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; ERK, extracellular-signal-regulated kinase; FGF, fibroblast growth factor; GABA, γ-amino butyric acid; GSI, gamma-secretase inhibitor; GTN, glyceryl-trinitrate; HER2, human epidermal growth factor receptor 2; HIF, hypoxia-inducible factor; HNSCC, head and neck squamous cell carcinoma; HR, homology-directed recombination; IL, interleukin; KRAS, Kirsten rat sarcoma; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MRP1, multidrug resistance protein 1; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NHEJ, non-homologous end joining; NRP2, neuropilin-2; NSCLC, non-small cell lung cancer; PDGF, plateled derived growth factor; PI3K, phosphoinositide 3-kinase; PIKK, phosphatidylinositol 3-kinase-related kinase; siRNA, small interfering RNA; SCLC, small cell lung cancer; SMAD, small mothers against decapentaplegic; SP, side population; STAT, signal transducer and activator of transcription; TGF-ß, transforming growth factor β; TMZ, temozolomide; TNBC, triple-negative breast cancer; TNFα, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; WNT, wingless-type MMTV integration site family.

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1. Introduction

Advances in preclinical and clinical cancer research have brought new diagnostic and treatment options for cancer patients and resulted in a remarkable progress in cancer cure and prevention [1]. Nevertheless, cancer remains a major health problem in many regions of the world causing about 20% of all deaths in developed countries. Genomic instability and genetic diversity was defined as one of the hallmarks of cancer that contribute to the treatment failure and disease progression [2]. The first investigations of the intratumor heterogeneity demonstrated that a high degree of genetic instability in melanoma cancer cells corresponds to a higher rate of generation of cell clones resistant to the chemotherapeutic drugs methotrexate and N-(phosphonacetyl)-L-aspartate [3]. Recent data suggest that tumor stratification according to the genomic instability rate could be beneficial for predicting therapy resistance and disease relapse [4]. The recent deep sequencing technologies revealed a high genetic heterogeneity and plasticity of the individual tumors that may present a principal challenge to the targeted therapy. The accumulating evidence coming from a number of whole genome sequencing studies shattered a widely accepted concept that tumor arises from one single clonogenic cell which accumulates multiple mutations in a stepwise manner. In addition, recent study revealed the co-existence of multiple genetically diverse clones within the same tumor [5–10]. Upon treatment, this intratumoral diversity which is associated with distinct treatment sensitivity, foster clonal evolution through Darwinian selection and promote emergence of tumor adaptations and therapeutic failure [11]. Because of genetic heterogeneity, different clones may exhibit distinct mechanisms of resistances within the same tumor. In addition to the genetic differences between tumor clones, there are also fundamental functional and phenotypic differences between cells of the same clone that might be explained by the stem cell model of cancer development. A growing body of research demonstrated that, similar to normal tissue, some cancers have a hierarchical organization where tumorigenic cancer stem cells (CSCs) differentiate into non-tumorigenic progenies [12]. The stem cell concept of cancerogenesis was first demonstrated by study of Dick and coworkers who showed that tumorigenic properties can be attributed only to minority population of leukemia cells that can be identified by expression of certain surface markers, which distinguish them from non-tumorigenic cells [13,14]. Although much controversy and uncertainty remain about the validity of the CSC model for different tumor types, as well as about specificity of the CSC markers, the hierarchical model of neoplasm development suggested a high clinical relevance of CSCs and therefore attracted a lot of interest. During the last decade CSC populations were discovered in many types of solid tumors and their phenotypical and functional characteristics are the subject of intensive investigation [12,15]. For many types of cancer, CSCs represent a distinct cell population that can be identified and prospectively isolated from the tumor tissues using CSC-specific markers. CSCs have specific functional features such as self-renewal capacity and long-term repopulation potential, which make CSCs different from the bulk tumor cells and enable them to initiate and maintain tumor development [15,16]. The frequency of CSC broadly ranges from a small population of less than 1%, as in acute myeloid leukemia (AML) up to 82% in acute lymphoblastic leukemia (ALL) [13,14,17]. However, the fact that tumor initiating cell are common in some human cancers concerned the hierarchical organization of these tumors [18]. Moreover, some evidences are emerging that, similarly to the differentiated somatic cells which can be dedifferentiated to the pluripotent cells, non-CSC tumor cells can be reprogrammed into CSCs [19,20]. However, the data suggesting tumor cell dedifferentiation are still limited and controversial. Therefore, even if not all the tumors might have a cellular hierarchy with CSCs at the apex, it might be hypothesized the CSC properties can be attributed to either stable or transient cell populations in a broad variety of human malignant neoplasms [16].

A host of studies have demonstrated that although CSC and their non-tumorigenic progenies within the same clone share common genotype, they display different epigenetic profiles which results in changes of multiple signaling pathways [21–24]. Many of these pathways confer cell adaptation to the microenvironmental stresses including inflammation, hypoxia, low pH, shortage in nutrients, and anti-cancer therapies [1]. Indeed, recent experimental reports suggest a number of molecular mechanisms contributing to resistance of certain CSCs to conventional cancer therapy [12,15], Tables 1–3. This intrinsic resistance of the tumor-initiating cells to anti-cancer therapy along with their genetic evolution and epigenetic plasticity might be the source of disease relapse and progression. It is important to note that although therapy resistance has been demonstrated for CSC cells in certain types of tumors, this property should not be generalized since there is also compelling evidences suggesting that different CSC populations can be eradicated by conventional therapy, such as radiotherapy and chemotherapy. However, taking into account that cancer can potentially arise from a single CSC, it becomes clear that efficient anti-cancer therapy might require targeting of all CSCs within a given patient [25–27]. In this review we discuss the mechanisms of CSC therapy resistance and possible therapeutic strategies for improving cancer treatment.

2. Mechanisms of CSC therapy resistance

2.1. Drug efflux by ABC transporters

Cancer stem cells can be detected in tumor tissues and cell cultures by expression of CSC-specific cell surface proteins, or markers, such as CD133, CD44, CD24, $\alpha 2\beta 1$ integrin and some others [15]. In addition, CSC can be identified by using functional approaches based on the biochemical activity of the marker proteins. These methods, for example, include Aldefluor assay based on a high enzymatic activity of aldehyde dehydrogenase (ALDH) in putative tumor initiating populations or identification of CSC by their capability to rapidly efflux lipophilic fluorescent dye Hoechst 33342. The cells negative for the dye staining create a tail-like structure called side population (SP) [28]. This SP phenotype is linked to proteins of the ATP-Binding Cassette (ABC) transporter superfamily which contribute to the maintenance of chemical homeostasis and defense against environmental insults in various normal tissues such as epithelial cells in gastrointestinal tract, brain capillary endothelial cells which form the blood-brain barrier, placenta and normal stem cell populations [29,30]. In addition to important physiological functions, ABC-transporters are known for their contribution to multiple drug resistance in various human cancers [31]. The ABC transporter family includes 49 proteins and three of them were extensively investigated as regulators of the multidrug resistance in tumors, including P-glycoprotein (P-gp, MDR1, ABCB1), multidrug resistance protein 1 (MRP1, ABCC1), and breast cancer resistance protein (BCRP, ABCG2) [32,33]. Enhanced expression of these proteins in some types of tumor such as breast, lung, bladder, ovarian cancer, acute myeloid leukemia (AML), myeloma and sarcoma results in ATP-dependent efflux of cytotoxic drugs from cells and maintaining the drug concentration inside the cells below the toxic level [34]. These three transporters have a broad spectrum of the substrates and a large overlap in drug specificity providing tumor resistance to the major classes of chemotherapeutic drugs including taxanes, antimetabolites, topoisomerase inhibitors as well as molecularly targeted therapies such as tyrosine kinase inhibitors Sorafenib, Imatinib, Nilotinib, Gefitinib, Erlotinib [32,33,35], Table 1. Populations of cancer stem cells in