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Review

Apoptosis signaling in cancer stem cells

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ABSTRACT

Since the discovery of specific populations of cells with stem-like characteristics in human leukemias, phenotypically and/or functionally similar tumor-promoting cells have been identified in a variety of human cancers. By dint of the similarities to normal human stem cells in terms of self-renewal, differentiation, long life span, and proliferative capacity, these defined populations of cells within the bulk tumor are referred to as "cancer stem cells (CSCs)". The presence of CSCs has challenged the age-old dogma of carcinogenesis, which posits that all cells within a tissue retain the capacity to generate tumors. With respect to the frequency of CSCs, there is still a lack of consensus as in some recent models the notion that these cells constitute a very small proportion within the tumor has been challenged. Another issue that remains unresolved is the existence of a "global" marker, although reference has been made to the $CD133^+$, $CD34^+CD38^-$, and $CD44^+CD24^-$ populations as the functional stem-like cells in different cancers. Nevertheless, the identification of this sub-set within the bulk tumor and its contribution to chemotherapy resistance suggest that the CSCs could be the Achilles heel in terms of chemosensitization. Therefore, a paradigm is emerging that an effective therapeutic approach against cancers is to target this critical pool of cells that have the capacity to self-renew and proliferate as well as evade death signals. Here we provide a brief review of the literature *vis a vis* the various mechanisms of defective apoptotic signaling in CSCs with potential for therapeutic intervention.

Contents

Abbreviations: ABCB5, ATP-binding cassette B5; AIF, apoptosis inducing factor; ALDH1, aldehyde dehydrogenase 1; AML, acute myeloid leukemia; BCNU, Bischloronitrosourea; cFLIP, cellular FLICE-like inhibitory protein; CSC, cancer stem cell; cIAP1, cellular IAP1; cIAP2, cellular IAP1; DIABLO, direct IAP binding protein with low pI; DISC, death inducing signaling complex; FADD, Fas-associated Death Domain; HtrA2, high temperature requirement protein A2; IAP, inhibitor of apoptosis; IKK, IκB kinase; ML-IAP, melanoma-IAP; NAIP, neuronal apoptosis inhibitory protein; NGFR, nerve growth factor receptor; NF-κB, nuclear factor-kappaB; SCID, severe combined immunodeficient; Smac, second mitochondria-derived activator of caspase; SP, side population; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis inducing ligand; XIAP, X-linked inhibitor of apoptosis.

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1. The CSC hypothesis

Implicit within the conventional model of carcinogenesis is the development of the first mutation en route to transformation, which is generally a prolonged process. Considering the relatively short life span of mature cells in many tissues from which cancers originate, the probability of picking up successive rounds of mutations would have to be low, which calls into question the validity of the '*stochastic*' model of carcinogenesis. In the process of trying to understand and unravel the problem of cancer development, an alternative hypothesis was proposed, which postulated that cells with longer life spans must exist within the bulk population to sustain multiple rounds of mutations necessary for cancer formation. According to this provocative and non-dogmatic '*CSC model*' (Fig. 1), human cancers originate from tissue stem or progenitor cells, and only a small fraction of these cells (CSCs) have the capacity to proliferate indefinitely (Bonnet and Dick, 1997; Lobo et al., 2007). First described in patients with acute myeloid leukemia (AML) (Bonnet and Dick, 1997), CSCs share many of the hallmarks of normal stem cells. For example, both of these cell types have the capacity to self-renew and differentiate (Spangrude et al., 1988; Goodell et al., 1996; Singh et al., 2004; Ricci-Vitiani et al., 2007; O'Brien et al., 2007; Al-Hajj et al., 2003; Zhou et al., 2008), however, unlike the highly regulated self-renewal and differentiation decisions of normal stem cells, it has been suggested that cancer cells undergo uncontrolled self-renewal and abnormal differentiation (Singh et al., 2004; Ricci-Vitiani et al., 2007; O'Brien et al., 2007; Al-Hajj et al., 2003; Zhou et al., 2008; Vermeulen et al., 2008). Furthermore, CSCs metastasize to distant organs and tissues much like somatic stem cells migrate to distant tissues, and most importantly both cell types exhibit resistance to apoptotic stimuli (Domen et al., 1998, 2000). This remarkably similar hierarchical order shared among normal progenitor cells and CSCs has been elegantly demonstrated by studies from Irving Weissman's group. The group demonstrated that the limited life span of progenitor cells together with their inability to self-renew were inherent cancer suppressive mechanisms, which were perturbed upon repeated mutational events targeting the stem cell population (Rossi et al., 2008). Of note, the mutations and/or epigenetic events required for this functional perturbation included loss of immunogenicity and apoptosis evasion. Therefore, any disturbance of the tightly regulated processes that control self-renewal, cell fate (proliferation vs. apoptosis) and differentiation of tissue stem or progenitor cells may favor the emergence of CSCs and the subsequent development of cancer.

While the precise identity of CSCs in a given type of cancer remains to be identified, it appears that CSCs may arise either from the malignant transformation of a tissue stem or progenitor cell, or alternatively, from the abnormal re-activation of stem cell pathways in a committed progenitor cell (Visvader and Lindeman, 2008). The seemingly distinct (from the bulk tumor) and relatively small population of CSCs possess unlimited self-renewal and proliferation capacity and ultimately sustain tumor growth. However, the proportion of CSCs within the bulk population remains questionable and controversial.

2. CSCs in leukemia and solid tumors

Given that the developmental biology and hierarchy of the hematopoietic system has been extensively characterized, it is not surprising that the CSC model initially stems from work in haematological malignancies. Using the severe combined immunodeficiency (SCID) leukemia xenotransplantation model, it was demonstrated that only a minor fraction (0.1–1%) of acute myeloid leukemia (AML) cells with $CD34^+CD38^-$ phenotype and harboring stem cell characteristics was sufficient to produce leukemia in SCID mice (Lapidot et al., 1994). Following this, AML has been the main hematological malignancy in which bona fide CSCs have been identified (Dick, 2008). Interestingly, the AML phenotypic marker ($CD34^+CD38^-$) is identical to the normal hematopoietic stem cell (HSC) surface marker, thus suggesting that AML stem cells were derived from HSC (Bonnet and Dick, 1997; Reya et al., 2001, 2003). However, it should be pointed out that a recent study has revealed that the $CD34^+CD38^+$ fraction within certain AMLs contain leukemia initiating capacity, thus suggesting a greater degree of phenotypic variation in the leukemia initiating population than previously suggested (Taussig et al., 2008). More convincing argument for the CSC model is provided by studies involving chronic myeloid leukemia (CML), where the highly active BCR-ABL oncoprotein is found in the most primitive precursors (early stem cell progenitors), and detected in several cell lineages (lymphoid, myeloid, and platelets) (Kavalerchik et al., 2008). Failure to treat the disease results in the generation of highly aggressive sub-populations carrying additional mutations that disrupt the differentiation process, and produce life threatening acute leukemia. Since the initial studies in leukemia, CSCs have now been identified in a range of solid tumors, including breast carcinoma (Al-Hajj et al., 2003; Kakarala and Wicha, 2008), lung cancer (Eramo et al., 2008; Peacock and Watkins, 2008), gastric carcinoma (Takaishi et al., 2008), head and neck squamous cell cancer (Prince et al., 2007; Vazquez et al., 2008), prostate cancer (Maitland and Collins, 2008), colon cancer (O'Brien et al., 2007; Ricci-Vitiani et al., 2007; Boman and Huang, 2008), pancreatic cancer (Zhou et al., 2008; Ma et al., 2008), liver carcinoma (Yang et al., 2008; Sell and Leffert, 2008; Zobalova et al., 2008), melanoma (Schatton et al., 2008), multiple myeloma (Huff and Matsui, 2008), medulloblastoma (Yang et al., 2008) and brain tumors (Singh et al., 2004; Kim and Dirks, 2008). Various cell surface markers have been used for the isolation and characterization of CSCs from solid tumors, for example CD133, CD44, CD24, CD90, epithelial cell adhesion molecule, THY1, ATP-binding cassette B5 (ABCB5) and aldehyde dehydrogenase 1 (ALDH1) (Singh et al., 2004; Ricci-Vitiani et al., 2007; O'Brien et al., 2007; Al-Hajj et al., 2003; Zhou et al., 2008; Eramo et al., 2008; Yang et al., 2008; Schatton et al., 2008; Zobalova et al., 2008; Ginestier et al., 2007; Hermann et al., 2007; Prince et al., 2007). Furthermore, CSC identity was demonstrated by transplantation experiments showing re-establishment of phenotypic heterogeneity of the primary tumor and self-renewing capability upon serial transplantation (Singh et al., 2004; Ricci-Vitiani et al., 2007; O'Brien et al., 2007; Al-Hajj et al., 2003; Zhou et al., 2008; Eramo et al., 2008; Yang et al., 2008; Schatton et al., 2008; Ginestier et al., 2007; Hermann et al., 2007; Prince et al., 2007) (Table 1).

In glioblastoma, $CD133^+$ cells have been reported to represent the population that confers radioresistance (Bao et al., 2006). Moreover, the presence of greater than 2% $CD133^+$ cells in tumor lesions has been associated with poor prognosis in glioblastoma patients (Pallini et al., 2008).

Since stem cells and CSCs share some key properties, e.g. unlimited self-renewal and proliferation capacity, there are also similarities in the signaling pathways that are operative in normal and malignant stem cells. For example, some developmental