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The bad seed: Cancer stem cells in tumor development and resistance

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ABSTRACT

Over the past two decades cancer stem cells (CSCs) have emerged as essential players in the pathogenesis of cancer, with the capacity to initiate, maintain and repopulate different tumors. Within the tumor bulk, CSCs represent a small subpopulation, bestowed with the capacity to self-renew and yield heterogeneous lineages of cancer cells. In many scenarios, CSCs exhibit increased resistance toward irradiation and chemotherapy, and given their spectacular ability to replenish the tumor, they constitute a substantial therapeutic challenge. In this review, we provide a brief overview of the concept of CSCs and the experimental methodology utilized for identifying and isolating these unique cells. We discuss how CSCs are regulated within the tumor microenvironment as well as the role they portray in seeding fresh tumors. Finally, we explore the mechanisms that enable CSCs to evade modern therapeutic approaches and the possible strategies that can be utilized to prevent CSCs from resurrecting the disease.

1. Introduction

For giving humanity the gift of fire, Zeus punished Prometheus by binding him eternally to a rock, where an eagle would come daily to devour his self-renewing liver. In the tumor microenvironment, Prometheus would be analogous to the "cancer stem cell" and the eagle to modern anticancer treatments. In such a depiction, Prometheus' epic escape symbolizes the challenge we face today in cancer therapeutics: tumor recurrence due to cancer stem cell (CSC) resistance to therapy.

CSCs are characterized by the ability to self-renew and sustain long-term maintenance of a tumor, by giving rise to every cell type in a particular cancer (Reya et al., 2001). It is hypothesized that CSCs reside in the tumor as a distinct subpopulation, harboring the potential to seed metastasis and drive tumor relapse by re-initiating and repopulating new tumors. Several explanations are offered to describe CSC-driven tumor initiation. The accumulation of oncogenic mutations in adult stem cells (SCs) or progenitor cells is an attractive model for explaining how cancer initiation and formation occurs in highly proliferative tissues, such as the skin, intestine and hematopoietic system (Fuchs, 2008; Sancho et al., 2004; Seita and Weissman, 2010; White and Lowry, 2015). Another hypothesis suggests that CSCs may arise via a dedifferentiation program, where any differentiated cell can regress from its specialized state and acquire cancer stem-like properties (Visvader, 2011). Theoretically, it is possible for both of these tumorigenic processes to co-exist. For the purpose of this review, the CSC will be defined as a malignant tumor-propagating cell that displays properties attributed to normal SCs; namely, differentiation potential and the capacity to self-renew.

Regardless of the origin, resistance of CSCs to current therapeutics is a well-known phenomenon (Colak and Medema, 2014), providing an explanation as to why conventional therapies are often ineffective at eradicating cancer cells (Ferreira et al., 2016; Gonen and Assaraf, 2012; Livney and Assaraf, 2013; Niewerth et al., 2015; Zhitomirsky and Assaraf, 2016). Hence, given the remarkable regenerative capacity of CSCs, our future vision of cancer therapy must aim, not simply to reduce tumor mass, but to extinguish the burning flame of the tumor.

2. Historical Perspective

The ingenious concept that SCs could be responsible for generating tumors was presented over 100 years ago in an attempt to explain the formation of teratomas (Askanazy, 1907). Askanazy

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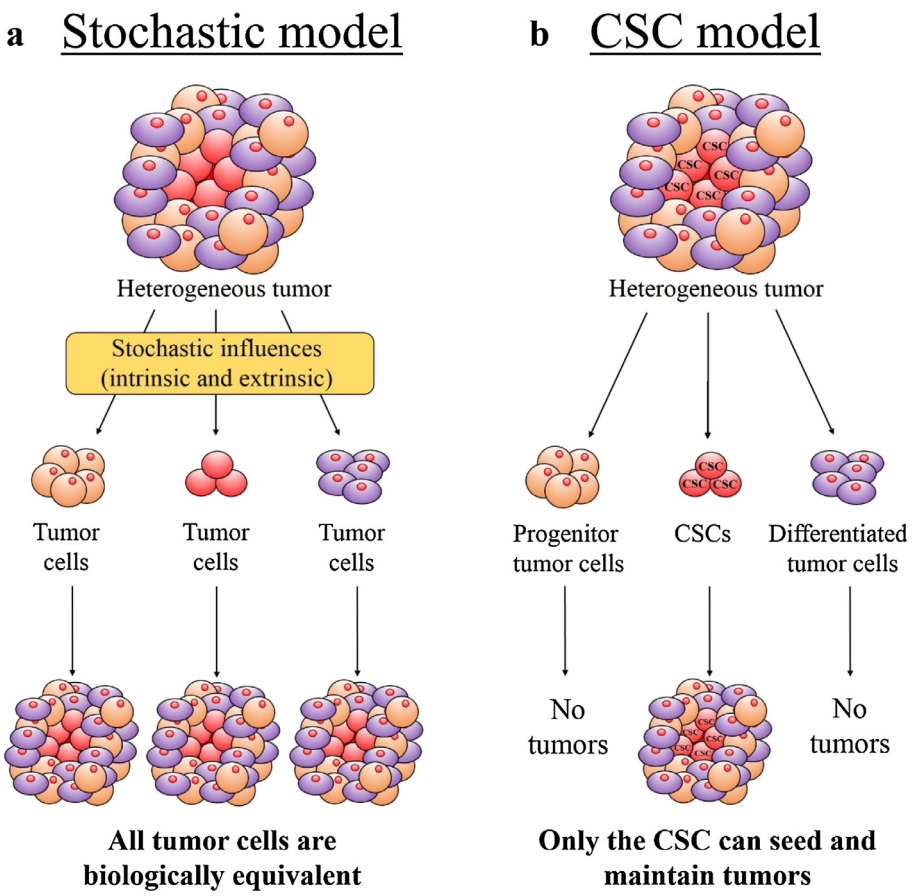

Fig. 1. Modes of tumor growth. (a) In the stochastic model of cancer, all tumor cells are believed to be biologically equivalent and possess equal tumorigenic capabilities. Variation in behavior arises from intrinsic and extrinsic stochastic influences. (b) The CSC, or hierarchical model, in contrast, proposes that tumor subpopulations are functionally distinct and that only the CSCs have the capacity to initiate, maintain and seed new tumors. According to this model, tumor cells with tumor-initiating abilities can be separated based on intrinsic properties.

proposed that these unique tumors, comprised from each of the three embryonic germ layers, resulted from residual embryonic cells that had segregated, and were delayed or arrested in development (Askanazy, 1907; Maehle, 2011). Thirty years later, Furth and Kahn elegantly demonstrated that xenotransplantation of a single malignant leukemia cell could result in transmission of the disease (Furth et al., 1937). Furthermore, their data revealed that only a very limited number of tumor cells possessed the capacity to induce tumorigenesis. Further supporting the CSC hypothesis, it was shown that a small subpopulation of undifferentiated teratocarcinoma cells could differentiate into both malignant and non-malignant cells (Kleinsmith and Pierce, 1964). Notably, upon transplantation, freshly seeded tumors recapitulated the original histopathology of the primary tumor and more importantly, these tumor-initiating cells (TICs) could not only proliferate, but also retained the potential to differentiate and self-renew. Regrettably, the supporting evidence for the CSC hypothesis was largely ignored for several decades. It was believed that tumors were comprised of biologically equivalent cells, all with equal tumorigenic potential, which behaved differently due to stochastic influences (Dick, 2009). Today, this is referred to as the stochastic model of cancer (Nguyen et al., 2012; Reya et al., 2001) (Fig. 1). A breakthrough in the field was the pioneering studies of Dick and colleagues in the 1990s, which presented the first *bona fide* CSC detected in acute myeloid leukemia (AML). Sorted $CD34^+/CD38^-$ leukemia cells engrafted into immunodeficient mice gave rise to leukemia with many disease characteristics akin to human AML (Lapidot et al., 1994). Subsequently, it was shown that only a minute fraction of AML tumor cells could initiate tumors, verified by their capability to self-renew and differentiate into non-tumorigenic leukemia cells (Bonnet and Dick, 1997). Nearly a decade later, the existence of CSCs within solid tumors was reported. Less than one hundred $CD44^{high}/CD24^{low}$ cells could be sorted from human breast tumors, which could proliferate and initiate tumors. In contrast, tens of thousands of other breast tumor cells displaying various diverse phenotypes, failed to initiate tumors (Al-Hajj et al., 2003). Following this study, CSCs have been detected in solid tumors from the prostate, brain, colon, liver, lungs and various other tissue types (Visvader and Lindeman, 2008).

3. The CSC: a seed that sprouts, blooms and buds

The origin of the first CSC, that is, the first normal cell to acquire the initial cancer-promoting mutation, is a matter of ongoing debate. Some argue that CSCs arise through mutations acquired in regular tissue SCs, while others posit that CSCs originate from differentiated or progenitor cells that have regained 'stemness', a term used to refer to the intrinsic molecular pathways, epigenetic modifications and particular transcription factors that regulate and maintain the SC form (Shackleton et al., 2009). Regardless, any cell that acquires mutations restoring the capacity for self-renewal, whilst suppressing the terminal differentiation program, could potentially serve as the original CSC of a particular cancer. We refer the reader to insightful reviews on the origin of cancer cells (Visvader, 2011; White and Lowry, 2015).

Although most heterogeneous tumors are able to develop from a single cell, two separate models describe tumor growth and