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Current evidence for cancer stem cells in gastrointestinal tumors and future research perspectives

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ABSTRACT

Cancer stem cells (CSCs) are a very heterogeneous subpopulation of "stem-like" cancer cells that have been identified in many cancers, including leukemias and solid tumors. It is believed that CSCs drive tumor growth, malignant behavior and are responsible for the initiation of metastatic spread. In addition, CSCs have been implicated in chemotherapy and radiotherapy resistance. Current evidence supports the theory that CSCs share at least two main features of normal stem cells: self-renewal and differentiation, properties that contribute to tumor survival even in the presence of aggressive chemotherapy; however, the mechanism(s) governing the unique biology of CSCs remain unclear. In the field of gastrointestinal cancer, where we face very low survival rates across different tumor types, unraveling the role of CSCs in gastrointestinal tumors should improve our knowledge of cancer biology and chemoresistance, ultimately benefiting patient survival. Towards this end, much effort is being invested in the characterization of CSCs as a means of overcoming drug resistance and controlling metastatic spread. In this review we will cover the concept of CSCs, the current evidence for CSCs in gastrointestinal tumors and future research directions.

1. Introduction

Cancer stem cells (CSCs), also known as tumor-initiating cells or tumor-propagating cells, have been defined as a subpopulation of tumor cells with intrinsic stem-like properties that afford these cells unlimited self-renewal, enhanced chemoresistance and multipotency, such that CSCs have the ability to exclusively recapitulate the heterogenous parental tumor cellular makeup upon transplantation into an immunocompromised host (Reya et al., 2001; Ishizawa et al., 2010; Jimeno et al., 2009; Vermeulen et al., 2008a). Whether CSCs arise from normal stem cells or acquire mutations that confer upon them stem cell-like properties, it is important to note that CSCs are not "bona fide" stem cells (Lamprecht and Fich, 2015; Adorno-Cruz et al., 2015) and thus CSCs should not be confused with normal stem cells becoming cancerous (Nguyen et al., 2012). Rather, CSCs are believed to have acquired, over time, phenotypes and characteristics of normal stem cells such as unlimited self-renewal, the capacity to divide indefinitely and at the same time maintain the ability to generate multiple cell lineages, including differentiated progenies. A CSC can thus divide (1) asymmetrically (differentiation) giving rise to one CSC and a specialized differentiated cell or (2) symmetrically (self-renewal) giving rise to two identical CSCs. In both cases, the capacity of self-renewal remains intact, and assures the survival of the CSC pool and supports the hierarchical model of tumor cell heterogeneity (Nguyen et al., 2012). The clinical implication of this model suggests that only elimination of the CSCs will result in eradication of the tumor, while failure to do so will inevitably lead to tumor relapse. Due to these characteristics it is believed that CSCs play a very critical and central role in the initiation, development, metastatic spread and relapse of many tumors (Visvader and Lindeman, 2008).

The CSC concept was first demonstrated by Hamburger and Salmon in 1977 by showing that 1 in 1000 to 1 in 5000 tumor cells could form colonies in soft agar (Hamburger and Salmon, 1977). Twenty years later, the CSC theory would be definitively validated in hematological malignancies by Dick and Bonnet, by identifying a subpopulation of human leukemia cells that was able to initiate leukemia when injected in immunodeficient mice (Bonnet and Dick, 1997). This subpopulation of CSCs was identified using the cell-surface marker profile CD34+ and CD38-, and only these cells were able to reproduce tumors in recipient mice. The identification of CSCs in solid tumors, however, would not come until 2003, when Al-Hajj et al. identified and isolated tumorigenic cells from breast tumors and showed that these cells could form new tumors when transplanted in nude mice. Specifically, they showed that CD44+ and CD24-/low lineage breast tumor cells had the unique ability to proliferate *in vivo* and give rise to diverse cell types (Al-Hajj et al., 2003). In the past two decades CSCs have been identified in a wide variety of tumors, including lung, ovarian, brain, colon, pancreas, prostate, and melanoma (Kim et al., 2005; O'Brien et al., 2007; Collins et al., 2005; Szotek et al., 2006) and their identification has raised growing interest in the scientific community. In the field of gastrointestinal tumors, CSCs have been indentified in gastric, pancreas, colon, liver and neuroendocrine tumors. The discovery of CSCs in gastrointestinal tumors will undoubtedly help to advance our understanding of these cancers and should at the same time provide us with new strategies to eradicate these deadly diseases.

2. Cancer stem cell theory

2.1. Principles

It is well known that human primary tumors harbor heterogeneous cell populations and contain phenotypically different cancer cells. Previously it was thought that cellular heterogeneity was secondary to genetic instability (*e.g.* somatic mutations and changes in chromosomal numbers), which were believed to give rise to cells that were selected for based on survival advantages, initiating the process of clonal differentiation and expansion (Nowell, 1976). While the clonal evolution model addressed many of the aspects of tumor evolution (Nowell, 1976), it failed to address the increasing extent of tumor heterogeneity observed in many tumor entities (Marusyk et al., 2012; McGranahan and Swanton, 2015). Thus the CSC model emerged (Fig. 1), proposing a hierarchal cellular organization with the CSC giving rise to all of the cells present within the tumor (Reya et al., 2001). The CSC model is based on the assumption that CSCs are exclusively responsible for tumor formation, while non-CSCs do not have tumor-initiating activity. Thus identifying the "true" tumor initiating CSCs and dissecting the cellular and molecular mechanisms driving their "stem-like" properties is crucial, and at the same time challenging due to genetic instability and CSC diversification. Nonetheless, the clinical potential to be gained from understanding and characterizing these cells warrants further investigation.

2.2. Identification of CSCs

To successfully study and understand CSCs, it is essential that we develop methodologies to distinguish CSCs from other tumor