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Lung cancer stem cells: Molecular features and therapeutic targets

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ABSTRACT

Lung cancers are highly heterogeneous and resistant to available therapeutic agents, with a five year survival rate of less than 15%. Despite significant advances in our knowledge of the genetic alterations and aberrations in signaling pathways, it has been difficult to determine the basis of lung cancer heterogeneity and drug resistance. Cancer stem cell model has attracted a significant amount of attention in recent years as a viable explanation for the heterogeneity, drug resistance, dormancy and recurrence and metastasis of various tumors. At the same time, cancer stem cells have been relatively less characterized in lung cancers. This review summarizes the current understanding of lung cancer stem cells, including their molecular features and signaling pathways that drive their stemness. This review also discusses the potential startegies to inhibit the signaling pathways driving stemness, in an effort to eradicate these cells to combat lung cancer.

Contents

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1. Introduction: stem cell model of cancer

Lung cancers cause maximum number of cancer-related deaths worldwide and is highly correlated with smoking (Proctor, 2001; Parkin et al., 2005; Siegel et al., 2012). The risk of lung cancer remains significantly high for long-term heavy smokers even after smoking cessation. Fifty percent of new lung cancer patients are former smokers and many of them stopped smoking five years or more prior to diagnosis (Halpern and Warner, 1993; Tong et al., 1996). According to an estimate made by the World Health Organization (WHO), lung cancer will cause about 2.5 million deaths per year by the year 2030 (Proctor, 2001). In the United States, approximately 85% of the patients diagnosed with lung cancer die of this disease within 5 years and this rate has not changed significantly since 1970s (Jemal et al., 2008a,b). Despite significant advances in our knowledge about cancer, our ability to develop effective therapies to combat lung cancer has been limiting (Hanahan and Weinberg, 2011). Treatment of the primary lesions rarely prevents the development of the distant metastases, which is the major cause for fatality (Jemal et al., 2008b). These facts highlight a need for better understanding the cellular and molecular events underlying the genesis and metastasis of this disease for designing novel therapeutic strategies. In this context, a school of thought has emerged in the recent years that suggest that tumors arise from a subset of cancer cells, called cancer stem cells, which may remain dormant, have the capacity to evade therapeutic drugs and metastasize. This concept is different from the prevailing theory where all the cancer cells have equal and similar proliferative capacity and opportunity for initiating tumor growth and spread (Nowell, 1976; Visvader and Lindeman, 2008). Further, the cancer stem cell model suggests that cancers are organized into aberrant cell hierarchies which are driven by a subset of cells that have the ability to self-renew themselves and generate heterogeneous lineages of other cell types that comprise the tumor (Fig. 1) (Bonnet and Dick, 1997; Clarke et al., 2006). Thus, in principle, agents that can eliminate such cancer stem cells or tumor-initiating cells might be highly effective as anti-cancer agents.

First experimental evidence for the existence of cancer stem cells came in the year 1997, with the identification of leukemia stem cells (Bonnet and Dick, 1997; Lapidot et al., 1994). Later, in the year 2003, the first evidence for hierarchical stem cell origin of solid tumors was experimentally demonstrated in breast cancer (Al-Hajj et al., 2003). However the *de novo* existence of cancer stem cells within solid tumors had remained controversial until very recently (For review, see (Medema, 2013). In these recent studies using mouse models of brain (Chen et al., 2012), skin (Driessens et al., 2012) and intestinal (Schepers et al., 2012) tumors, three independent groups have provided convincing evidence that cancer stem cells do exist and are responsible for maintaining tumor growth in intact organs.

Self-renewal is a characteristic property of stem cells that allows them to maintain their numbers through symmetric or asymmetric mitotic cell division (Morrison and Kimble, 2006). During asymmetric division, each stem cell generates one daughter cell with stem cell fate (self-renewal) and one daughter cell (progenitor cell) that is destined to differentiate (Clevers, 2005). However, upon injuries or when stem cell pool has to be developed during development, stem cells undergo

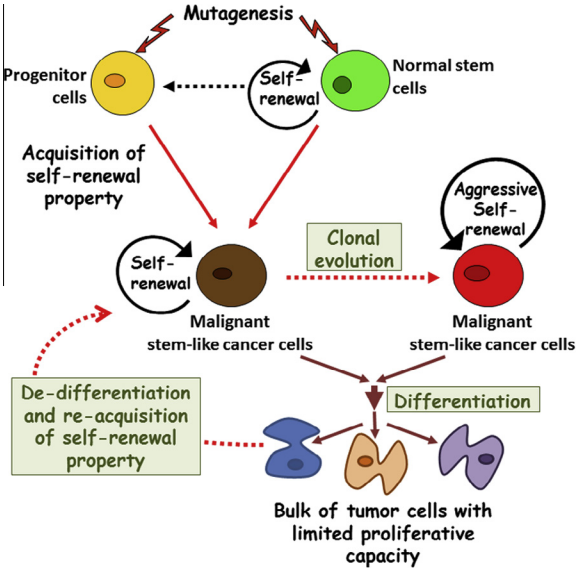

Fig. 1. Origin of heterogeneity among stem-like cancer cells. This diagram depicts our current understanding of stem cell model of cancer. Normal tissue stem cells with intrinsic properties of self-renewal and multi-lineage differentiation acquire oncogenic mutations, which results in their deregulated self-renewal and give rise to stem-like cancer cells. Additionally, mutations might also cause restricted progenitor cells to acquire self-renewal property and become malignant stem-like cancer cells. These cells self-renew themselves as well as differentiate to generate phenotypically diverse cancer cells, which constitute the bulk of the heterogeneous tumor. During cancer progression stem-like cancer cells may evolve and change in genotype and phenotype to produce subclonal heterogeneity. Recent evidence also suggests the potential for reversal of mature cancer cells to re-acquire the stem-like properties through de-differentiation.