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Stem cells and targeted approaches to melanoma cure

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ABSTRACT

Melanoma stem cells, also known as malignant melanoma-initiating cells, are identifiable through expression of specific biomarkers such as ABCB5 (ATP-binding cassette, sub-family B (MDR/TAP), member 5), NGFR (nerve growth factor receptor, CD271) and ALDH (aldehyde dehydrogenase), and drive melanoma initiation and progression based on prolonged self-renewal capacity, vasculogenic differentiation and immune evasion. As we will review here, specific roles of these aggressive subpopulations have been documented in tumorigenic growth, metastatic dissemination, therapeutic resistance, and malignant recurrence. Moreover, recent findings have provided pre-clinical proof-of-concept for the potential therapeutic utility of the melanoma stem cell concept. Therefore, melanoma stem cell-directed therapeutic approaches represent promising novel strategies to improve therapy of this arguably most virulent human cancer.

Contents

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1. Introduction

Melanoma, perhaps even more than many other cancers, is an ideal clinicopathological example of a malignancy that fits the cancer stem cell model. In early evolutionary phases, melanoma grows as a flat, non-tumorigenic lesion (radial growth phase) that is virtually incapable of establishing a durable, tumorigenic metastasis. Accordingly, the vast majority of these early, flat melanomas are curable simply by surgical excision. However, once tumorigenic growth of the invasive component develops within the dermal microenvironment, even at a microscopic level when tumor volume is in the range of a cubic millimeter, potentially lethal metastases may ensue that themselves may grow expansively at distant sites. The cancer stem cell (CSC) model involves different subpopulations of malignant cells (as opposed to a homogeneous 'clone'), and for many years it has been well-recognized that the tumorigenic component of primary melanoma is not homogeneous, as might be anticipated in a stochastic model of clonal tumorigenesis. Rather, melanomas exhibit 'polyclonism' (Laga and Murphy, 2010), a feature often characterized by a multiplicity of architectural, cytologic, and immunohistochemical compartments within a single tumor nodule. This patterning and apparent compartmentalization is consistent with hierarchically ordered subpopulations of tumor cells that may differ in their respective capacities to form and drive tumorigenesis through self-renewal, and engage in various pathways of cellular differentiation. Indeed, well before the discovery and experimental authentication of melanoma stem cells, Hendrix and co-workers noted differentiation heterogeneity in melanomas in the form of endothelial gene expression by tumor cells (Maniotis et al., 1999). This phenomenon, known as vasculogenic mimicry, was posited to be the consequence of differentiation plasticity in primitive, stem-like melanoma cells (Hendrix et al., 2003b), a prediction that more recently has been validated using melanoma stem cell biomarkers and experimental systems and clinical tissues (Boiko et al., 2010; Civenni et al., 2011; Fang et al., 2005; Klein et al., 2007; Monzani et al., 2007; Rappa et al., 2008; Schatton et al., 2008; Sharma et al., 2010; Vasquez-Moctezuma et al., 2010).

Primary melanomas are also highly immunogenic among human cancers, but seldom are they completely so. Two types of immune responses are involved in the primary evolution of melanoma, one directed against the more superficial component of the lesions, termed regression, and the other against the deeper invasive portion, referred to as the tumor infiltrating lymphocyte (TIL) response. Together, such immune responses may be remarkably successful at 'melting away' a substantial portion of the primary tumor, literally before the eyes of the afflicted patient. But success is generally only partial, and a portion of the tumor usually persists as cells that seem to be impervious to an otherwise impressive host immune response. This clinical phenomenon has suggested the possibility that subpopulations of virulent melanoma cells may preferentially express molecules that shield them from cytotoxic T cells, or alternatively fail to express melanoma-associated differentiation antigens. Accordingly, recent findings that cells expressing stem-like markers in human melanomas also selectively display co-stimulatory molecules capable of subverting host immune responses (Schatton and Frank, 2009; Schatton et al., 2010) now appear particularly relevant to melanoma as an informative paradigm for cancer stem cell behavior.

Once melanomas have spread beyond the primary site, they are extremely difficult to treat. In human cancer, this feature is known to be in part the result of resistance to drugs that effectively eradicate bulk tumor populations, but not melanoma stem cells. This protective attribute of stem cells may reside in expression of drug efflux transporters at the cell membrane capable of escorting cytotoxic agents to the extracellular space upon attempted entry (Aleman et al., 2003; Frank et al., 2005). Melanoma has turned out to be a paradigm for such stem-like drug resistance when it was shown to convert from a doxorubicin-resistant to a doxorubicin-sensitive phenotype upon experimental blockade of a drug efflux transporter later shown to be exclusively expressed by self-renewing, tumorigenic subpopulations (Frank et al., 2005). Thus, even on the surface, there exist a number of attributes to melanoma that suggest that it may be a neoplasm in which cancer stem cells play an important role. The review to follow unfortunately cannot possibly be inclusive and comprehensive, given the rapid proliferation of data supporting the existence of biomarker-identifiable melanoma cell subpopulations with self-renewing and tumorigenic properties. However, it is hoped that it will serve as an update regarding the translationally important new field of melanoma stem cell (MSC) biology, and will thus assist in driving forward the necessary research and clinical testing required to eradicate this most deadly of human cancers.

2. Conceptual definition of melanoma stem cells

The ability to recognize and study stem cells in any cancer depends on a rigorous and generally accepted definition. Failure to adhere to such criteria may result in overly restrictive definitions that contribute to unwarranted skepticism. The cancer stem cell concept recognizes that malignant tumors, like most healthy tissues, are hierarchically organized at a cellular level, with specific subpopulations that are primarily responsible for tumor initiation and propagation. According to this model, CSCs possesses (1) the capacity for *prolonged and sustainable self-renewal* that inexorably *drives tumor growth*; and