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Pharmacological and immunological targeting of tumor mesenchymalization

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ABSTRACT

Controlling the spread of carcinoma cells to distant organs is the foremost challenge in cancer treatment, as metastatic disease is generally resistant to therapy and is ultimately incurable for the majority of patients. The plasticity of tumor cell phenotype, in which the behaviors and functions of individual tumor cells differ markedly depending upon intrinsic and extrinsic factors, is now known to be a central mechanism in cancer progression. Our expanding knowledge of epithelial and mesenchymal phenotypic states in tumor cells, and the dynamic nature of the transitions between these phenotypes has created new opportunities to intervene to better control the behavior of tumor cells. There are now a variety of innovative pharmacological approaches to preferentially target tumor cells that have acquired mesenchymal features, including cytotoxic agents that directly kill these cells, and inhibitors that block or revert the process of mesenchymalization. Furthermore, novel immunological strategies have been developed to engage the immune system in seeking out and destroying mesenchymalized tumor cells. This review highlights the relevance of phenotypic plasticity in tumor biology, and discusses recently developed pharmacological and immunological means of targeting this phenomenon.

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1. Introduction

The spread of cancer to distant organs represents the foremost challenge in cancer treatment. Whereas localized disease can often be treated with surgery and chemotherapy or radiation, metastatic disease is generally not amenable to surgery, is resistant to chemotherapy and radiation, and is ultimately incurable for the majority of patients. The use of small-molecule inhibitors that target specific cancer molecular alterations (such as EGFR and BRAF inhibitors) or impede tumor angiogenesis (such as VEGFR inhibitors) can succeed in enhancing quality of life and delaying progression, but even these sophisticated treatments eventually become ineffective due to the development of acquired resistance. The current wave of new immunologically targeted therapies (such as anti-PD-1/PD-L1 antibodies) has raised hope for the successful treatment of metastatic disease (Borghaei et al., 2015; Garon et al., 2015; Powles et al., 2014; Ribas et al., 2016), yet even these approaches

Abbreviations: CSC, cancer stem cell; CTC, circulating tumor cell; EMT, epithelial-mesenchymal transition; HTS, high-throughput screening; MET, mesenchymal-epithelial transition.

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have so far proven effective for only a proportion of patients. While significantly more research and development in tumor immunotherapy will undoubtedly lead to further breakthroughs in cancer treatment, another novel approach is quietly emerging that endeavors to complement these treatment strategies by targeting the mechanisms underlying tumor progression to metastatic disease.

One mechanism that is increasingly being recognized as central to the progression of carcinomas is the phenomenon of tumor cell phenotypic plasticity, exemplified by the observation that the bulk of a tumor mass can be phenotypically and functionally distinct from its invasive front (Brabletz et al., 2001). This phenotypic plasticity of tumor cells often occurs in response to local conditions in the tumor microenvironment, such as hypoxia or inflammation, that lead to the activation of a molecular program designated as the epithelial-mesenchymal transition (EMT), or the reverse phenomenon known as the mesenchymal-epithelial transition (MET) (Kalluri & Weinberg, 2009; Nieto & Cano, 2012; Thiery, Acloque, Huang, & Nieto, 2009). During EMT, epithelial cells lose polarity and the expression of molecules distinctive of epithelial status, including cytokeratins, E-cadherin, and several other molecules involved in cell-to-cell adhesion (Fig. 1). The cells in turn gain motility, the ability to invade the basement membrane and surrounding tissues, and the expression of mesenchymal molecules, including vimentin, N-cadherin, and a set of transcriptional regulators that include the zinc finger proteins SNAI1/2, the zinc-finger homeodomain proteins ZEB1/2, the helix-loop-helix transcription factors TWIST1/2, the T-box protein brachyury, and others (Bolos et al., 2003; Cano et al., 2000; Eger et al., 2005; Fernando et al., 2010; Yang et al., 2004). These transcriptional regulators, called EMT-TFs, are ultimately responsible for orchestrating the phenotypic changes that take place during an EMT via downregulation and upregulation of epithelial- and mesenchymal-associated genes, respectively (Fig. 1). The EMT and MET differentiation programs occur extensively during normal embryonic development, and are also recapitulated in adult tissues during wound healing and fibrosis (Lim & Thiery, 2012). Evidence has now been found for the occurrence of these phenotypic transitions in tumors during the metastatic process, whereby EMT may facilitate the invasion of tumor cells through the basement membrane, their migration to blood and lymphatic vessels, and their extravasation into metastatic sites (Rhim et al., 2012; Tsai, Donaher, Murphy, Chau, & Yang, 2012), while MET might allow the proliferation of tumor cells at the distant site (Chaffer et al., 2006; Tsai et al., 2012).

Realization of the contributions of EMT to cancer pathophysiology has driven the development of novel therapeutic strategies that specifically target tumor cells undergoing this phenomenon. The aims of such strategies are to eliminate mesenchymalized tumor cells in patients that have more advanced disease, or to prevent the development of metastatic disease in high-risk patients with localized tumors. Most of these approaches can be classified as pharmacological and antibody-based targeting of the EMT process, but a novel immunotherapy targeting EMT has also been developed in recent years. In this review, we present a brief survey of the relevance of EMT in tumor biology, and then discuss recently developed pharmacological and immunological means of targeting this phenomenon.

2. Tumor cell EMT versus mesenchymalization

As noted above, the phenomenon of EMT was initially described as a developmental process characterized by the conversion of epithelial cells into highly migratory, invasive mesenchymal cells. During development, EMT allows for the remodeling of various embryonic tissues, including the emergence of the mesoderm from epithelial layers during gastrulation (Hay, 1995, 2005). Well-characterized in the context of embryonic development is also the reverse process named MET, which contributes to the formation of epithelia from mesenchymal cells (Kim, Jackson, & Davidson, 2016). While the epithelial and mesenchymal cell states are well-defined entities in the context of development, in the particular case of carcinomas, however, cellular phenotype is akin to a spectrum, in which intermediate phenotypes

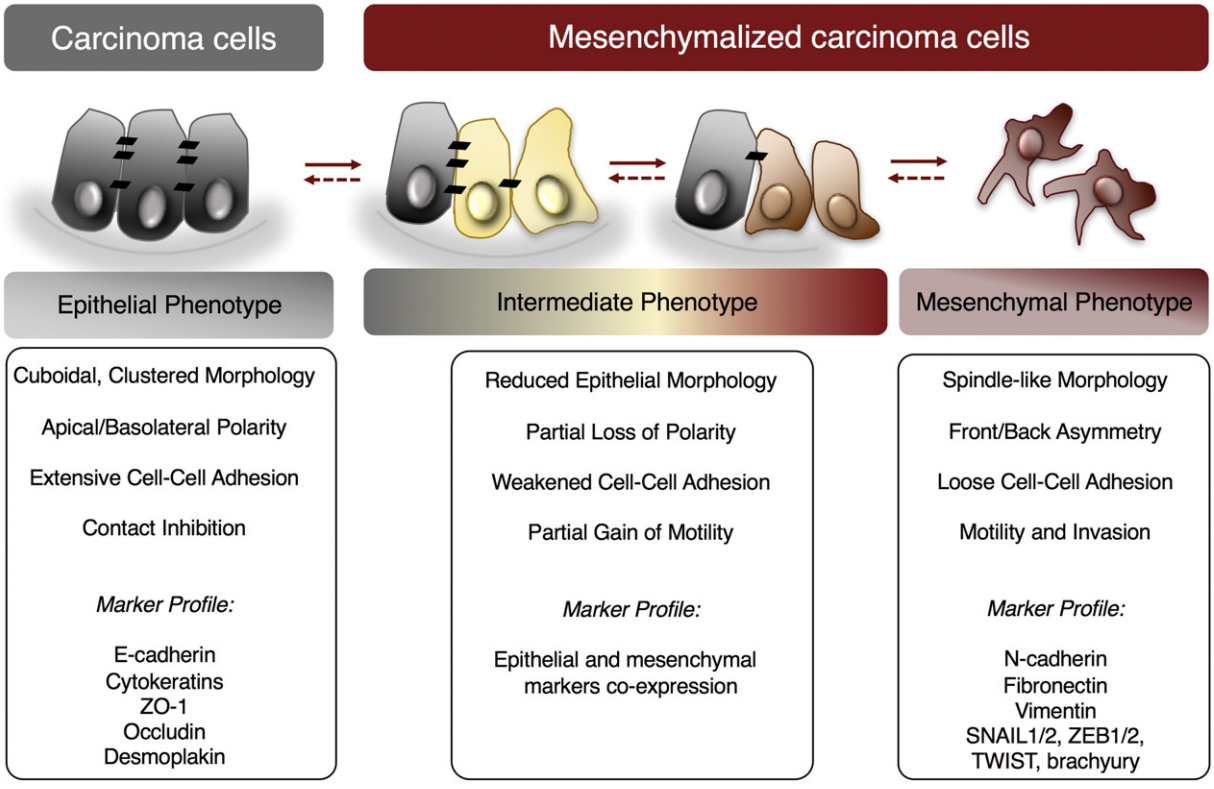

Fig. 1. Tumor plasticity generates a range of phenotypes in carcinoma cells. Phenotype characteristics and markers typically expressed are indicated below each phenotype. Arrows indicate the reversibility of the phenomenon.