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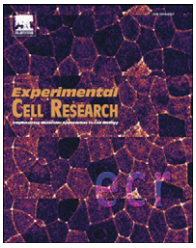

Review

Hallmarks of cancer: Interactions with the tumor stroma

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ABSTRACT

Ten years ago, Hanahan and Weinberg delineated six "Hallmarks of cancer" which summarize several decades of intense cancer research. However, tumor cells do not act in isolation, but rather subsist in a rich microenvironment provided by resident fibroblasts, endothelial cells, pericytes, leukocytes, and extra-cellular matrix. It is increasingly appreciated that the tumor stroma is an integral part of cancer initiation, growth and progression. The stromal elements of tumors hold prognostic, as well as response-predictive, information, and abundant targeting opportunities within the tumor microenvironment are continually identified. Herein we review the current understanding of tumor cell interactions with the tumor stroma with a particular focus on cancer-associated fibroblasts and pericytes. Moreover, we discuss emerging fields of research which need to be further explored in order to fulfil the promise of stroma-targeted therapies for cancer.

Contents

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Introduction

Tumors arise from normal cells through genetic alterations affecting the tightly controlled systems for growth control. Ten years ago, Hanahan and Weinberg enumerated six hallmarks of cancer that are essential for a cell to acquire on its way to any of the more than one hundred different types of human malignancies [1]. The specification of the traits of a tumor cell is the distillate of several decades of research dedicated to the malignant cell. However, the tumor cell-centric view of cancer does not take into account the context in which malignant cells subsist. As the cancer progresses, the surrounding microenvironment co-evolves into an activated state through continuous paracrine communication, thus creating a dynamic signaling circuitry that promotes cancer initiation and growth, and ultimately leads to a fatal disease. Indeed, many of the hallmarks of cancer delineated by Hanahan and Weinberg are provided by various stromal components, including endothelial cells, pericytes, fibroblasts, various classes of leukocytes, and extracellular matrix (Fig. 1). Herein, we review the pro-tumorigenic actions of tumor-associated mesenchymal cell types, *i.e.* cancer-associated fibroblasts (CAFs) and pericytes, in the context of the original hallmarks of cancer. Additionally, we discuss potential targeting opportunities for the development of drugs aimed at the tumor stroma, as well as delineate emerging areas of research.

Cancer-associated fibroblasts

The cancer-associated fibroblast is the most prominent cell type within the tumor stroma of many cancers, most notably breast and pancreatic carcinoma (Fig. 1) [2,3]. Recent studies highlight several different subpopulations of stromal fibroblasts within tumors designated by only partly overlapping marker expression, including α-smooth muscle actin (SMA), platelet-derived growth factor (PDGF) receptors, and fibroblast specific protein (FSP)-1 [4,5]. The heterogeneity in marker expression may in part be explained by a diverse origin of CAFs, which are variously reported to stem from resident local fibroblasts, bone marrow-derived progenitor cells or trans-differentiating epithelial cells [6]. Co-injection studies of tumor cells mixed with mesenchymal cells from different sources have conclusively demonstrated the importance of stromal fibroblasts for initiation, growth and metastatic spread of tumors [5,7,8].

Pericytes

Pericytes are contractile cells in close physical contact with endothelial cells in capillaries and venules (Fig. 1). In quiescent tissues, pericytes readily express markers such as PDGF receptor-β, NG2 and desmin, while lacking expression of α-SMA. However, tumor pericytes are characterized by a more loosely attached phenotype with a disparate pattern of marker expression, including α-SMA [9]. A range of signaling pathways, including PDGF, transforming growth factor (TGF)-β, angiopoietin and Notch family members, are implicated in pericyte recruitment, differentiation and function [10]. Recruitment of pericytes into tumors is crucially dependent on PDGF receptor-β expression, as well as on production of the PDGF-B ligand by endothelial cells [11]. In line with this notion, pericyte progenitor cells recruited into tumors from remote sources are denoted by expression of PDGF receptor-β [12].

Contributions of CAFs and pericytes to the "Hallmarks of cancer"

Self-sufficiency in growth signals

CAFs directly stimulate tumor cell proliferation through provision of various growth factors, hormones and cytokines in a context-dependent manner. Prototypical epithelial mitogens, such as hepatocyte growth factor (HGF), and members of the epidermal growth factor, fibroblast growth factor (FGF) and Wnt families, as well as cytokines such as stromal-derived factor (SDF)-1α (CXCL12) and IL-6, are all highly expressed by CAFs in different tumor types [13]. Intriguingly, many of these factors acting in isolation are sufficient to induce transformation of epithelial cells, indicative of a tumor-initiating capability of CAFs. One illustrative example comes from studies in which the gene for Notch1 was deleted in epidermal keratinocytes in mice [14]. Consequential to an impaired barrier function of the skin, a chronic wound healing response ensued and ultimately led to the formation of papillomas and subsequent overt invasive carcinomas, demonstrating that prolonged activation of a normal stroma may be a causal factor in the development of cancer. Direct evidence for the cancer-initiating capacity of CAFs is provided by a study by Bhowmick and colleagues, in which the TGFβ type II receptor was selectively ablated in fibroblasts by expression of the Cre recombinase from the FSP-1 promoter in genetically modified mice [15]. Upon loss of TGFβ responsiveness in fibroblasts, the mice spontaneously developed intraepithelial neoplasia of the prostate and invasive carcinoma of the forestomach. The induction of malignant progression was accompanied by stromal expansion and an increased expression of HGF, leading to augmented signaling by c-Met in epithelial cells. Whether genetic alterations in stromal fibroblasts leading to transformation of adjacent epithelia are frequent events in the initiation of cancer is still unclear. Strikingly, isolated skin fibroblasts from patients predisposed to develop basal cell carcinoma because of germline mutations in one allele of the gene encoding *PTCH1* (Gorlin syndrome) exhibit features of CAFs, including the secretion of keratinocyte growth factor and SDF-1α [16]. Moreover, several studies demonstrate tumor-promoting effects of *Trp53* inactivation in the stromal compartment, and genetic inactivation of *Pten* in fibroblasts accelerates initiation and progression of mammary tumors [17–19].

Evasion of apoptosis

In addition to providing cues permissive for proliferation, oncogenic signaling invariably also triggers apoptotic pathways