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Review

Activation of fibroblasts in cancer stroma

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ABSTRACT

Tumor microenvironment has emerged as an important target for cancer therapy. In particular, cancer-associated fibroblasts (CAF) seem to regulate many aspects of tumorigenesis. CAFs secrete a variety of soluble factors that act in a paracrine manner and thus affect not only cancer cells, but also other cell types present in the tumor stroma. Acting on cancer cells, CAFs promote tumor growth and invasion. They also enhance angiogenesis by secreting factors that activate endothelial cells and pericytes. Tumor immunity is mediated via cytokines secreted by immune cells and CAFs. Both immune cells and CAFs can exert tumor-suppressing and -promoting effects. CAFs, and the factors they produce, are attractive targets for cancer therapy, and they have proven to be useful as prognostic markers. In this review we focus mainly on carcinomas and discuss the recent findings regarding the role of activated fibroblasts in driving tumor progression.

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Introduction

Tumorigenesis is a multistep process, analogous to Darwinian evolution, whereby genetic changes lead to growth advantage in a subset of cells paving way to progression from normal to malignant cells [1]. Hanahan and Weinberg proposed the six hallmarks of cancer, that most, if not all tumors require for progression from benign to malignant growth. These hallmarks are: self-sufficiency in growth signals, insensitivity to antigrowth signals, capability to evade apoptosis, unlimited replicative potential, sustained angiogenesis and tissue invasion together with metastasis [2]. Recently, a seventh hallmark, cancer-related inflammation (CRI) was proposed by Colotta et al. [3]. CRI refers to induction of genetic instability by inflammatory mediators, leading to accumulation of genetic alterations. CRI is accompanied by tissue remodeling and angiogenesis [4,5].

The majority of human cancers are carcinomas. They arise from the epithelial cell layer that under normal conditions is separated by basal lamina from the supporting connective tissue known as stroma [6]. Carcinoma was long viewed as a disease of transformed epithelial cells, and treatment strategies focused only on tumor cells. However, tumor progression is not achieved solely by the evolving cancer cells, but stromal components – the microenvironment of the tumor – play a key role in this process [7]. Co-evolution of tumor and stromal cells can occur in two ways: stromal changes may take place first leading to transformation of epithelial cells, or transformed epithelia may activate stromal cells in a paracrine fashion [8]. Various cell types are present in the tumor stroma. Vasculature, consisting endothelial and smooth muscle cells and pericytes, provides nutrients and oxygen [9]. Inflammatory and immune cells, recruited by chemokines and cytokines, have both tumor-suppressing and -promoting functions [10]. Quiescent fibroblasts become activated in tumor stroma and are key regulators of the paracrine signaling between stromal and cancer cells [11].

Activation of fibroblasts

Fibroblasts form the structural framework – the stroma – of tissues by synthesizing extracellular matrix (ECM) components, such as collagens and fibronectin. They are the most abundant cell type in connective tissues [12]. In normal conditions fibroblasts are in an inactive quiescent state. Fibroblasts become activated in wound healing and fibrosis, both conditions requiring tissue remodeling. These activated fibroblasts, myofibroblasts, were originally described by Giulio Gabbiani in 1971 during wound healing in granulation tissues [13]. Granulation tissue is composed of myofibroblasts, small vessels and inflammatory cells. Myofibroblasts differ morphologically and functionally from quiescent fibroblasts. It has been proposed that mechanical tension is required for the acquisition and maintenance of the myofibroblast phenotype [14]. In response to mechanical stress myofibroblasts acquire contractile stress fibers (microfilament bundles) and start to express α-smooth muscle actin (α-SMA), which is instrumental in the force generation, and ED-A splice variant of fibronectin, and form direct cell–cell contacts through gap junctions [15]. Once the wound healing process is completed, most of the myofibroblasts are removed by apoptosis from the granulation tissue [16].

Tumors have been referred to as wounds that do not heal because of the similarity with granulation tissue [17], and activated fibroblasts, which are not removed by apoptosis as in wound healing, are prominent contributors in carcinogenesis [18]. Like immune cells, which initially suppress malignant growth, fibroblasts also inhibit early stages of tumor progression. This inhibitory effect is implied to be mediated by gap junctions that are formed between activated fibroblasts [19,20]. Later in the tumor progression these cancer-associated fibroblasts (CAFs) promote both tumor growth and progression [21]. In addition to secretion of a variety of factors promoting carcinogenesis, CAFs also modify the tumor stroma mechanically. Gaggioli et al. [22] demonstrated that CAFs generate force- and protease-mediated tracks into ECM, and cancer cells follow these leading fibroblasts along the tracks. The force-mediated matrix remodeling was dependent on integrins α3 and α5 [22]. Furthermore, CAFs convey signals via mechanotransduction. Mechanotransduction is a process by which activated fibroblasts convert physical stimulation into chemical signals leading to activation of cancer-promoting signaling pathways [23]. Tumor-induced stromal stiffening is caused by increased matrix deposition by CAFs, cross-linking and bundling, compounding to the high interstitial pressure caused by the expanding tumor mass [24]. Compression of the ECM in turn leads to concentration of soluble factors promoting tumorigenesis in an autocrine and paracrine manner [25].

CAFs, like myofibroblasts, are highly heterogeneous, and are thought to be derived from the same sources as myofibroblasts. The main progenitor for activated fibroblasts seems to be the local residing fibroblast; they can also originate from pericytes and smooth muscle cells from the vasculature, from bone marrow-derived mesenchymal cells, such as fibrocytes, or by epithelial/endothelial–mesenchymal transition (EMT/EndMT) [26–28]. EMT is a biological process relevant in development, tissue regeneration and cancer progression. EMT is achieved by down-regulation of epithelial proteins like E-cadherin and ZO-1 leading to loss of epithelial polarization and *de novo* expression of mesenchymal proteins such as α-SMA and fibronectin. This transition enables the migratory spindle-shape phenotype of a mesenchymal cell, leading to invasion and metastasis [29]. Like EMT, EndMT operates both in physiological and pathological settings; the expression of endothelial cell–cell junction proteins such as VE-cadherin and CD31 is replaced with expression of mesenchymal proteins. It has been estimated that up to 40% of CAFs in the tumor stroma could be EndMT-derived and these cells might have an important role in angiogenic sprouting that requires a motile phenotype [30]. Senescent fibroblasts, secreting factors that promote tumorigenesis [31], have also been implied as a source [32]. The activation stages and possible origins of fibroblasts are depicted in Fig. 1. Later in tumor progression the dependence of cancer cells on CAFs decreases, partly due to a switch from paracrine to autocrine regulation in the cancer cells [33].

The term CAF is itself rather ambiguous due to the various origins that these cells derive from, as is the distinction between myofibroblasts and CAFs. *De novo* expression of α-SMA is the most commonly used marker for CAFs, but because of their heterogeneity, employing solely α-SMA expression will not identify all CAFs [34–36]. Other widely used CAF markers are fibroblast specific protein 1 (FSP1, aka S100A4), fibroblast activation protein (FAP, aka seprase) and platelet-derived growth factor receptor