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Review

Catabolic cancer-associated fibroblasts transfer energy and biomass to anabolic cancer cells, fueling tumor growth

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ABSTRACT

Fibroblasts are the most abundant "non-cancerous" cells in tumors. However, it remains largely unknown how these cancer-associated fibroblasts (CAFs) promote tumor growth and metastasis, driving chemotherapy resistance and poor clinical outcome. This review summarizes new findings on CAF signaling pathways and their emerging metabolic phenotypes that promote tumor growth. Although it is well established that altered cancer metabolism enhances tumor growth, little is known about the role of fibroblast metabolism in tumor growth. New studies reveal that metabolic coupling occurs between catabolic fibroblasts and anabolic cancer cells, in many types of human tumors, including breast, prostate, and head & neck cancers, as well as lymphomas. These catabolic phenotypes observed in CAFs are secondary to a ROS-induced metabolic stress response. Mechanistically, this occurs via HIF1-alpha and NFκB signaling, driving oxidative stress, autophagy, glycolysis and senescence in stromal fibroblasts. These catabolic CAFs then create a nutrient-rich microenvironment, to metabolically support tumor growth, via the local stromal generation of mitochondrial fuels (lactate, ketone bodies, fatty acids, glutamine, and other amino acids). New biomarkers of this catabolic CAF phenotype (such as caveolin-1 (Cav-1) and MCT4), which are reversible upon treatment with anti-oxidants, are strong predictors of poor clinical outcome in various types of human cancers. How cancer cells metabolically reprogram fibroblasts can also help us to understand the effects of cancer cells at an organismal level, explaining para-neoplastic phenomena, such as cancer cachexia. In conclusion, cancer should be viewed more as a systemic disease, that engages the host-organism in various forms of energy-transfer and metabolic co-operation, across a whole-body "ecosystem".

1. Introduction

One of the hallmarks of cancer is altered cellular metabolism [1]. Research in cancer biology has historically focused on cancer cells and did not consider the interactions between cancer cells and other cells in the tumor microenvironment. The importance of tumor stroma is now well recognized (Figs. 1–2). However, there has been little emphasis on tumor-stromal metabolism. Instead, most studies have focused on structural support and the wound healing properties of cytokines and growth factors.

Homogenous glycolytic metabolism is the traditional view of cancer metabolism [2]. However, recent studies demonstrate that there is metabolic compartmentalization and heterogeneity within tumors [3]. Autophagy in cancer, whereby cells digest their organelles to utilize the catabolites for their metabolism, is also now recognized as a driver of tumorigenesis and cancer progression [4]. Altered autophagy and metabolism are important features, differentiating cancer cells from non-cancerous cells.

Here, we describe the role of cell signaling pathways, oxidative stress (ROS) and autophagy in regulating the metabolic phenotype of tumor-associated fibroblasts. The metabolism discussed encompasses the catabolism of glucose, free fatty acids, lactate, ketone bodies and amino acids (such as GLN; glutamine). The impact of these factors on cancer aggressiveness is also discussed. Each of the factors contributes toward driving cancer cell aggressiveness. However, as detailed below, they should not be studied in isolation, as we highlight that there are important reciprocal interactions, between epithelial cancer cells and stromal cells.

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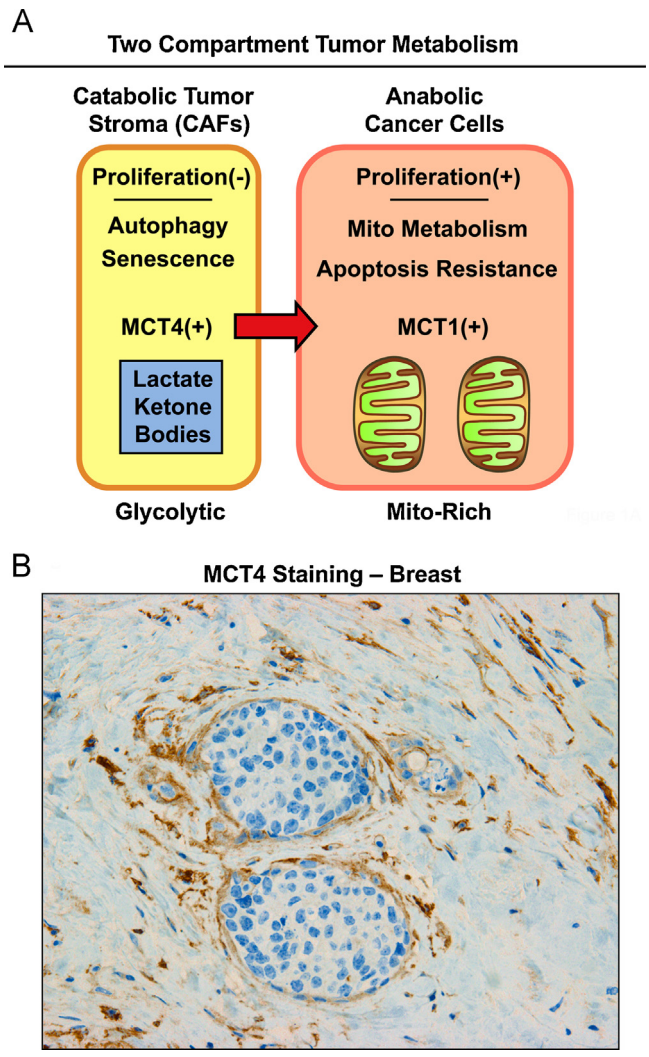

Fig. 1. Two-compartment tumor metabolism. (A) The two-compartment model. Catabolic stromal cells are metabolically coupled to anabolic cancer cells, via catabolite transporters. Exporters of catabolites, such as monocarboxylate transporter 4 (MCT4), are active in stromal cells, while as cancer cells have importers of catabolites, such as monocarboxylate transporter 1 (MCT1). The metabolic support that stromal cells provide via catabolic reactions, such as glycolysis, allows for mitochondrial metabolism, such as oxidative phosphorylation (OXPHOS) in cancer cells, which drives proliferation and apoptosis resistance. (B) Stromal MCT4 expression exemplifies two-compartment metabolism. The stromal compartment expresses the catabolite exporter MCT4 and outlines the cancer cell compartment. Note that there is an absence of MCT4 expression in the cancer cell compartment, in this ductal carcinoma in situ (DCIS) sample. A representative image is shown. Original magnification, 40×. Modified with permission from [145].

2. Cell signaling pathways drive oxidative stress, autophagy and catabolism in cancer-associated fibroblasts

Loss of caveolin-1 (Cav-1) and the activation of transforming growth factor-β (TGF-β), hypoxia inducible factor (HIF) and nuclear factor-κB (NFκB) signaling, all drive the generation of reactive oxygen species (ROS), autophagy and catabolism in human cancer associated fibroblasts (CAFs). These signal transduction components also have reciprocal interactions with cancer cells. It is important to highlight that these interactions have been more precisely characterized, by simultaneously studying multiple pathways in model systems.

A subset of plasma membrane lipid rafts, caveolae, play important roles in cell signaling and the regulation of cellular metabolism. Caveolin proteins are required for caveolae formation. Caveolin-1 (Cav-1) is expressed mainly in differentiated cell types, such as normal fibroblasts. Loss of stromal Cav-1 is a marker of autophagy, reduced OXPHOS metabolism, glycolysis and oxidative stress [5].

The Caveolin Scaffolding Domain of Cav-1 binds to and regulates the function of numerous receptor tyrosine kinases, such as EGFR and Src, non-receptor tyrosine kinases, G-protein coupled receptors and enzymes such as nitric oxide synthase (NOS) [6]. In general, binding of a signaling molecule to Cav-1 leads to inactivation of the signaling molecule and pathway [7]. Oncogenically transformed fibroblasts have down-regulation of Cav-1 and restoration of Cav-1 can reverse tumor promoting features [8]. In fibroblasts, Cav-1 inhibits cell proliferation and cell cycle progression. Cav-1 represses transcription of the cyclin D1 gene, it inhibits multiple components of the Ras-p42/44 MAP kinase and Rac pathways and modulates p53 which leads to decreased proliferation and cell cycle arrest [6].

Loss of Cav-1 in fibroblasts facilitates tumor formation and progression, with invasion and metastasis, apoptosis-resistance, aneuploidy and genomic instability [9], possibly via altered interactions with integrins and integrin-linked kinase (ILK) [10,11]. shRNA mediated down-regulation of Cav-1 in fibroblasts promotes the breast cancer tumor growth in xenografts [12]. Loss of Cav-1 in the stroma also leads to hyperplasia and reduced differentiation of non-transformed prostate epithelial cells [13].

Poor outcomes are associated with loss of Cav-1 in fibroblasts in breast cancer, ductal carcinoma in situ (DCIS), gastric cancer and prostate cancer [14–19]. Loss of Cav-1 in the stroma and gain of monocarboxylate transporter 4 (MCT4) expression in the stroma have been found to be involved in the progression of DCIS to IDC [20]. MCT4 is the main exporter of lactate out of cells and its expression is regulated by HIF-1α [21].

Transforming growth factor-β (TGF-β) activation occurs in CAFs [22,23]. TGF-β activation in fibroblasts is sufficient to promote tumor growth, with increased autophagy and glycolysis in vivo [24]. Loss of Cav-1 is sufficient for TGF-β activation in fibroblasts and to generate a myofibroblast or CAF phenotype, with large amounts of extracellular matrix with matrix metalloprotease (MMP) activation, which can be reversed with Cav-1 rescue [25–27]. TGF-β activation leads to ROS generation, driving the activation of profibrotic gene expression in fibroblasts [28].

TGF-β activation is also crucial for CAF microenvironment remodeling with activation of MMPs, PAI-1 and migration stimulating factor (MSF), which promotes tumor growth, invasion and metastasis [24,29–31]. More specifically, MSF is a 70 kDa genetically truncated form of fibronectin, that is commonly overexpressed in embryonic fibroblasts. Overexpression of PAI-1 and MSF in fibroblasts is sufficient to induce stromal glycolysis and promote breast cancer tumor growth. Loss of Cav-1 increases expression of PAI-1 and MSF in fibroblasts [30,31].

IL-6 is generated at high levels in coculture of carcinoma cells and fibroblasts under conditions which lead to oxidative stress and autophagy [32]. IL-6 generation and secretion by fibroblasts promotes tumor growth in gastric cancer [33]. TNF alpha release by either carcinoma cells or fibroblasts is associated with decreased tumor growth in breast cancer [34]. Exposure of breast carcinoma or prostate carcinoma cells to TNFalpha reduces mitochondrial oxidative metabolism [35].

Stromal Cav-1 is a marker of tumor metabolic coupling. Tumors with stromal Cav-1 down-regulation have increased oxidative phosphorylation (OXPHOS) markers in the epithelial compartment, in addition to increased stromal aerobic glycolysis [36,37]. Loss of Cav-1 in prostate cancer stroma has been shown to be associated with a high Gleason score [38]. High MCT1 expression, which is the main importer of lactate into cells, is only found in prostate cancer carcinoma cells with no expression in stromal cells [38]. Human