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Metabolic hijacking: A survival strategy cancer cells exploit?

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ABSTRACT

The majority of human tumours are comprised of cancerous epithelial cells that coexist with a multitude of different cell types and extracellular matrix components creating the cancer microenvironment. Cancer-associated fibroblasts (CAFs) are the most abundant mesenchymal cell types present within most human carcinomas. Recent evidence suggests that nutrient deprived epithelial cancer cells are able to survive these conditions, as a result of their ability to undergo extensive metabolic reprogramming and exploit the metabolic capacities of surrounding CAFs. Although several studies support the role of CAFs in tumour progression and metastasis, the molecular mechanisms underlying this pro-tumourigenic interaction remains to be elucidated. This review will discuss the complex metabolic interaction that exists between epithelial cancer cells and CAF's: focussing primarily on their functional role in tumour progression, metastasis and chemotherapeutic resistance. Attempts are made at delineating the molecular mechanisms underlying this pro-tumourigenic interaction, and potential CAF-based targets are suggested.

1. Introduction

The majority of human tumours are comprised of cancerous epithelial cells that coexist with a multitude of different cell types (particularly, fibroblasts, adipocytes, immune and endothelial cells) and extracellular matrix components (McAllister and Weinberg, 2010) together creating what is termed the cancer microenvironment (stroma). Recent, evidence suggests that the different cell types comprising the tumour stroma form a complex signalling network which plays an essential role in the survival, growth and metastatic capabilities of the cancerous epithelial cells within solid tumours (Quail and Joyce, 2013).

During the initial process of tumour invasion, extracellular proteases degrade the basement membrane, leading to the migration of motile cancer cells through the basal lamina stroma. Subsequent, remodelling of the tumour stroma, both molecularly and architecturally, results in the invasion of these cells into the neighbouring tissue. A process which has been shown to rely heavily on immune cells, endothelial cells and most notably, proliferating "activated" fibroblasts (Tuxhorn et al., 2002). These "activated" fibroblasts within the tumour stroma have been identified as mesenchymal cells with characteristic signs of smooth muscle differentiation, and have thus been termed "myofibroblasts" (De Wever and Mareel, 2002). Myofibroblasts and their interactions with the surround-

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ing environment have been extensively studied for the critical role they play in both wound healing and chronic inflammation (Li et al., 2015). Due to their ability to promote angiogenesis, stimulate epithelial cell growth, migration and contraction during wound healing (Orimo and Weinberg, 2006a), it has been postulated that these cells may play a similar role within the tumour microenvironment, thereby facilitating the growth and progression of invasive cancers.

Olumi and colleagues (Olumi et al., 1999) demonstrated that stromal fibroblasts isolated from human prostate carcinomas, display potent tumour-promoting properties when injected in combination with non-tumourigenic prostate epithelial cells into immune-deficient mice, whereas normal prostate fibroblasts failed to initiate the same response. In cancer, myofibroblasts termed cancer associated fibroblasts (CAFs), are characterized by their concurrent production of α-smooth muscle actin (α-SMA) and vimentin (Sugimoto et al., 2006), and are found to be one of the most abundant mesenchymal cell types present within most human carcinomas. Morphologically CAFs are characterized by large spindle-shaped cells with stress fibres and highly developed fibronexi (transmembrane complex with extracellular fibronectin, integrins and intracellular actin) (Xing et al., 2010).

Resident fibroblasts in the surrounding stroma are an immediate source for the recruitment of CAFs. However, CAFs have been shown to originate from three other compartments. Firstly, the recruitment of CAFs from distant sites into the tumour can occur. Evidence suggests that bone marrow derived mesenchymal stem cells and precursor cells are a source of CAFs (Karnoub et al., 2007). Additionally, within the tumour stroma various other cell types, including endothelial, immune and epithelial cell, can undergo lineage reprogramming (known as trans-differentiation) and transform into mesenchymal cells. Furthermore, other mesenchymal cells within the stroma, such as adipocytes and vascular smooth muscle cells, could also potentially trans-differentiate and give rise to CAFs. Evidence suggests that the ability of CAFs to be recruited from a range of sources, leads to a heterogenous population of CAFs displaying common tumour growth promoting functions within the tumour microenvironment.

This review will therefore provide an extensive overview of the influence of cancer-associated fibroblasts within the tumour microenvironment: focussing primarily on their functional role in tumour progression, metastasis and chemotherapeutic resistance. In addition, the complex metabolic interaction between epithelial cancer cells and CAF's will be discussed and attempts are made at delineating the molecular mechanisms underlying this pro-tumourigenic interaction. Finally, the clinical implications of overcoming chemotherapeutic resistance by means of metabolic manipulation will be discussed and recommendations for potential CAF targets are suggested.

2. Cancer-associated fibroblasts and cancer progression

The role of these "activated" fibroblasts in tumour progression appears to be somewhat multifaceted, the initial stages of tumour progression has been shown to be repressed by the action of fibroblasts, predominantly due to the formation of gap junctions between adjacent "activated" fibroblasts thereby exerting contact inhibitory effects on epithelial cancer cells (Hinz et al., 2007). Subsequent to the degradation of the basement membrane and the infiltration of fibroblasts into direct contact with epithelial cancer cells, the resulting activation of CAFs leads to the remodelling of the extracellular matrix (ECM). CAFs are predominantly responsible for the production of essential ECM proteins (such as fibronectin and collagens) and proteases, including fibroblast activated protein (FAP) and matrix metalloproteases (MMPs).

In solid tumours, progressive stiffening of the ECM with a concurrent increase in matrix deposition is frequently observed, as such CAFs play a pivotal role in the remodelling of the ECM during tumour progression. Additionally, numerous cancer types show an increase in desmoplasia (increased fibrosis), characterized by an increase in collagen type I and III with a decrease in collagen type IV, which is often associated with a poor cancer prognosis (Kauppila et al., 1998). Interestingly, peritumoural CAFs have been implicated in the initiation of desmoplasia, through their ability to secrete a fibrillar network identical to that seen during wound healing. A consequence of this increased desmoplasia is that the tumour stromal environment becomes more rigid, which stimulates the expression of integrins, the function of which is to mediate cell–cell and cell-ECM interactions and signalling across the plasma membrane, making them important cell adhesion molecules (Campbell and Humphries, 2011).

In addition to their ECM modulatory capabilities, integrins have also been shown to be key regulators in tumour angiogenesis. Integrins in conjunction with various pro-angiogenic factors directly influence the migratory, adhesion and proliferative abilities of endothelial cells during their formation of mature blood vessels. In terms of tumour angiogenesis the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins are of specific importance, as both are highly expressed in a variety of tumour cells as well as on neovascular endothelial cells (Cai et al., 2009). However, on mature endothelial cells in normal tissue they are not expressed to the same degree, making them a promising target for anti-angiogenic therapies.

It is widely accepted that cell shape and adhesion are governed by integrin signalling and as anchorage dependence is an essential requirement for cell viability, integrins are therefore also seen as critical regulators of cell viability. Their response to intracellular stress can occur through a range of mechanisms, as they are known to regulate both the expression and activity of several Bcl-2 protein members. Increased resistance to serum starvation in both HT29 colon carcinoma cells (O'Brien et al., 1996) and Chinese hamster ovary (CHO) cells (Zhang et al., 1995) for example is mediated by the ligation of the integrin $\alpha_5\beta_1$ which has a protective effect against apoptosis. Additionally, the binding of the integrin $\alpha_6\beta_1$ to its ligand, laminin, has been shown to be protective against apoptosis in mammary epithelial cells (Farrelly et al., 1999).

Furthermore, the invasiveness of gastric cancer cells has been shown to be promoted by the secretion of the chemokine CXCL12 (stromal-derived factor 1) through its ability to increase integrin β1 clustering (Izumi et al., 2016). In patients with chronic lymphoblastic leukemia, the tissue localization and trafficking of B cells was initially identified to be regulated by CXCL12 and its associated receptor CXCR4 (Möhle et al., 1999). Subsequently, it was proposed that the invasion of breast cancer cells to distant metastatic sites is also under the regulation of CXCR4. The expression of CXCR4 has been shown to be highly expressed in over 23 different tumour types, including those of the brain, pancreas, and breast, whereas in normal tissue its expression level is absent or very low. Additionally, CXC12 expression is highly expressed in lymph nodes, lungs and bone marrow, organ sites where breast cancer metastasis is most frequently found (Müller et al., 2001). As such the CXCL12/CXCR4 chemotactic pathway has been implicated as a critical determinant in the destination of tumour metastasis.

Increased expression of hypoxia inducible factor 1α (HIF1α) in response to a lack of oxygen availability, results in the HIF1α-dependent gene expression of both CXCL12 and CXCR4 (Hill et al., 2009). Recently, CXCR4 has been identified as being a CAF-associated gene, signifying the existence of an autocrine feedback loop. The secretion of CXCL12 by CAFs has been shown to increase CXCL12/CXCR4 signalling, thereby promoting angiogenesis and tumour growth in both non-small lung cancer (Wald et al., 2011) and breast cancer (Orimo and Weinberg, 2006b). Furthermore,