Seminars in Cancer Biology 25 (2014) 69–77

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Regulation of the anti-tumour immune response by cancer-associated fibroblasts

James Harper, Richard C.A. Sainson*

MedImmune Ltd., Granta Park, Cambridge CB21 6GH, UK

ARTICLE INFO

Article history:
Received 8 August 2013
Received in revised form
23 December 2013
Accepted 30 December 2013

Keywords:
Cancer associated fibroblasts
Immune cells

ABSTRACT

The microenvironment of established tumours is often immunosuppressed, and this allows tumours to grow and disseminate without being eliminated by the patient's immune system. The recent FDA approval of immunotherapies such as ipilimumab and sipuleucel-T that directly activate the adaptive and innate immune responses has triggered interest in developing other novel anti-cancer approaches that modulate the immune system. Understanding how the different constituents of the tumour microenvironment influence the immune system is thus crucial and is expected to generate a plethora of factors that can be targeted to boost immunity and trigger long lasting anti-tumour efficacy. Cancer associated fibroblasts (CAFs) are a crucial component of the tumour microenvironment. Through secretion of multiple growth factors, cytokines and proteases, CAFs are known to be key effectors for tumour progression and can promote cancer cell growth, invasiveness and angiogenesis. However, recent publications have also linked CAF biology to innate and adaptive immune cell recruitment and regulation. Here, we review recent findings on how CAFs can influence the immune status of tumours through direct and indirect interaction with immune cells and other key components of the tumour microenvironment.

1. The origin and role of CAFs in cancer progression

As our understanding of the complexities of the mutational landscape involved in the formation of cancer has increased, so too has our understanding that cancers are not a homogenous cellular entity consisting of one cell type, the cancer cell. Instead, cancer is now seen as an almost "organismal" entity whereby complex interactions between the tumour cell and its surrounding microenvironment are sculpted to nurture and protect the cancer from the host's innate defence against neoplasia [1]. More recently, one particular cell type in the tumour microenvironment, "cancer associated fibroblasts" (CAFs, also known as activated fibroblasts, myofibroblasts, or tumour associated fibroblast, TAFs) has been prominently investigated based on their pro-tumourigenic potential in a number of different circumstances. These include the support of primary tumour growth through the secretion of growth factors such as HGF, TGF-β, VEGF and NK4 [2–4], the support of invasion and metastases [5,6], promoting angiogenesis [7], regulating inflammation [8] remodelling the ECM [9], motility and maintenance of stemness [10,11], and promoting a hospitable metabolic environment [12]. All of these properties tend to result in the presence of an active stroma "fuelling" cancer progression. The presence of this reactive stromal microenvironment is not only a hallmark of cancer but has also been described as a prerequisite for tumour invasion and metastasis formation, suggesting a role at different stages of cancer progression. In common carcinomas, CAFs can account for up to 90% of the tumour mass and correlate with a desmoplastic phenotype important for the aetiology of the disease [13–15]. However, pre-clinical modelling shows that even low fibroblast activated protein (FAP)-positive CAF content (around 2% of the cells in the Lewis lung carcinoma syngeneic model) can have a preponderant role in disease progression [16]. For the above reasons, it is not surprising that CAFs have been associated with poor prognosis [17].

The dichotomy between the ordered epithelial structures of the normal tissue, which often contain high levels of non-activated fibroblasts, and the highly reactive stromal content observed in tumours originating in the same tissue raises three major questions: (1) from where do CAFs originate; (2) what is their main role throughout tumourigenesis and (3) what is the therapeutic potential of these cells?

Depending on the tissue analysed or the models they are isolated from, it seems that activated fibroblasts demonstrate a high degree of heterogeneity. This is due to the fact that CAFs have been reported to originate from a number of sources and through a variety of different mechanisms (Fig. 1). It seems that the majority of CAFs appear to originate from the activation of resident fibroblasts and are activated through similar processes to those

* Corresponding author at: MedImmune Ltd., Granta Park, Cambridge CB21 6GH, UK
E-mail addresses: harperj@medimmune.com (J. Harper), sainsonr@medimmune.com (R.C.A. Sainson).

1044-579X/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.semcancer.2013.12.005

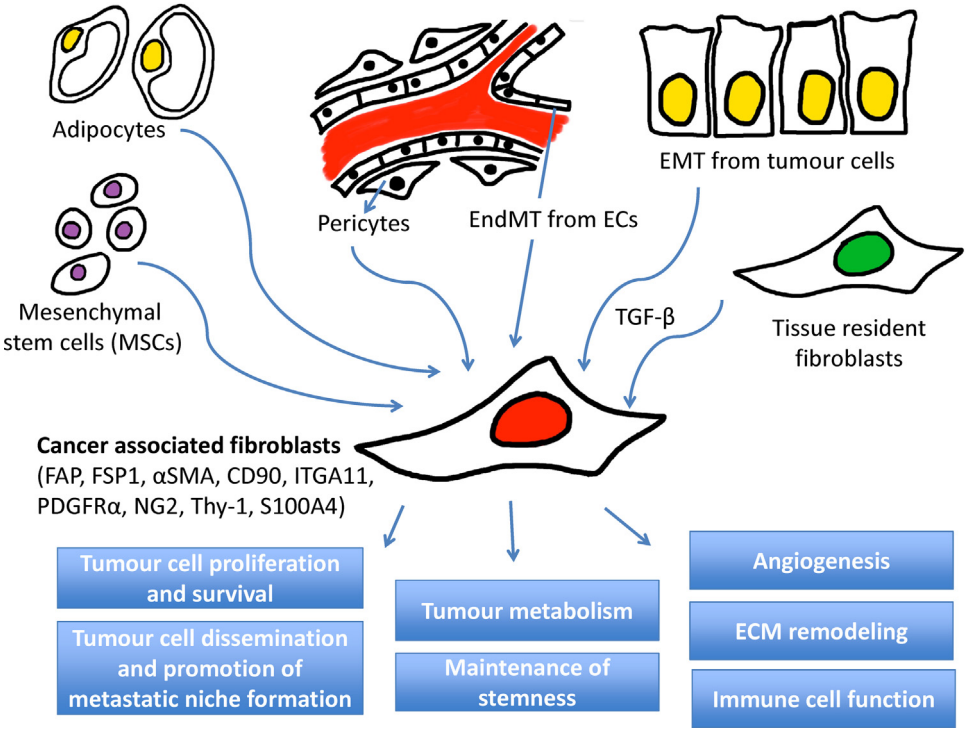

Fig. 1. Cellular origins of cancer associated fibroblasts and the processes by which they affect cancer progression. CAFs can originate from a variety of tissue types through a number of different cellular processes. These include EMT and EndMT from tumour epithelia and endothelial cells, respectively. They can also derive from pericytes, adipocytes and circulating mesenchymal stem cells originating from the bone marrow. Increased levels of transforming growth factor beta (TGF-β) in the microenvironment can also cause resident tissue fibroblasts to acquire a CAF phenotype, which is associated with expression of a variety of CAF-specific markers (as indicated). Once present in the tumour microenvironment, they can affect tumour growth, survival, progression and dissemination through the processes stated.

observed during wound healing. However, unlike wound healing, the activated phenotype of CAFs is not reversible and is long lasting. Inactivation of both P53 and PTEN have been described in CAFs that are in close proximity to tumour cells, suggesting that these cells could originate, like cancer cells, through genetic alteration which could partially explain the non-reversibility of their activated phenotype [18]. On the other end, an important source of CAFs seems to be mesenchymal stem cells (MSCs) residing in the bone marrow. MSCs were shown to be attracted to and to proliferate within the tumour microenvironment to become myofibroblasts [19,20]. For example, human bone marrow-derived MSCs were shown to acquire an activated CAF phenotype solely upon culture with conditioned media obtained from tumour cells [21]. In breast cancer, myofibroblasts have been demonstrated to trans-differentiate from epithelial cells (via EMT) [22] and this may constitute another source of CAFs. Similarly endothelial cells have been described as undergoing transformation into fibroblast-like cells through the action of TGF-β. This involves the delamination of endothelial cells and the down-regulation of E-cadherin in a process described as endothelial to mesenchymal transition (EndMT) [23]. Another cell type linked to blood vessels and demonstrated to be a source of activated fibroblasts is the pericyte. In fact, as demonstrated with endothelial cells, TGF-β triggers the trans-differentiation of quiescent perivascular pericytes into myofibroblasts to promote tumour growth and metastasis [24]. Finally, breast adipose tissue-derived stem cells were also shown in vitro to differentiate in CAFs when cultured in breast cancer cell line-conditioned media [25]. Understanding this diversity of origin and if these cells harbour the same [26] roles depending of their tissue of origin, remains a key task for scientist working in the field.

Similarly due to the various origins of CAFs, identification of definitive markers that distinguish CAFs from normal myofibroblasts is still challenging. The most used marker is de novo expression of α-SMA (smooth muscle actin) but this has been demonstrated to not exclusively label CAFs [27]. Due to this discrepancy, other markers have been used to identify CAFs and include FAP, which appears to be expressed selectively on pericytes and activated fibroblasts during tumour/stroma reaction, fibroblast specific protein 1 (FSP1), which regulates both cytoskeletal integrity and cell cycle progression, neuron–glial antigen-2 (NG2), CD90 [28], vimentin, integrin alpha 11, and platelet-derived growth factor receptor α/b (PDGFR α/β). Although we now have a bigger toolbox of potential markers to identify, isolate and study CAFs, it is clear that none of these markers can identify all CAFs and that each CAF, even within the same tumour, may not express all these markers.

A large body of scientific literature now supports the tumour-promoting role of CAFs [29], and a number of pro-tumourigenic properties have been assigned to CAFs. These include the modulation of the stroma in a paracrine fashion through the release of factors involved in the degradation of the extracellular matrix (ECM), a process that is critical for the growth, invasion and dissemination of cancer cells. These factors include plasminogen activators and matrix metalloproteinases [30]. As mentioned above, CAFs are not only a direct source of growth factors (such as HGF, VEGFA, b-FGF and EGF), but they can also release these factors via proteolysis of the ECM by secreting the necessary proteases. Another role attributed to CAFs is the establishment of the metastatic niche (the seed and soil hypothesis). The idea is that early stroma activation can subsequently contribute to the homing of metastatic tumour cells. In contrary, a recent study suggests that long term interactions between CAFs and tumour cells in lung cancer are required before normal mouse lung fibroblasts can acquire a secretory CAF-like signature, which results in the release of IL-6 and CLCF1 that exert paracrine effects to promote tumour growth [31]. This may argue that the CAF phenotype appears subsequently to the tumour cell phenotype. CAF have been extensively linked to the