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Activation of fibroblasts in skin cancer

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Abstract

Fibroblasts have emerged as a dominant component of the tumour microenvironment, but despite the surging interest in the activation of fibroblasts and their role in cancer, they remain an elusive and complex cell-type. In this review, we discuss recent findings on cancer-associated fibroblasts in melanoma and non-melanoma skin cancer obtained by genome-wide transcriptomic studies and focus on the molecular pathways underlying their activation. These studies reveal distinct fibroblast activation profiles depending on tumour type and stage. A better understanding of skin CAF heterogeneity in origin and function will guide novel therapeutic approaches targetting this cell-type in clinical cancer care.

Introduction

Fibroblasts are mesenchymal spindle-like cells that provide structural integrity for connective tissue by production and maintenance of the extracellular matrix (ECM), and are involved in coordinating the function of other cell-types within tissues. Fibroblasts reside in the dermis and are largely quiescent in homeostatic skin conditions. They become activated in inflammatory conditions and wound repair, but also during cancer development and are then referred to as cancer-associated fibroblasts (CAFs) (Kalluri 2016; Lynch and Watt 2018). Tumour-promoting as well as tumour-suppressive functions have been attributed to skin CAFs (Rinkevich et al. 2015; Siljamäki et al. 2020; Zhou et al. 2016). CAFs can affect tumour initiation and progression in distinct ways (Figure 1). They are a major source of growth factors (GFs) enabling CAF proliferation and invasion in an autocrine fashion or promoting tumour growth by paracrine signalling (Kalluri and Zeisberg 2006). CAFs also produce angiogenic factors,

inducing growth of new blood vessels or influencing vascular permeability, thereby affecting immune cell infiltration, cancer cell invasion, oxygen supply and sensitivity to therapeutics (Dvorak et al. 1999; Fukumura et al. 1998; O'Connell et al. 2011). Furthermore, CAFs secrete cytokines that reprogram the microenvironment by immune cell recruitment, activation or suppression (De Boeck et al. 2013; Erez et al. 2010; Monteran and Erez 2019; Tjomsland et al. 2011). CAFs directly alter the metabolism of cancer cells by providing energy-rich metabolites, such as lactate, ketone bodies, fatty acids and amino acids (Martinez-Outschoorn et al. 2014).

CAFs remodel the ECM during tumorigenesis. Matrix-crosslinking enzymes increase ECM stiffness, altering integrin signalling which perturbs epithelial morphogenesis and induces pro-survival and pro-proliferation signalling (Paszek et al. 2005; Zeltz et al. 2020). Matrix proteases can cleave the basement membrane facilitating invasion into surrounding tissue, or remodel the ECM in a way that generates permissive tracks enabling migration of immune cells or cancer cells (Gaggioli et al. 2007; Walker et al. 2018). Moreover, ECM has immunomodulatory functions as it acts as a reservoir for growth factors and cytokines and provides ligands for cell surface receptors (Bhattacharjee et al. 2019). ECM alteration by CAFs changes the adhesive properties of cancer cells which can drive epithelial-to-mesenchymal transition (EMT), enabling cancer cells to resist therapy and metastasize (Costea et al. 2013; Dongre and Weinberg 2019; Lochter et al. 1997; Wang et al. 2018). Recent studies have unveiled distinct embryonic origins of the different fibroblast populations that reside in the dermis, and lineage-specific depletion of fibrotic dermal cells results in reduced melanoma growth (Driskell et al. 2013; Rinkevich et al. 2015).

Here, we summarize the phenotypic plasticity of CAFs in skin cancer, thereby focussing on the three most common cutaneous cancers: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. We discuss recent insights into skin CAFs based on genome-wide transcriptomic studies. Subsequently, we address how heterogeneity of fibroblasts relates to their function in tumour control.

Skin CAFs: insights obtained by genome-wide transcriptomic studies

Fibroblasts enhance their proliferative capacity during skin tumorigenesis and are activated to stimulate epithelial growth (Erez et al., 2010). They constitute a major component of the skin tumour microenvironment in both melanoma and non-melanoma skin cancer. BCCs and SCCs represent the most common non-melanoma skin cancer types. BCCs are slow-growing tumours that can locally invade into the underlying stroma, but rarely metastasize. They initiate out of basaloid keratinocytes in the interfollicular epidermis and the upper infundibulum (Youssef et al. 2010), and are often associated with uncontrolled activation of Hedgehog signalling (Hutchin et al. 2005). SCCs are more

aggressive than BCCs and arise from stem cells in the hair follicle bulge and interfollicular epidermis (Lapouge et al. 2011). As skin CAFs represent a complex population of different fibroblast subtypes, genome-wide transcriptomic studies and especially single-cell RNA sequencing (scRNAseq) efforts will be indispensable to deconvolute their diversity and functionality.

Recent skin cancer profiling studies have revealed distinct fibroblast clusters with differential gene expression profiles in both melanoma and SCC (Puram et al. 2017; Tirosh et al. 2016). The first large scale scRNAseq study on human melanoma profiled multiple primary and metastatic lesions (Tirosh et al. 2016). CAF abundance was shown to vary between tumours and melanomas with a high CAF abundance correlating with a drug-resistance phenotype. CAF-exclusive expression of complement genes was associated with enhanced T-cell infiltration, demonstrating a potential crosstalk between these cell-types based on the complement system (Tirosh et al. 2016). In murine melanoma, subclustering of stromal cells based on global gene expression changes in scRNAseq data revealed three distinct populations: i) CAFs engaging in immune crosstalk, ii) fibroblasts expressing a fibrotic signature and iii) a contractile subset. In the early stages of tumour development, the first two subtypes were more prevalent, while in the later stages the contractile subset became more prominent. These fibroblast subtypes were largely conserved in mouse models for breast and pancreatic cancer and could be distinguished in human melanomas and SCCs (Davidson et al. 2020). In a heterogeneous spheroid model incorporating melanoma cell lines with human dermal fibroblasts, three distinct fibroblast clusters could be distinguished by scRNAseq, namely a fibroblast cluster upregulating genes related to the ECM, one expressing a pro-inflammatory gene signature and one upregulating genes of the TGF-β superfamily (Novotný et al. 2020).

scRNAseq analysis of primary and metastatic tumours from human SCCs identified three main fibroblast subsets: resting fibroblasts, myofibroblasts expressing alpha smooth muscle actin (α-sma) and CAFs. The CAF subset could be divided into two subtypes: i) CAFs expressing high levels of genes involved in ECM remodelling, such as several collagens, MMP11 and periostin; and ii) CAFs upregulating cytokines, GFs and GF receptors (Puram et al. 2017). This study also demonstrates that the relative amounts of CAF subtypes, evolves during the different stages of SCC progression. This was confirmed in a scRNAseq study on mouse oesophageal SCCs, describing transcriptional changes in fibroblasts at various pathological changes. In inflammatory, pre-cancerous skin lesions a predominant interferon response was observed, while high expression of chemokines and angiogenic signalling molecules was present in oesophageal SCCs (Yao et al. 2020).

These scRNAseq studies reveal that fibroblasts expressing pro-inflammatory genes coexist with fibroblasts expressing fibrotic markers within skin tumours. This dichotomy in CAF identity is also

apparent in microarray studies on fibroblasts isolated from murine squamous carcinomas. Microarray analysis on fibroblasts isolated from dysplastic skin regions in the keratin-14 human papillomavirus 16 (K14-HPV16) mouse model showed that CAFs express a pro-inflammatory gene signature (Erez et al, 2010), while fibroblasts isolated from squamous tumours in a mouse model expressing constitutively active MEK1 (MAP kinase kinase-1) showed a fibrotic signature (Van Hove et al., 2021). Interestingly, the latter study showed that overexpression of inflammatory genes is present in pre-cancerous inflamed skin, while the fibrotic gene signature dominates in CAFs, implicating that the relative contribution of these populations shifts during skin cancer progression.

Molecular activation of the CAF phenotype: iCAF versus myoCAF

During tumorigenesis, resident fibroblasts receive signals triggering their activation. The molecular mechanisms inducing the CAF phenotype in dermal fibroblasts involve a multiple step process with a central role for the Notch effector CSL (CBF-1 Suppressor of hairless Lag-2, also known as RBPJ) (Procopio et al. 2015). Both transforming growth factor-beta (TGF-β) and fibroblast growth factor 2 (FGF2) can activate human dermal CAFs. However, TGF-β stimulation generates CAFs that are α-SMA positive, produce large amounts of ECM and induce EMT, while FGF2 induces inflammatory CAFs promoting macrophage infiltration. Both CAF states are present in SCCs in varying proportions (Bordignon et al. 2019). Activation of dermal fibroblasts can result in expression of fibroblast activation protein-alpha (FAPα) and depletion of FAPα-expressing cells inhibits antitumour immunity and slows down tumour growth (Kraman et al. 2010). A recurring distinction made in CAF characterization is that between fibroblasts with a matrix-producing, contractile phenotype that typically express TGF-β, and fibroblasts with an immunomodulating secretome, which have been labelled 'myoCAFs' and 'iCAFs' respectively (Sahai et al. 2020). The fact that unbiased clustering of skin CAF scRNAseq data often results in a distinction between 'immune' and 'fibrotic' CAF populations, indicates that the iCAF-myoCAF paradigm holds true in cutaneous tumours (Figure 2).

MyoCAFs

The main function of fibroblasts is ECM production and remodelling, which can serve as an important barrier restraining tumour growth. However, myoCAFs can remodel the ECM in a way that promotes cancer progression (Kalluri and Zeisberg 2006; Lu et al. 2012). MyoCAFs represent a fibroblast subtype that can contract the ECM through interaction of cytoskeletal proteins with ECM proteins, resulting in ECM stiffening, which potentiates cell migration (Liu et al. 2019; Lu et al. 2012). Skin myoCAFs express α-sma, the prototypical fibrotic growth factor TGF-β and a range of ECM-remodelling enzymes, such as matrix metalloproteinases (MMPs). This fibrotic expression profile is partially shared with myofibroblasts present in wound healing (Costea et al. 2013; Rockey et al. 2013). Human SCCs and

BCCs express enhanced levels of MMP-2 relative to normal skin (O'Grady et al. 2007). MMP-13 is essential for the invasive growth of SCC cells in a murine tumour transplantation model (Vosseler et al. 2009). Other ECM remodelling enzymes that can influence skin tumorigenesis are PRSS35 and ADAMTS4 (Van Hove et al. 2021; Rao et al. 2013).

iCAFs

CAFs can display a secretory phenotype with immunomodulatory signalling functions (Kalluri 2016). These iCAFs secrete signalling molecules affecting recruitment and activation of immune cells and other cells, thereby suppressing or promoting anti-tumour immunity (Barrett and Puré 2020). Expression of the pro-inflammatory cytokines IL6, CXCL8, TNF, and VEGF was higher in CAFs from patients with head and neck SCCs compared to normal fibroblasts (Takahashi et al. 2015). As mentioned above, CAFs in a K14-HPV16 mouse SCC model display a pro-inflammatory gene signature, which was confirmed in human SCCs. These inflammatory CAFs stimulate macrophage recruitment and angiogenesis thereby promoting NF-κB dependent tumour growth. This pro-inflammatory program in CAFs can be induced by macrophage-specific production of IL-1β (Erez et al. 2010).

Conclusions

Transcriptomic studies reinforce the complexity of CAFs within skin tumours, but depict the existence of the myoCAF and iCAF substates, with relative abundances depending on tumour stage. The plasticity of skin CAF populations remains to be further elucidated as are their potencies to modulate immune reactions within skin tumours, but it is clear that the specific secretomes of CAF substates provide interesting therapeutic targeting opportunities.

Conflict of interest

The authors have no conflict of interest to disclose.

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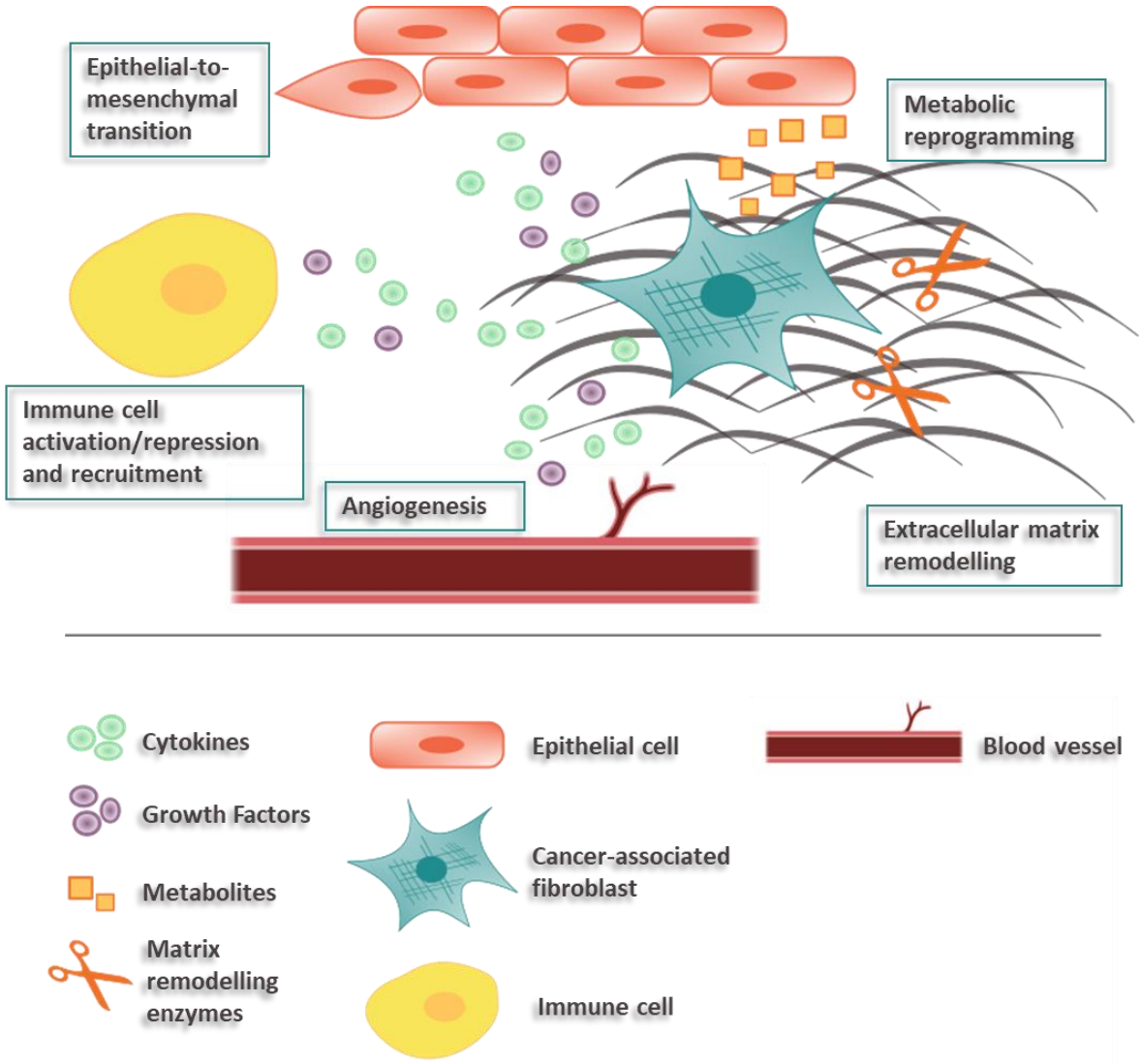
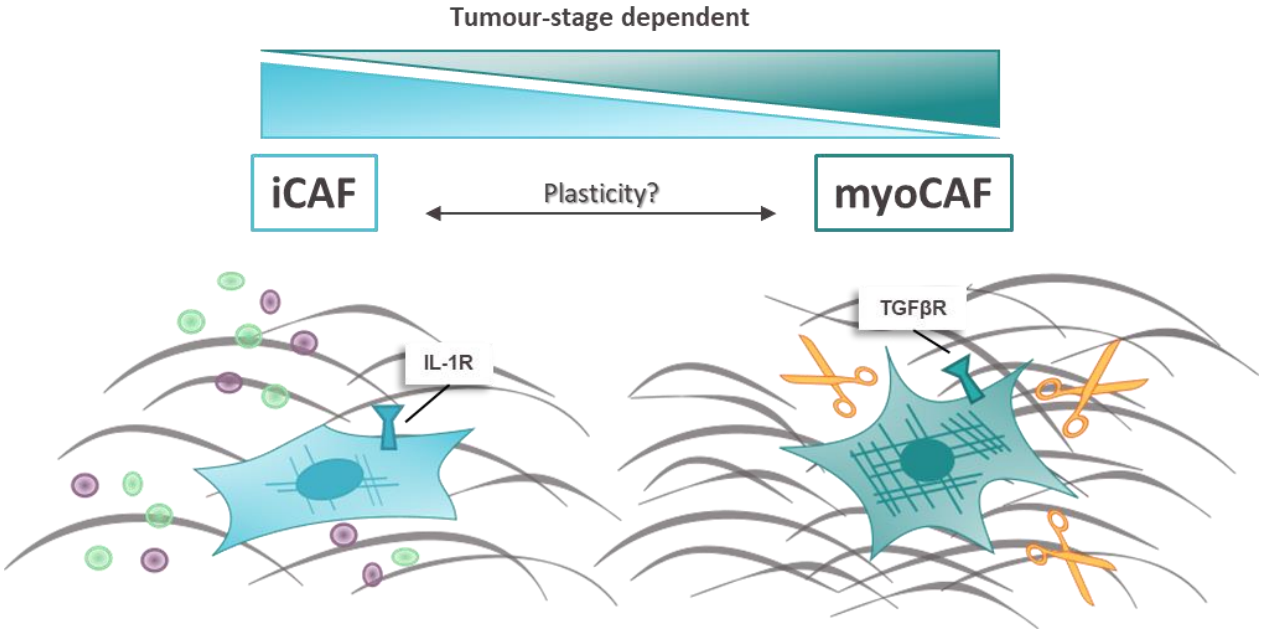


Figure 1: Regulation of the tumour microenvironment by CAFs



	iCAF	myoCAF	Refs.	
Activated by	IL-1β, FGF2	TGF-β	(Bordignon et al. 2019; Erez et al. 2010)	(Bordignon et al. 2019)
Produced proteins	IL-6	αSMA	(Qin et al. 2018; Takahashi et al. 2015)	(Davidson et al. 2020; Puram et al. 2017)
	CXCL8	ECM proteins	(Novotný et al. 2020; Takahashi et al. 2015)	(Costea et al. 2013; Davidson et al. 2020; Puram et al. 2017)
	IFN-β	Matrix remodelling enzymes	(Yao et al. 2020)	(Van Hove et al. 2021; Rao et al. 2013; Vosseler et al. 2009)
Functions	Immune regulation	Contractility ↑	(Erez et al. 2010; Tirosh et al. 2016)	(Davidson et al. 2020)
	Cancer cell stemness ↑	ECM remodelling↑	(Costea et al. 2013; Erez et al. 2010; Qin et al. 2018)	(Van Hove et al. 2021)

Figure 2: iCAF versus myoCAF