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Fibrocytes in the Tumor Microenvironment

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Abstract

Tumors have long been compared to chronic wounds that do not heal, since they share many of the same molecular and cellular processes. In normal wounds, healing processes lead to restoration of cellular architecture, while in malignant tumors these healing processes become dysregulated and contribute to growth and invasion of neoplastic cells into the surrounding tissues. Fibrocytes are fibroblast-like cells that differentiate from bone marrow-derived $CD14^+$ circulating monocytes and aid wound healing. Although most monocytes will differentiate into macrophages after extravasating into a tissue, signals present in a wound environment can cause some monocytes to differentiate into fibrocytes. The fibrocytes secrete matrix proteins and inflammatory cytokines, activate local fibroblasts to proliferate and increase extracellular matrix production, promote angiogenesis, and because fibrocytes are contractile, they also help wound contraction. There is now emerging evidence that fibrocytes are present in the tumor microenvironment, attracted by the chronic tissue damage and cytokines from both cancer cells and other immune cells. Fibrocytes may aid in the survival and spread of neoplastic cells, so these wound healing cells may be a promising target for anti-cancer research in future studies.

Keywords

Tumor; Microenvironment; Stroma; Cancer; Fibrocyte; Fibroblast; Myofibroblast; Monocyte; Scar; Wound; Fibrosis; Benign; Malignant; Metastasis

Introduction

A major advance in the understanding of tumor biology came in 1986 when Dvorak et al. published an essay detailing the similarities between tumors and chronic wounds that do not heal.[1] In the wound environment, repair of tissue damage was originally thought to be dependent upon fibroblasts which were quiescent cells resident in the local tissues that only became activated after tissue damage occurred. These local cells would then migrate to the site of injury, proliferate, and engage in tissue repair. Another school of thought held the possibility that the wound environment is populated in part by cells that originated from distant sites. Sir James Paget in his “Lectures on Surgical Pathology” first published the

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observation of circular mononuclear cells entering a wound site from the blood and transforming themselves into long spindle-shaped cells in the wound bed.[2] These cells were characterized in 1994 when Bucala et al. discovered the presence of large numbers of fibroblast-like cells coinciding with the entry of circulating inflammatory cells in wound chamber experiments. These cells, termed fibrocytes, were found to enter sites of sites of tissue injury and contribute to connective tissue and scar formation.[3]

Over the past 25 years there has been a significant amount of progress on research of the differentiation and roles of fibrocytes in physiologic and pathologic processes. Fibrocytes differentiate from a $CD14^+$ peripheral blood monocyte precursor population.[4] Fibrocytes express both hematopoietic (CD45, MHC II, CD34) and connective tissue markers (Collagen I and III and fibronectin).[3,4] Mature fibrocytes secrete inflammatory cytokines and extracellular matrix proteins to promote angiogenesis and wound contraction.[5,6] Fibrocytes can be specifically identified in culture by their unique co-expression of CD45RO, 25F9, and S100A8/A9, but not PM-2K. Fibrocytes also change expression of some markers with longer time in culture after differentiation from monocytes, including a loss of CD34, increased expression of Mac-2/galectin 3, and expression of CD49c.[7] Fibrocytes can further become activated by local inflammatory signals such as TGFβ and begin expressing α-smooth muscle actin, transitioning into myofibroblasts, as has been shown in bronchial asthma.[8] Fibrocytes are antigen presenting cells, participating in parts of the innate response to tissue damage and invasion.[9] Since their identification, fibrocytes have been found in a variety of disease processes, including aberrant wound repair such as hypertrophic scarring and keloid formation, fibrosing diseases such as idiopathic pulmonary fibrosis and myelofibrosis, and autoimmunity.[10–15] More recently, studies have also identified fibrocytes in neoplastic processes. In this chapter, we briefly review our understanding fibrocytes in the tumor microenvironment.

Fibrocytes in benign tumors

One of the first studies that described CD34 positive spindle shaped cells in benign and malignant tumors was the pathological study of skin lesions by Kirchmann et al. in 1994, the same year as the discovery of fibrocytes by Bucala and colleagues.[16] CD34 positive spindle shaped cells, which were likely fibrocytes, were found around trichoepithelioma, a benign skin tumor with follicular differentiation. Basal cell cancers were also surrounded by similar spindle cells, however the spindle-shaped cells did not appear to express CD34, leading the authors to conclude that a loss of CD34 expression was an indicator of malignancy.[16] This was a finding that was reproduced in many studies to come. Fibrocytes identified by spindle shaped morphology and CD34 expression were observed surrounding breast ducts containing intraepithelial hyperplasia, ductal carcinoma in situ (DCIS), fibroadenomas, and phyllodes tumors.[17] Of note, there was an observed loss of CD34 positivity as DCIS specimens were higher in grade, and a variable expression of αSMA in the different tumors.[17] Given these pathologic observations, one hypothesis is that local factors from the tumor influence the further differentiation of a fibrocyte into a myofibroblast, including loss of CD34 and gain of αSMA. As we will discuss more in the next section, the mechanisms and prognostic effects of this transition are not known at this time, but this staining pattern may be a method of differentiating benign from malignant processes. CD34 positive spindle

shaped cells have been observed to be interspersed in benign tumors of adipose tissue such as lipomas, angiolipomas, angiomyolipomas, and intramuscular lipomas.[18] Although this study did not specify that these cells were fibrocytes, the presence of CD34 staining on a spindle shaped cell strongly suggests that it is a fibrocyte.

Fibrocytes in malignant tumors

In 1997, Suster et al. reported one of the earliest descriptions of what were likely fibrocytes in malignant tumors.[18] They described $CD34^+$ spindle shaped cells that were present not only on benign fatty tumors but also on locally aggressive and malignant fatty tumors such as atypical lipomatous tumors, well-differentiated liposarcomas, myxoid liposarcomas, and the sarcomatous component of dedifferentiated liposarcomas.[18] Since then, multiple studies that we will describe below found $CD34^+$ fibrocytes in malignancies. These studies also often observed that the spindle-shaped cells show less CD34 expression in proximity to the tumor, and more expression of αSMA.[17,19–24] This may in fact reflect the transition of a fibrocyte to a myofibroblast in reaction to cytokines expressed by the tumor. This pattern has been found in pancreatic cancer, ductal carcinoma in situ and invasive ductal carcinoma of the breast, invasive lobular carcinoma of the breast, high grade cervical intraepithelial neoplasia and squamous cell carcinoma of the cervix, squamous cell carcinomas of the oropharynx and larynx, and urothelial carcinoma of the bladder.[17,19–23,25,26] Figure 1 shows immunofluorescent staining of fibrocytes in pancreatic adenocarcinoma and invasive ductal carcinoma of the breast. Instead of staining for CD34, we identified fibrocytes by colocalization of Collagen-I and CD45RO. We have found this to be a more accurate method to identify fibrocytes, as we and other groups have found CD34 expression to be lost as fibrocytes become more mature and activated.

To understand the possible of contribution of fibrocytes to tumor growth, we will discuss the stroma of pancreatic adenocarcinoma in more detail, as it is known to have a strong desmoplastic component, in that the majority of the tumor volume is fibrotic stroma rather than neoplastic cells.[27] The tumor cells of solid tumors such as pancreatic cancer attract fibrocytes through paracrine signaling. These solid tumors produce Th2 cytokines such as interleukin-4 and 13, and high expression of these cytokines have been linked to cancer cell survival, invasion, and metastasis, and poor prognosis.[27–32]

We previously found that Th2 cytokines such as IL-4 and IL-13 promote fibrocyte differentiation from monocytes.[34] This desmoplastic reaction also promotes angiogenesis, resulting in numerous disorganized, small, leaky blood vessels and capillaries that provide the tumor cells with oxygen.[35] This environment created by the tumor cells and the tumor stroma drives forward its own progression in a positive feedback cycle by production of factors such as transforming growth factor β (TGF-β), matrix-metalloproteinases (MMPs), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF).[36] In pancreatic ductal adenocarcinoma, $\alpha\text{-SMA}^+$ myofibroblasts form thick sheets surrounding the infiltrating tumor cells. In the pancreatic tissue surrounding the tumor, there is a local concentration of CD34+ fibrocytes around the infiltrating border of the carcinoma. The gradient from tumor-free tissue to invasive carcinoma reveals an abrupt loss of the CD34 positivity.[19] One explanation for this could be

that after $CD34^+$ fibrocytes are recruited to the edge of the expanding tumor, they begin secreting ECM and become trapped by abundant ECM and new fibrocytes, myofibroblasts, and stellate cells being recruited around them. Once they are trapped and come under the influence of paracrine signals such as TGF-β, they lose CD34 expression and increase α-SMA expression, thereby becoming a contractile myofibroblast and secreting even greater amounts of ECM in a futile attempt to seal this ever growing wound environment, unknowingly also contributing to tumor survival by secreting growth factors and promoting angiogenesis. Fibrocytes secrete many of the growth factors found in the tumor microenvironment, such as PDGF, VEGF, TGF-β, MMP-9, and FGF, and these could enhance neoplastic cell proliferation by a paracrine effect.[36,37] ECM proteins such as collagen and fibronectin that are produced by fibrocytes have been shown to contribute to proliferation, survival, metastasis, and drug resistance of cancer cells.[38–45] Bone marrow derived fibrocytes were also found to be the source of cancer-associated fibroblasts (CAFs) in a mouse model of gastric cancer, and caused significantly larger tumors when inoculated along with the cancer cell line.[46]

Fibrocytes also appear to contribute to resistance of cancer to therapeutic drugs. In mouse models of malignant pleural mesothelioma and lung cancer, fibrocytes were found to mediate resistance to bevacizumab, an FDA-approved VEGF inhibitor used as a treatment for several cancers, by production of fibroblast growth factor 2 (FGF2).[47]

Fibrocytes in metastasis

Following in his aforementioned father's footsteps, the surgeon Stephen Paget contributed a profound theory to cancer research in his "seed and soil" hypothesis. He suggested that the metastasis of cancer is not coincidental and just a matter of random travel through blood vessels of lymphatics, but that a receptive microenvironment must be present for malignant cells to establish a metastatic tumor.[48] Recent studies have shown that fibrocytes are one of the cell types that are necessary for tumor metastases. In a mouse model of melanoma, fibrocytes were found to prepare lungs for pulmonary metastases by recruiting Ly-6G monocytes, and the process was dependent on MMP9, CCL2, CCR2 and CCR5.[49,50] Fibrocytes have also been observed in liver metastases in a mouse model of colon cancer, and in this study fibrocyte recruitment was dependent both on $CCR1^+$ neutrophils and subsequent expression of MMP2 and MMP9.[51] Another study found that myeloid-derived suppressor cells (MDSC) may ultimately be the source of fibrocytes in cancer metastases, and that by inhibiting monocyte differentiation from these MDSCs by knocking out Kruppel-like factor 4 (KLF4) in a mouse model, there were significantly less fibrocytes and myofibroblasts in the lungs and significantly fewer pulmonary metastases of melanoma and breast cancer cell lines[52].

In addition to being present in the stroma surrounding solid tumors, one study has identified higher numbers of fibrocytes in the circulating blood of metastatic cancer patients. These fibrocytes were identified as a novel subset of circulating MDSCs which were expanded in metastatic pediatric sarcoma patients but absent from healthy controls.[53] These cells expressed previously described fibrocytes markers including CD34, CD45, HLA-DR, αSMA (for activated fibrocytes), Collagen I/V, MMP9, S100A8/A9, fibronectin, and LSP-1,

and had the capability to produce ECM and promote angiogenesis, however these cells functioned as immune suppressors rather than antigen presenting cells as in healthy controls. In the same study, fibrocytes from cancer patients inhibited T-cell proliferation in vitro through production of indoleamine oxidase.[53] Taken together, this work suggests that fibrocytes may have a role in global immune suppression in addition to their local effects in the tumor microenvironment, and as a result help metastatic tumor cells initiate new tumors.

Conclusion and Future Directions

Fibrocytes appear to play an important role in the tumor microenvironment, likely participating in most if not all of the hallmarks of cancer as described by Hanahan and Weinberg, which include activating invasion and metastasis, inducing angiogenesis, resisting cell death, sustaining proliferative signaling, and evading growth suppressors.[54] As demonstrated by the recent successes with immunotherapy, the next frontier of cancer treatment is to continue learning how to harness the normal cells of the body in order to prevent and fight cancer growth. Further research in controlling fibrocytes and their signals for differentiation may become an attractive target for new methods of anti-cancer therapeutics.

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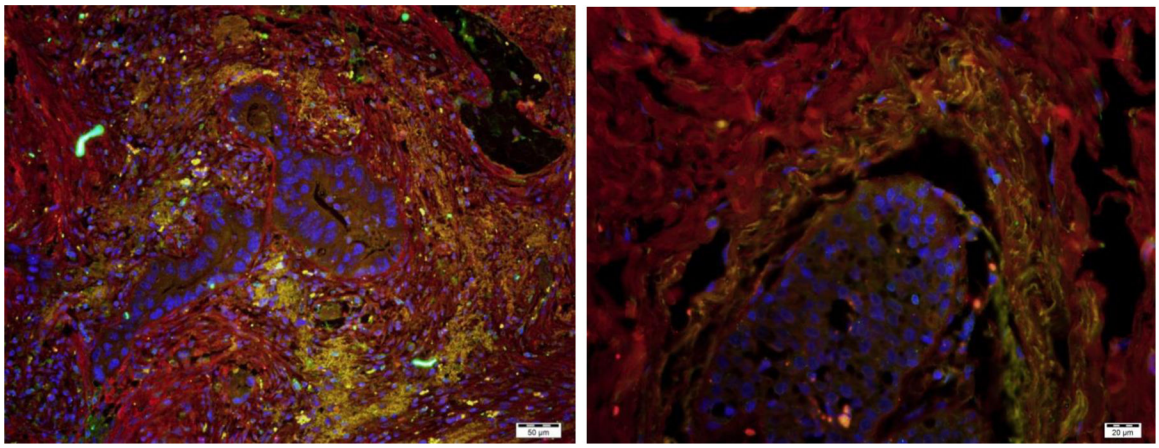

Figure 1:

Fibrocytes surrounding neoplastic ducts in pancreatic adenocarcinoma (left) and invasive ductal carcinoma of the breast (right). The fibrocytes are identified by co-expression (yellow) of Collagen-I (red) and CD45RO (green). DAPI staining of nuclei is shown in blue. Bar is 50 μm on left, 20 μm on right.