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ROLE OF CANCER ASSOCIATED FIBROBLASTS IN SOME COMMON CANCERS WITH SPECIAL FOCUS ON CXCL12 – CXCR4 AXIS

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Abstract: Cancer immunotherapy has been rendered largely ineffective due to the presence of the tumor microenvironment (TME). The importance of TME has been looked over for a long time and now it is essential that we give back its fair amount of attention. The TME is made up of a diverse group of cells and cancer associated fibroblasts (CAFs) are the most abundant. Tumor cells modulate fibroblasts to differentiate into CAFs, which becomes anatomically and functionally different from normal fibroblasts. CAFs express markers like fibroblast activation protein (FAP) and α smooth muscle actin (αSMA). They interact with tumor cells and impart an anti-apoptotic effect. It also induces cell proliferation, migration, invasion as well as reducing T cell infiltration. This review encompasses the role of CAFs in some cancers such as hepatocellular carcinoma, pancreatic cancer, gastric cancer, squamous cell carcinoma and breast cancer. Although CAFs interact through several pathways, a major part of the interaction occurs through the CXCL12-CXCR4 axis. CAFs secrete the chemokine CXCL12 which binds to its G protein coupled receptor CXCR4 on the tumor cells and tumor associated immune cells to induce downstream cascades leading to above mentioned effects. Several research groups have tried using molecules like BL-8040 and AMD3100 to inhibit the receptor CXCR4 with positive outcomes. However, this domain of research is still in its infancy and needs further investigation in order to come up with clinically viable drugs.

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Introduction

Immunotherapy has been in the limelight of cancer treatment for the last couple of decades and has made significant strides in the last decade. Recent discoveries regarding immune checkpoints has opened new horizons of treatment. The presence of T cells in tumor microenvironment has been directly related to better prognosis in patients for various malignancies. Intra-tumoral infiltration of T cells is a positive prognostic marker for colorectal and ovarian cancers (Leun et. Al. 2020). Harnessing this power of the T cell mediated immune response by inhibiting their regulatory signalling has led to several investigations with positive outcomes. The role of Forkhead box P3 (FOXP3+) regulatory T cells in cancer progression and immune evasion has been elucidated. In addition, inhibitors of checkpoint proteins such as cytotoxic T lymphocyte antigen – 4 (CTLA – 4) and programmed cell death protein – 1 (PD – 1) have been developed (Webb et al., 2018) (Odunsi, 2017).

Studies revealed that melanomas with enriched mutations in DNA repair genes like BRCA2 responds well to the treatment. However, there are tumors that bears an innate resistance to the immunotherapy. One such group is termed as IPRES or Innate anti-PD-1 Resistance. These group of tumors reveals overexpression of genes involved in ECM remodeling, mesenchymal transition and angiogenesis (Hugo et.al., . 2016). The limited success due to theseshortcomings depends largely on the presence of tumor microenvironment (TME). TME plays a major role in protecting tumors from an effective immune response. The TME consists of several cells but the majority are cancer associated fibroblasts (CAFs). CAFs are

responsible for maintaining and regulating the TME. It produces a niche that renders cytotoxic T lymphocytes (CTLs) inactive, in both primary cancers and metastases (Bai et al., 2008). The recruitment of several immunosuppressive cells such as regulatory T lymphocytes (Treg), tumor associated macrophage (TAM), myeloid derived suppressor cells (MDSC) is also performed by CAFs through secretion of various cytokines (Liu & Cao, 2016). In addition, CAFs also reduces the infiltration of cytotoxic T lymphocyte populations (I. X. Chen et al., 2019).

Chemokines are a group of cytokines which induce migration in a myriad of cells including malignant epithelial cells. They are classified based on the number of non-conserved amino acid residues between the N terminal cysteine residues: C has only one cysteine residue, CC has no amino acid residue between the cysteine, CXC has one and CX3C has three non-conserved amino acid residues between them. Cytokines bind to their G protein coupled receptors (GPCRs) which activates several downstream receptors (Cojoc et al., 2013).

Based on the above knowledge, it is key to study these cells of the tumor microenvironment. Hence, it is important to review the cancer associated fibroblasts in this article. This review will discuss critical concepts such their origin, specific markers that they bear, molecular mechanisms regarding their role in tumor progression and few immunotherapeutic strategies against CAFs.

What are cancer associated fibroblasts and how are they different from peri tumor fibroblasts?

The tumor microenvironment or the tumor stroma consists of different cell types and cancer associated fibroblasts (CAFs) are one of them. These are also known as tumor associated fibroblasts (TAFs). The origin or predecessors of CAF is a debatable topic and there is no conclusive experimental data. Rather, several studies claim that they have a varied lineage. Bone marrow derived mesenchymal stem cells, peri tumor fibroblasts, resident fibroblasts are some of the contenders (Shiga, Hara, Nagasaki, Sato, & Takahashi, 2015).

Cancer associated fibroblasts have typically cytoplasmic protrusions smaller than those of regular fibroblasts and are often arranged in an un-orderly manner. Contact inhibition is also absent in CAFs. The loss of contact inhibition is a typical characteristic of a cancer cell(Ba et al., 2019) (Hanahan & Weinberg, 2011). Unlike tumor cells, CAFs seldom undergo genetic alterations. Post transcriptional and translational modifications are more common in them. Also, histone modifications, DNA methylation, changes in non-coding RNA like epigenetic variations has been reported by various research groups (Qiu et al., 2008).

CAF markers

Biomarkers are quantifiable indicators of certain pathological conditions. Several research groups have revealed that cancer associated fibroblasts show increased expression of several cell surface, cytoskeletal and secretory proteins that are designated as markers for cancer associated fibroblasts. The expression of such proteins are otherwise moderate in other fibroblasts such as the myofibroblasts or the peri – tumor fibroblasts.

One of the most prevalent and studied cell surface marker for CAFs are integrins. Integrin subunit α3β1 has high expression in CAFs, whereas they are expressed in low to moderate amounts in regular fibroblasts. Such over-expression in vulvar and pancreatic cancers positively correlates with augmented migration of tumor cells as well as maintenance of CAFs. Expression of subunit α5β1is even higher in squamous cell carcinoma and vulvar cancers. In a pro – metastatic niche, integrin α4β1is expressed, which is a receptor for fibronectin. Fibronectin is a pro – angiogenic protein and this interaction leads to a setting for secondary tumor formation. In addition, head and neck carcinoma, non-small cell lung cancer, breast cancer along with other several cancers revealed a hyper expression of integrin subunit α11β1 in the cancer associated fibroblasts. Activities like CAF migration, collagen remodelling are reported when such over expression takes place (Chen & Song, 2019).

In addition, fibroblast activation protein (FAP) and α smooth muscle actin (αSMA) are two widely studied

markers in the CAFs and TME. FAP is a cell surface serine protease which has a low/negligible expression in normal fibroblasts but are overexpressed in activated fibroblasts in tumor stroma.Processes such as wound healing, tissue remodelling and activation of fibroblasts in the stroma requires FAP (Mhawech-fauceglia et al., 2015). siRNA mediated silencing of FAP in attenuates proliferation and reduction in production of ECM components such as collagen I, laminin and fibronectin. Overexpressing results in inflammation, proliferation and ECM remodeling factors (Puré at. Al. 2018).

Similarly, αSMA (α smooth muscle actin) are the actin proteins which are primarilyexpressed in the smooth muscle cells, myofibroblasts. Along with FAP, αSMA is markerwidely used to screen CAFs in both benign and malignant tumors. Vimentin, fibronectin, FAP and αSMAs are expressed in fibroblasts associated with cancer (Da Silva, Jammal, Etchebehere, Murta, &Nomelini, 2018). It plays a role in myofibroblast contraction and regulation of microtubule and stress fibers. Expression of αSMA has been correlated to recurrence of colon cancer and lower survival in breast cancer patients (Nurmik et. Al. 2020).

Role of CAFs in tumor physiology

A myriad of recent studies has tried to examine the role of CAFs in several types of solid tumors such as hepatocellular carcinoma, pancreatic cancer, breast cancer, gastric cancer and squamous cell carcinoma.

A. ***Hepatocellular Carcinoma (HCC).*** Fibrosis and cirrhosis is when the liver presents an ideal premalignant environment (PME). Data suggests that 80 – 90% of the HCC arises in the fibrotic liver. Such fibrosis occurs mainly due to the accumulation of collagen fibers along with other ECM proteins. Liver fibrosis can be determined using αSMA as a positive marker of myofibroblasts. Myofibroblasts are differentiated fibroblasts before they further differentiate into smooth muscle cells.Such conditions are present not only in PME but also in the hepatic TME. Clinical data correlates decreased survival rates, recurrence and augmented metastasis in HCC patients having higher levels of αSMA (Wang et al., 2013).

The underlying molecular mechanisms behind the complex interactions among the myofibroblasts and tumor cells is not still clear. However, the presence of increased collagen and other ECM proteins alters the behaviour of the tumor and stromal cells (Carloni, Luong, &Rombouts, 2014). The cells have an increased expression of integrins which helps them to receive signals from the extracellular environment. Integrin signalling induces numerous cascades like mitogen activated protein kinase (MAPK) and phosphoinositide 3 kinase (PI3K). Such signalling cascades are widely considered to promote cell proliferation, differentiation, survival and metastasis (Yang, Sau, Lai, Cichon, & Li, 2015).

In addition, liver provides a favourable site for metastases from colorectal and breast cancers. Such secondary cancers increase complications in patients and result in death. Many researchers have identified that CAFs express and induce expression of many proliferation markers via CXCL12-CXCR4 axis. Blocking the chemokine receptor (CXCR4) with antagonist AMD3100 *in vivo*resulted in reduction of metastatic foci in the liver and attenuated SMA expressing cell recruitment (Benedicto, Romayor, &Arteta, 2018).

B. ***Pancreatic cancer.*** As mentioned earlier, CAFs have a varied lineage. Mesenchymal stem cells (MSCs), which are derived from bone marrow, serve as a potent source of CAFs. In addition, pancreatic stellate cells (PSCs) and native fibroblasts also give rise to CAFs via numerous cascades of activation. Epithelial to mesenchymal transition (EMT) plays a prominent role in such activation. Factors like tumor necrosis factor α (TNFα), tumor growth factor β (TGFβ), interleukins (ILs), cytokines and other growth factors are involved in these pathways (Apte et al., 1999)(Mews et al., 2002).

A research group from National and Kapodistrian University of Athens, Greece tried immunostaining methods to identify fibroblasts and myofibroblasts in pancreatic ductal carcinoma (PDAC). Proteins like vimentin and αSMA were targeted due to their abundance in CAFs. The results revealed a dense distribution of αSMA+ cells in the stroma of the tumor. These cells also formed a ring around any structure bearing carcinoma. However, the density reduced significantly around blood vessels. (Lakiotaki et al., 2016).

C. ***Gastric cancer (GC).*** Although infections and inflammation has been largely considered responsible for gastric cancers, the role of CAFs are being taken seriously these days. A research group noticed that IL-6 is often detected in tissues of gastric cancer. The cells secreting IL-6 also stained positive for αSMA, a marker for CAFs. In a gastric tumorigenesis model (N-methyl-N-nitrosourea being the carcinogen), they knocked out IL-6 (IL-$6^{-/-}$ mice) and compared them with the wild type (WT). The IL-$6^{-/-}$ mice revealed a significant decrease in development of tumor compared to the wild type. *In vitro*, fibroblasts cultured in gastric cancer cells – conditioned media presented an augmented increase in IL-6 production (Kinoshita et al., 2013).

In a similar study pertaining to IL-6 secretion by CAFs, investigators have shown that the epithelial to mesenchymal transition (EMT) in GC cells takes place under the influence of IL-6. The induction of EMT occurs via JAK2/STAT3 pathway. Furthermore, inhibition of the pathway attenuates the phenotype in the tumor cells (Wu et al., 2017).

In addition, CAFs are known to secrete the chemokine CXCL12. The GC cells have its cognate receptor CXCR4, which produces a signalling cascade augmenting clustering of integrin β1 in these cells leading to progression of gastric cancer (Izumi et al., 2016).

D. ***Squamous cell carcinoma (SCC).*** The stromal cells, including CAF, provide support to certain SCC cells as many of them are unable to sustain a growing and surviving environment for themselves (Tarin, 2011). The fibroblasts are induced by tumor cells to express a pro inflammatory gene signature which is a typical characteristic of CAFs. This includes genes like CXCL1, CYR61, IL – 6, Cox – 2 and IL - 1. Such gene expression leads to inflammatory response and recruitment of macrophages. Also, angiogenesis is stimulated in the presence of such conditions(Erez, Truitt, Olson, & Hanahan, 2010).

Moreover, tongue cancer associated fibroblasts (TCAFs) present an average 4-fold increase in secretion of stromal derived factor 1 (SDF1) when compared to normal fibroblasts. SDF1 is also known as CXCL12, which is known to promote invasion and metastasis of tumor cells (Zhou et al., 2014).

E. ***Prostate cancer.*** Studies have reported that the secretion of tumor growth factor β (TGF β) is responsible for the presence of CAFs in the tumor microenvironment (TME). TGF β1attracts mesenchymal stem cells (MSCs) to prostate cancer and stromal components in the TME. It is also responsible for further differentiation of the MSCs into cancer associated fibroblasts (Barcellos-de-Souza et. Al. 2016).

CAFs promote angiogenesis in the tumor by expressing increased levels of SDF1. The SDF1, in turn, induces the recruitment of endothelial progenitor cells (EPCs) which promotes angiogenesis. Furthermore, the SDF1 works as a growth factor and enhances the proliferation of the tumor via a SDF1-CXCR4 signalling cascade, where CXCR4 is the chemokine receptor expressed on the carcinoma cells of human breast cancer (Orimo et al., 2005).

Immunotherapeutic strategies against CAFs

Owing to the vast array of modulation of tumor growth and extensive tumor cross talks that CAFs undertake, they have become a novel target to develop anti-cancer immunotherapies. In a recent experiment, a group of investigators co–cultured dendritic cellsfrom bone marrow BALB/c mice with CAFs from H22 mouse hepatoma cells. The fusion of CAFs expressing FAP and αSMA with the DCs produced cytokines like TNF-α, IL-1β, IL-6, and IL-12p70. This vaccine efficiently stimulates cytotoxic T cells which generated strong CTL response against CAFs *in vitro* and could inhibit growth of H22 xenografts *in vivo*(Qian et al., 2018).

In another study from Harvard Medical School, the researchers presented a reduction in immunosuppression and fibrosis in murine metastatic breast cancer models by inhibiting the CXCL12 receptor, CXCR4, using the drug plerixafor containing the molecule AMD3100. They even confirmed this claim by deleting CXCR4 in CAFs and other αSMA+ cells (Chen et al., 2019).

Summary

Tumor microenvironment and its associated cells were thought to be a mere physical support and their effect in cancer physiology remained largely obscured for a very long time. Upcoming research in this domain of tumor biology will provide a holistic approach in our understanding of this complicated disease. Although several molecules targeting CAFs are in clinical and pre-clinical trials, yet many questions remain unanswered.

There is no conclusive information regarding the lineage and precursors of CAFs, which makes it difficult to trace their origin. In addition, CAFs share its protein markers with other cells in the TME and remains one of the concerns regarding their isolation. Data suggests that CAFs use several molecular pathways for its interaction and functioning. Although, the omnipresence of CXCL12-CXCR4 axis seems to make it their favourite choice. Plerixafor is a CXCR4 antagonist which has been approved by the FDA and other molecules, such as BL-8040, are in the pipeline (Borthakur et al., 2014). However, molecular details and characterization of this infamous signalling pathway needs careful consideration in order to decipher its role tumor physiology.

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