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The Mechanism by Which CAFs Maintain the Tumor Cell Stemness to Promote Tumor Drug Resistance

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Abstract: Cancer fibroblasts (CAFs) are the most abundant stromal cells in the solid tumor microenvironment (TME), many different CAF subtypes regulate the TME directly or indirectly. CAFs are an important cell population that promotes tumor cell stemness and maintains the function of cancer stem cells (CSCs). CSC is a kind of special cells that have the characteristics to continue forming some new tumor cells. They play an important role in tumor recurrence and drug resistance. They are the important factors that affect the effectiveness of cancer treatment. At present, the effectual methods that directly target the tumor stem cells are still exploring, but the CAFs can affect the proliferation and growth of CSCs through direct contact between cells and secretion of factors to promote signal pathways, thereby providing a suitable microenvironment for CSCs. Some CAF subtypes have been identified now, but not all, and the mechanisms by which CAFs affect tumor progression still need to be researched. This review analyzes the different sources of CAFs, the role of secreted factors in promoting cancer stemness and drug resistance, also about the regulatory and remodeling role of CAFs in ECM. To summarize how to deal with the cancer-promoting effect of CAFs, thereby reducing their influence on stemness and drug resistance. Therefore, to review how CAFs promote tumor cell stemness to enhance their drug resistance and discuss and analyze the therapy with CAFs, to develop therapy strategies based on the origin of CAFs and the mechanism of CAFs promoting cancer.

Keywords: TME, CAFs, Cancer stemness, drug resistance.

1. Introduction

TME refers to the ecological environment outside the tumor cells, which is composed of various immune cells, endothelial cells, CAFs, extracellular matrix (ECM), and a variety of cytokines present in the ECM.

As an important component of TME, CAFs affect the biological characteristics of tumors before they occur and participate in the entire process of tumor development [1]. Their infiltration degree is positively correlated with tumor progression and resistance after chemotherapy, playing an important role in cancer progression [2]. CAFs are a complex group. Most of them exhibit tumor-promoting effects [3], and a small part of them exhibit tumor-suppressing effects. A major manifestation of CAFs in promoting tumors is that they promote the acquisition of tumor cell stemness and thus promote tumor drug resistance. How to regulate this process to reduce the drug resistance caused by tumor stemness is the key point of current research and analysis.

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Since 2020, researchers have focused on exploring the characteristics of different CAF subpopulations. For example, some researchers have found that the GPR77+/CD10+ CAF type is linked to the drug resistance observed in breast cancer cells. They enhance the stemness of CSCs through dormant microenvironments and growth factors. In addition to exploring the mechanism more deeply. Research has found that CAFs can activate multiple signaling pathways (such as the TGF-β/SMAD pathway) to play a role in TME to affect tumor stemness. For example, factors like TGF-β and CXCL6 are secreted by CAFs can enhance their stemness characteristics. CAFs can also affect CSC through their metabolites. CAFs in a senescent state will produce a senescence-associated secretory phenotype (SASP), thereby enhancing the stemness of tumor cells, leading to increased resistance to chemotherapeutic drugs, and promoting tumor recurrence and metastasis [4].

However, the phenotype of CAFs has not been fully identified, now the researchers are focused on phenotypic characteristics and use single-cell sequencing technology to gain insight into the specific effects of CAFs with different phenotypes on CSCs, with the intention of directly targeting CAFs in order to develop a more targeted treatment.

Some researchers target its secreted factors and block the interaction between them to reduce the acquisition of cancer cell stemness for reducing drug resistance and improving the effectiveness of cancer treatment.

This review involves previous research on the direct contact between CAFs and cells, secretion of related factors to activate pathways, regulation of TME, and remodeling of ECM. It explores the mechanisms of CAFs in regulating tumor cell stemness and reviews CAFs' inhibition of tumor progression and regulation of drug resistance.

2. Source of CAFs: inducing activation factors

CAFs have various origins, and different sources CAFs may have similar phenotypic characteristics, but their functions and mechanisms may be significantly different. Focusing on the origin is important for the identification of their phenotypic and functional characteristics.

CAFs can be activated by NFs through cytokine recruitment, and these activated CAFs exhibit enhanced proliferation capacity and the ability to secrete multiple growth factors. Invasive gastric cancer active NF to CAF according to secret TGF-β1. TGF-β1 active P-Smad2/3 pathway to increase IGFBP expression. IGFBP7 enters the TME to improve the transfer ability and cell stemness ability [5]. Moreover, MSCs differentiate into tumor-associated mesenchymal stem cells/stromal cells (TA-MSCs) in the tumor microenvironment, leading CAF markers to increase [6]. Epithelial cells can transform into CAFs through the process of epithelial-mesenchymal transition (EMT), to support tumor development. Endothelial cells can induce Endothelial-to-Mesenchymal Transition (EndMT) according to the exosome from Human Squamous Cell Carcinoma and Human Breast Cancer. ADSCs can differentiate into CAFs that contribute to the tumor-supportive microenvironment due to the loss of the gene encoding α-integrin 7 (ITGA7) [7]. HSCs can be activated by TGF-β1 and PDGF, then change to CAFs, thereby interacting with cancer cells to influence tumor progression.

CAFs also can be active by adipocytes, epithelial cells, pericytes, and smooth muscle cells, and even reactivate themselves according to an antagonist of bone morphogenetic protein (Grem1) [8]. There are significant differences in responses according to the different sources. Analysis based on the source of CAFs can provide the basis for how to inhibit the formation of CAFs to inhibit their effects.

However, it should be noted that not all CAFs promote the development of CSCs. Identifying their phenotypic types can help better target CSCs. There are currently subtypes of CAFs, including myofibroblast CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs) [9]. The heterogeneity of these phenotypes provides a new way for targeted therapy. Figure 1 shows the different sources of CAFs.

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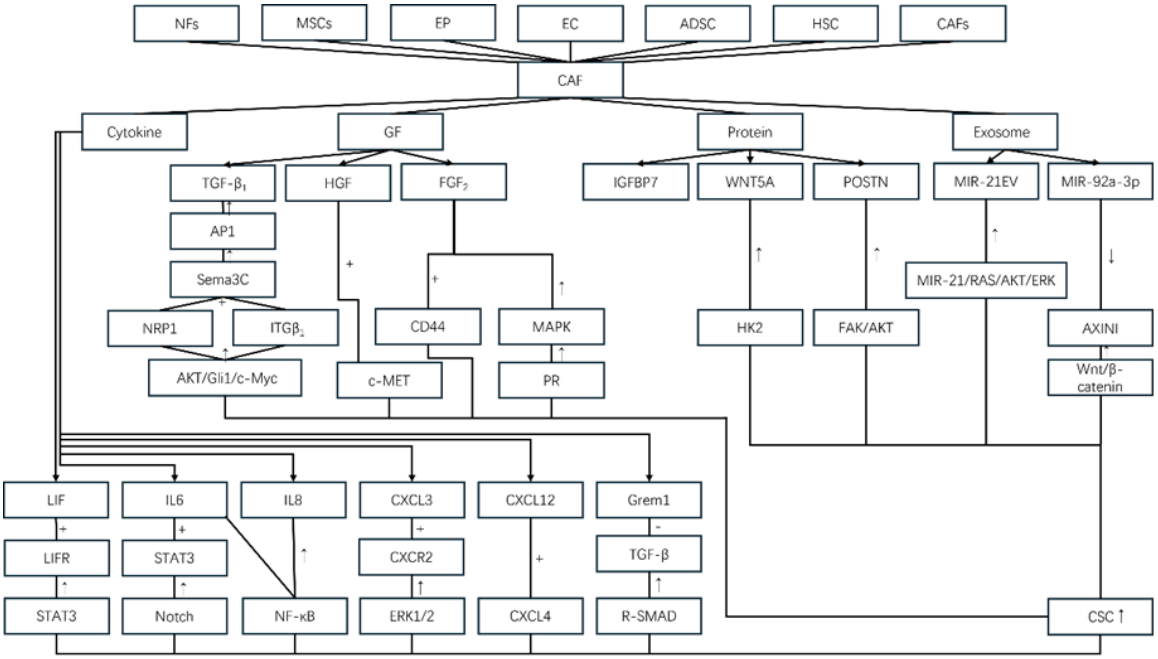

+:Combine ↑: Active -↓:Inhibit NFs: Normal Fibroblasts MSCs: Mesenchymal Stem Cells
EP: Epithelial Cell EC: Endothelial Cell ADSC: Adipose-Derived Stem Cells HSC: Hepatic Stellate Cells
CAFs: Cancer-Associated Fibroblasts LIF: Leukemia Inhibitory Factor LIFR: Leukemia Inhibitory Factor Receptor
STAT3: (Signal Transducer and Activator of Transcription 3) pathway
IL6: Interleukin 6 Notch: Notch Signaling Pathway IL8: Interleukin 8
NF-KB: (Nuclear Factor Kappa-light-chain-enhancer of activated B cells) signaling pathway
CXCL3: C-X-C Motif Chemokine Ligand 3 CXCR2: C-X-C Motif Chemokine Ligand 2
ERK1/2: (Extracellular Signal-Regulated Kinases 1 and 2) signaling pathway
CXCL12:C-X-C Motif Chemokine Ligand 12 CXCL4: C-X-C Motif Chemokine Ligand 4
Grem1: Gremlin 1 TGF-β: Transforming Growth Factor Beta) signaling pathway
R-SMAD: Receptor-regulated SMAD GF: Growth Factor TGF-β1: Transforming Growth Factor β1
AP1: Activator Protein 1 SemaC3: Semaphorin C3 NRP1: Neuropilin 1 ITGβ1: Integrin β1
AkT/Gli1/c-Myc: AKT (Protein Kinase B), Gli1 (a transcription factor in the Hedgehog signaling pathway), and c-Myc (an oncogene that regulates cell cycle progression).
HGF: Hepatocyte Growth Factor c-MET:A type of Receptor Tyrosine Kinase
FGF2: Fibroblast Growth Factor 2 CD44: CD44 molecule MAPK: Mitogen-activated protein kinase signaling pathway
PR: Progesterone Receptor IGFBP7: Insulin-like Growth Factor Binding Protein 7
WNT5A: Wnt Family Member 5A HK2: Hexokinase 2 POSTN: Periostin
FAK/AKT: Focal Adhesion Kinase/Protein Kinase B Signaling Pathway
MiR-21EV: MicroRNA-21 Extravesicle
MiR21/RAS/AKT/ERK: MiR-21/RAS/AKT/ERK Signaling Pathway
MiR-92a-3p: MicroRNA-92a-3p AXINI protein: AXIN Interacting Protein
Wnt/β-Catenin: Wnt/β-Catenin Signaling Pathway CSC: Cancer Stem Cell

Figure 1: The sources of CAFs.

3. CAFs-secreted factors and their mechanisms that affect tumor stemness

Through the research can find that CAFs can secrete various factors that affect signaling pathways, thereby promoting tumor stemness and affecting tumor cell growth, metastasis, and drug resistance. This overview is divided into four classes to discuss, namely cytokines, growth factors, proteins, and exosomes.

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3.1. Cytokines

The research has shown that CAFs can secrete IL-6 and IL-8, continuously activate the NF-κB pathway, induce CSC enrichment, and promote tumor chemoresistance. Experiment shows that knocking out CAFs can significantly inhibit CSC enrichment and tumor drug resistance [2]. High levels of IL-6 can activate the signal transducer and activator of STAT3 by phosphorylating the tyrosine 705 site (Tyr705), thereby activating Notch signaling and promoting the stem cell-like properties of hepatocellular carcinoma (HCC) cells. Research has shown that IL-6 is the most significant cytokine secreted by CAFs in HCC [10].

CAFs also can secrete the representative oncogenic super-enhancer LIF, which promotes LIF transcription through enhancer elements E1, 2, and 4 within LIF-SE by recruiting SOX2/SMAD3/BRD4/EP300. LIF binds to the downstream low-affinity LIFR to form a heterodimeric complex to activate downstream STAT3 signaling to drive the expression of stem cell markers such as SOX2 to maintain LIF overexpression and CSC stemness. In clinical samples, the abundance of LIF is associated with malignant clinical pathological features and patient prognosis. The content of LIF in blood has a significant difference before and after surgery, suggesting that it can be used as a new marker and potential therapeutic target [11].

In addition, experimental data showed that tumor cells cultured in CAFs-conditioned medium manifest enhanced resistance to sunitinib, of which the expression of CXCL3 was closely related. The stimulation of tumor-associated fibroblast culture medium (CAFs-CM) and CXCL3 promoted the expression of genes related to stem cell characteristics. The experimental results showed that CXCL3 secreted by CAFs can activate its receptor CXCR2 to promote the phosphorylation of ERK1/2, thereby activating the downstream ERK1/2 signaling pathway [12].

SDF-1 expression in CAFs can promote CRC cell migration and invasion through autocrine and paracrine signaling, also can enhance sphere formation, and promote cancer stem cell properties in CRC cells. Experimental results found the expression levels of CSC markers such as CD44, CD133, and OCT4 are significantly higher [13].

Breast CAFs can express the bone morphogenetic protein (BMP) antagonist Grem1 both inside and outside of people. Grem1 blocks the bone morphogenetic protein (BMP)/SMAD signaling in breast cancer cells, which belongs to the TGF-β signaling pathway, and stimulates the phosphorylation reaction of SMAD1/5/8 (R-SMAD), thereby promoting their mesenchymal phenotype, stemness properties, and invasiveness to affect drug resistance [8]. Therefore, it is inferred that treatment of patients with high expression of Grem1 in breast cancer may be beneficial.

3.2. Growth factors

TGF-β1 secreted by CAFs activates the AP1 signal pathway enhanced Sema3C in HCC cells. Sema3C promotes the proliferation and activation of hepatic stellate cells (HSCs). Sema3C activates the downstream AKT/Gli1/c-Myc signaling pathway to enhance HCC self-renewal and tumor initiation by binding to receptor NRP1 and ITGβ1. It can also stimulate the release of IL-6 through the NF-κB pathway. CAFs can also stimulate the HGF/c-MET axis in tumor cells by secreting HGF, activating tyrosine kinase signaling pathways, and further enhancing tumors.

In addition, iCAF, an inflammatory CAF subtype found in recurrent bladder cancer, activates the CD44 receptor on the surface of rCSC-M cells by secreting FGF2. This interaction enhances the self-renewal ability of tumor stem cells and promotes epithelial-mesenchymal transition [14].

In ER+ luminal breast cancer, the growth factors in the conditioned medium secreted by CAFs enable tumor cells to continue to grow in the absence of anchoring support while still relying on the signal of PR. This enhances their stem properties, promotes the formation of tumor spheres by tumor cells, and enables these cells to self-renew. The increase in CD44 expression levels further indicates

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stronger stem properties and invasive ability. CAFs also secrete FGF2, which activates PR by phosphorylating the 294th serine residue in PR through the MAPK pathway, thereby enhancing the stemness of tumor cells [15].

3.3. Protein

CAFs significantly affect the stemness and drug resistance of cancer cells in TME by secreting multiple proteins.

CAF-derived IGFBP7 can promote gastric cancer (GC) migration, and enhance its invasion and stemness in spheroid formation [5]. Some researchers have found that WNT5A is upregulated in various cancers and is associated with poor prognosis. CAFs affect the glucose metabolism of tumor cells by inducing the upregulation of WNT5A in GC cells and regulating HK2. The increase in cell stemness was detected by spheroid formation assay, confirming that CAFs-derived WNT5A promotes the stemness of GC cells [16].

In addition, there is a class of CAFs with high podocyte protein (PDPN) expression that has a positive circulation with CSC in the progression of gastric cancer. CAFs with PDPN expression can secrete POSTN to induce FAK/AKT phosphorylation, thereby promoting self-renewal and drug resistance of tumor cells and maintaining the characteristics of CSC. This type of CAF can also activate the FAK/YAP signaling pathway in GC cells to produce more IL-6, which in turn induces phosphorylation modification of PI3K/AKT in PDPN (+) CAFs. Due to the enrichment of IL-6, the PI3K/AKT pathway in PDPN (+) CAFs performed long-term activation, thereby maintaining the production of POSTN and affecting CSC enrichment and GC cell migration [17].

3.4. Exosomes

CAFs play an important role in TME through their secreted exosomes, activating corresponding signal transduction to induce cellular phenotypic changes to affect the stemness of cancer cells and promote drug resistance.

Research has shown that CAFs in pancreatitis secrete high levels of miR-21EVs under hypoxic conditions or through the interaction of HIF-1α and miR-21. miR-21EVs activate the miR-21/RAS/AKT/ERK pathway, thereby triggering the maintenance of PC stemness and GEM resistance. In this process, the protein levels of stem cell markers increase. [18].

In addition, the comparison of miR-92a-3p in NFs and CAFs revealed that the secretion level in CAFs was higher, which could significantly enhance the stemness of HCC cells. miR-92a-3p can promote tumor growth and stemness of HCC by activating β-catenin/CD44 signaling through inhibiting AXIN1, an important scaffold protein in the Wnt signaling pathway [19]. Exosomes released by CAFs can transfer FOSL1 to colorectal cancer (CRC) cells, thereby promoting the stemness and resistance to oxaliplatin of CRC cells through transcriptional activation of ITGB4 [20].

CAFs significantly affect the stemness of cancer cells and promote drug resistance by secreting many factors like cytokines, growth factors, proteins, and exosomes. Cytokines (such as IL-6 and IL-8) released by CAFs can activate signaling pathways associated with cancer stemness, such as the NF-κB pathway and Notch pathway, thereby enhancing the self-renewal ability and the survival of cancer cells. In addition, growth factors secreted by CAFs (such as WNT5A and POSTN) promote the development of spheroid formation and drug resistance of cancer cells. Through exosomes, CAFs can also deliver molecules such as miRNA, which regulate the growth and stemness of tumor cells and enhance their resistance to chemotherapeutic drugs.

These mechanisms suggest that CAFs play a key role in maintaining tumor stemness and promoting drug resistance, providing potential targets for novel therapeutic strategies targeting CAFs.

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4. CAFs promote tumor cell stemness by affecting ECM

CAFs can affect cell stemness by influencing changes in other processes in the ECM.

4.1. Promote epithelial transformation

During the EMT process, cancer cells lose their epithelial characteristics and acquire mesenchymal characteristics, which are manifested by reduced cell-to-cell adhesion and enhanced motility. This transformation process makes cancer cells more invasive and enhances their stem cell-like properties, thereby increasing their tolerance to chemotherapeutic drugs. Various cytokines secreted by CAFs, such as TGF-β1, SDF-1, EGF, PDGF, and HGF, can activate the EMT process, causing them to transform from an epithelial phenotype to a mesenchymal phenotype. This transformation enables tumor cells to acquire stronger migration and invasion capabilities while enhancing their stemness characteristics.

CXCL12γ and CXCR4 interact with each other, and overexpression of CXCL12γ induces EMT, leading to a significant increase in the expression of CSC phenotype [21].

Recently, a CAF subtype with increased IL-10 was discovered in endometrial cancer, marked as CD146 +CAF. After IL-10 activates and phosphorylates receptor-related tyrosine JAK1 and TYK, it recruits and activates STAT3. STAT3 activated in the cell nucleus binds to the promoter region of the target gene and regulates the expression of genes related to the epithelial-endothelial transition [22].

CAFs promote tumor stemness by facilitating the epithelial transformation process and also provide support for the TME, making it more advantageous for cancer development.

4.2. Remodel the ECM

CAFs can regulate the remodeling of ECM by secreting a variety of cytokines and growth factors, thereby affecting the acquisition of ECM stemness in cancer.

On the one hand, CAFs regulate the extracellular matrix by producing enzymes such as matrix metalloproteinases (MMPs) to degrade ECM components. This degradation destroys the original intercellular adhesion structure and provides a channel with cancer cells which make is easier to migrate and invade. On the other hand, as the ECM is remodeled, the mechanical properties in the ECM change, such as increased hardness and density, which creates a barrier effect on the infiltration of drugs and immune cells. CAFs promote the solidification of tumor extracellular matrix to inhibiting the penetration of immune cells and anti-tumor drugs recruited by chemokines secreted by tumor tissues, thereby affecting ECM and indirectly affecting tumor cells.

The increased of LOX caused by CAFs is closely related to the poor prognosis of CCA patients. CAFs remodel the ECM by regulating the expression activity of lysyl oxidase (LOX) in cholangiocarcinoma (CCA), enhancing the oxidative phosphorylation and metabolic adaptability of CCA cells, and supporting cholangiocarcinoma activity through the protein interaction with mitochondrial transcription factor A [23]. When CAFs perform glycolysis, a large amount of lactic acid and hydrogen ions are released, forming an acidic microenvironment, which inhibits the activity of immune cells and leads to resistance. However, the upregulation of core proteoglycan (DCN) in breast CAF cells can indirectly affect breast cancer cells and inhibit their ability to promote EMT and stemness [24].

This demonstrates the dual nature of CAFs in regulating ECM. On the one hand, they promote ECM remodeling by secreting factors to support tumor growth and metastasis. On the other hand, they inhibit tumor progression by upregulating specific components. CAFs affect EMT, causing tumor cells to lose epithelial characteristics and show higher stemness. These cells can form tumor

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spheres in vitro and induce tumor formation in vivo. By remodeling the ECM and changing the structural characteristics of the TME, they are closely related to cancer stemness and cancer resistance.

5. Treatment

In order to solve the problem of CAFs inducing cancer cell stemness and promoting drug resistance, a variety of strategies can be adopted, such as using specific cytotoxic drugs (such as paclitaxel, ABT263, etc.), to selectively kill CAFs through nanocarrier technology, thereby alleviating the tumor suppressive microenvironment and increasing the penetration of anti-tumor drugs.

CAFs or their related pathways or exosome activity can also be targeted by drugs or small molecule inhibitors, such as brucein D, which reduces CAFs activity and reduces Notch1-Jagged1/NF-κB (p65) signaling in primary tumors of tumor-bearing mice [25]. By regulating the microenvironment, the number or function of CAFs can be reduced, thereby reducing their ability to induce CSCs. CAFs can also be reprogrammed, such as using miR-200c to reprogram fibroblasts into METs [26]. Or directly prevent NF from turning to CAFs [27], solve the problem of inducing stemness, and thus improve the treatment effect and prognosis of cancer patients.

6. Conclusion

CAFs play an important role in tumor. This review discusses the origin and activation factors of CAFs, and summarizes the factors, proteins, and exosomes secreted by CAFs that affect tumor cell stemness and drug resistance. It also discusses the important role of CAFs in regulating EMT and the function of CAFs in remodeling ECM.

Through the discussion of these aspects, concluded that CAFs can promote the stemness of tumor cells by secreting multiple factors. The methods of directly and indirectly targeting CAFs are explored, which provides a theoretical basis for the subsequent targeting of CAFs, and is expected to inhibit its cancer-promoting effects, thereby improving the effect of cancer treatment.

However, the limitation of this review is that the discussion on its phenotype is not enough and not discuss all the roles of CAFs in inhibiting tumor stemness. It is worth exploring to clarify its specific phenotype CAFs and use the new technology like CRISPR/Cas9 to knock out the specific tumor stemness-promoting genes in CAFs.

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