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Cancer-associated fibroblasts: Origins, heterogeneity and functions in tumor microenvironment

Kevin Dzobo[1,2 *]

[1]International Centre for Genetic Engineering and Biotechnology (ICGEB), Cape Town Component, Wernher and Beit Building (South), UCT Medical Campus, Anzio Road, Observatory 7925, Cape Town, South Africa; kdzobosnr@yahoo.com (K.D)

[2]Division of Medical Biochemistry and Institute of Infectious Disease and Molecular Medicine, Department of Integrative Biomedical Sciences, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

***Correspondence: kdzobosnr@yahoo.com; Tel: +27 842953708**

Abstract: Current therapeutic strategies targeting cancer cells within solid tumors have displayed limited success owing to the presence of non-cancer components referred to as the tumor stroma within the tumor microenvironment (TM). These stromal cells, extracellular matrix and blood vessels influence cancer cell response to therapy and play key roles in tumor relapse and resistance. Of the stromal cells present in the TM, a lot of attention has been given to cancer-associated fibroblasts (CAFs) as they are the most abundant and are important in cancer initiation, progression and therapy resistance. In this updated review I emphasize the role of CAFs in the regulation of tumor cell behaviour and reveal how CAF-derived factors and signaling influence tumor cell heterogeneity and development of novel strategies to combat cancer. To investigate the expression of CAF markers in tumor tissues versus normal tissues, transcriptomic data from The Cancer Genome Atlas (TCGA) and the Gene Expression Profiling Interactive Analysis (GEPIA) databases was used. Bioinformatic analysis reveals differential expression of CAF markers in several cancer types, underscoring the need for further multiomics and biochemical studies on CAFs, CAF subsets and markers. Differences in CAF markers' expression could be due to different cellular origins as well as the effect of cancer-specific tumor microenvironmental effect on CAFs. Lastly, I present recent advances in therapeutic targeting of CAFs and the success of such endeavours or its lack thereof. It is recommended that for patients' outcomes to improve, cancer treatment be combinatorial in nature, targeting both cancer cells and stromal cells and interactions.

Keywords: Tumor microenvironment, tumor stroma, cancer-associated fibroblasts, heterogeneity, biomarkers, cancer, The Cancer Genome Atlas, gene expression, computational biology.

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1.0 **Introduction**

Recent cancer incidence and mortality statistics indicate an always increasing burden of cancer in the coming years, with most new cases occurring in countries of low and middle income [1-3]. Based on GLOBOCAN estimates and others, there is need for a new drive to find and develop new strategies to reduce this burden worldwide [1, 2, 4-7]. The cancer incidence and mortality statistics provided are likely lower than the actual figures given the limited and strained surveillance systems found in many low and medium income countries [1, 2, 8-10]. It is important to note that progress has been made in raising awareness to cancer and several cancer prevention strategies are being adopted, however, the picture still looks gloomy going forward.

While great success has been achieved in treating cancer via different therapeutic strategies directed at cancer cells, reports show that cancer deaths are likely to increase globally [1, 2, 6, 7, 11]. Significant progress made in understanding the underlying causes and molecular mechanisms involved in tumor initiation and development has led to better patients' outcomes [12-18]. Two major contributors to cancer deaths still requiring better understanding are cancer relapse and metastasis [13, 19, 20]. Research into tumor relapse and metastasis is ongoing with several studies reporting novel drugs and effective strategies aimed at limiting these processes [13, 21-23]. Furthermore, studies have revealed the TM as key to tumor initiation, response to therapy, relapse and metastasis, ultimately influencing patients' management in the clinic [17, 18, 24, 25]. Specifically, the TM has been shown to provide some form of protection to cancer cells, reduce cancer cell response to therapy and ultimately promote therapy resistance [17, 18, 26]. The TM can also modify cancer cells resulting in cancer cell heterogeneity [26, 27]. Studies have shown that subpopulations of cells within the TM, including cancer-associated fibroblasts (CAFs), can affect cancer cells differently [28-30]. In addition, several studies have shown that the extracellular matrix can influence cancer cell proliferation, migration and response to therapy [17, 31]. This has resulted in increased attention being given to the role of tumor-associated cells and -extracellular matrix and the development of therapies directed at the tumor stroma. Recently, studies also demonstrated the gut microbiota's influence on cancer response to therapy through modulation of TM [32-34]. Whilst underscoring the importance of microbiota in disease treatment and outcome, these studies show that modulation of TM play a huge part in cancer cell response to treatment. In addition, the activation of the immune system has been shown to influence cancer cell sensitivity to radiotherapy [35]. Thus, the targeting or modulation of the TM has real therapeutic value with the potential to improve patients' outcomes. A deeper

understanding of the TM and its contribution to cancer cell behaviour is pertinent. This comprehensive review presents advances in our knowledge on CAFs and the role played by these cells in disease initiation and progression. This review bring to the fore the strategies being adopted to include TM-directed therapies in the clinic, with the aim of reducing fatal disease.

TM is used to describe the cells, extracellular matrix and blood vessels found within the vicinity of cancer cells in a tumor. Included in this definition are cells such as fibroblasts, macrophages, endothelial cells, lymphocytes and myeloid-derived cells and the extracellular matrix (ECM). Several studies have shown that depending on the stage of tumor development, the TM can provide both an inhibitory and promoting environment to cancer cell growth [17, 18]. Cells within the TM can be from the local vicinity or migrated from distant environments [36, 37]. CAFs are the most abundant cells within the TM and play key roles in tumor initiation and progression [24, 38]. Immune cells within the TM are mostly macrophages [39, 40]. Endothelial cells mostly function to form new blood vessels necessary for the supply of nutrients to the growing tumor and removal of toxic waste [41]. In addition, endothelial cells also secrete platelet-derived growth factor (PDGF) which attract pericytes to tumor blood vessels and these pericytes are involved in stabilisation of newly formed blood vessels [42]. Stromal cells such as fibroblasts and macrophages are also involved in the synthesis and maintenance of the extracellular matrix [43-45]. By releasing enzymes such as matrix metalloproteinases, and growth factors, stromal cells contribute to tumor ECM remodelling [43]. ECM remodelling enables cancer cells to migrate and invade surrounding tissues [46]. As the tumor develops, both tumor cells and the TM components co-evolve and transform through release of various growth factors and other biomolecules, with the TM initially being tumor-restrictive but tumor-promoting at later stages [17, 18].

Several studies have demonstrated stromal cell heterogeneity especially of CAFs and macrophages [28, 38, 47, 48]. This heterogeneity manifests as either tumor-restrictive or tumor-promoting activities of the cells [49-51]. Elaborate studies by Su and colleagues as well as by Ohlund and co-workers demonstrated the presence of distinct populations of fibroblasts within tumors that have specific functions and that they influence cancer cell response to therapy [28, 38, 50]. Lately, the use of cell surface markers to isolate and characterise these distinct population of fibroblasts has allowed a deeper analysis of their behaviour and functions [28, 38]. The identification and use of specific cell surface markers can allow targeted manipulation of specific

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fibroblasts populations to achieve a specific goal during cancer treatment. Under normal physiological conditions, fibroblasts are dormant/quiescent or inactive but can be activated by various growth factors, cytokines and chemokines [16, 46]. Currently, very few clinical trials have been done targeting CAFs to treat cancer. This is partly because the translation of laboratory scientific evidence into clinical use requires more resources. It is therefore imperative that a deeper understanding of stromal cell behaviour and biology is obtained to improve strategies targeting such cells. This review describes in detail the involvement of CAFs in cancer pathogenesis.

2.0 Cancer-Associated Fibroblasts: Origins and Heterogeneity

In a landmark publication in 1858, Virchow described fibroblasts as cells that were spindle shaped and were responsible for the synthesis of collagen [52]. Further studies showed that fibroblasts are mostly dormant cells within the extracellular matrix and are transformed under conditions such as inflammation, fibrosis and wound healing [53-55]. With both inflammation and fibrosis being associated with cancer initiation and development, fibroblasts are therefore activated during these processes [56-58]. These activated fibroblasts associated with cancer are referred to as CAFs or tumor-associated fibroblasts (TAFs) [16, 55]. Whilst initially having an anti-tumorigenic phenotype as normal fibroblasts, CAFs eventually become pro-tumorigenic through mechanisms still under intense investigations [18, 29]. CAFs will eventually become the dominant stromal cell type within the TM and promote tumor progression via release of several factors and the synthesis of the ECM [17, 18, 24, 55, 57].

Irrespective of their cell of origin, CAFs are large spindle shaped cells showing increased stress fibres and well developed cellular-extracellular matrix connections [59]. Although their shape appear identical to normal fibroblasts, CAFs show increased numbers of ribosomes and rough endoplasmic reticulum [59]. Early markers used for positive identification of CAFs include α-smooth muscle actin (α-SMA), vimentin and desmin [10, 60]. Unlike their normal equivalent, CAFs demonstrate increased proliferation and migration capacity and show increased expression of ECM proteins and ECM degrading enzymes [61, 62]. The resulting remodelling of the TM, referred to as desmoplasia, results in fibrosis and stiffening of the tissue [63, 64]. The presence of CAFs and tissue stiffening have been associated with cancer relapse implying that CAFs and desmoplasia contribute to cancer progression and therapy resistance [65, 66]. Calvo and

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colleagues demonstrated that ECM remodelling is a requirement for CAFs continuous presence within the TM [67]. Thus there is a feedback loop whereby CAFs build and maintain the TM and remodeling of the ECM whilst the remodeling is needed for both the generation and maintenance of CAFs [67, 68]. The balance between ECM synthesis and degradation is needed for homeostasis maintenance. ECM proteins such as collagens and fibronectin can block immune cells from infiltrating into the tumor [69]. In addition, the ECM provides the 'theatre' in which all the cellular interactions takes place, blood vessels are formed as well as allow cancer cells to escape immune detection [69-71]. CAFs promote angiogenesis through release of MMPs which degrade the ECM and allows the release of VEGF-A sequestered by the ECM [72]. The release of VEGF-A promotes the formation of the vascular system, allowing the tumor to grow large with enhanced exchanged of nutrients and toxic substances [72, 73]. CAFs are known to release several growth factors and cytokines known to promote inflammation and to assist in the evasion of the immune system [39, 74, 75]. In short, CAFs are the builders and are involved in the maintenance of the TM via synthesis and release of ECM proteins and protein factors [17, 18, 24, 26, 46, 50, 55, 59]. In turn, the TM promotes tumor initiation, progression and metastasis [24, 29, 41, 47, 55, 57, 59]. Increased knowledge on the origins and role of CAFs within the TM may allow the development of new anti-cancer strategies [76-81].

Several studies show that CAFs originate from different cell types and this has been suggested to cause the heterogeneity observed in these cells [18, 29, 55, 59]. Beside the activation of fibroblasts within the vicinity of the cancer cells, CAFs can also originate from bone marrow-derived fibrocytes and mesenchymal stem/stromal cells (MSCs) that are recruited to the tumor; the transdifferentiation of pericytes, smooth muscle cells and adipocytes; epithelial cells that underwent epithelial mesenchymal transition (EMT); endothelial cells that underwent endothelial to mesenchymal transition (EndMT); and finally the activation of quiescent stellate cells (Figure 1) [28, 82, 83]. As demonstrated in breast cancer, bone marrow-derived fibrocytes which are normally inactive and present in circulation can be recruited to the tumor and become CAFs over time [84]. Our study show that MSCs can be converted to 'CAFs' over time through interaction with cancer cells [18]. We demonstrated that transformation of MSCs into CAFs was dependent on the release of transforming growth factor-β (TGF-β) by both cancer cells and the MSCs [18]. Several other studies have also shown that MSCs can transform/differentiate into CAFs in several cancers [85-87]. For example, Weber and colleagues demonstrated that osteopontin mediates TGF-β-dependent transformation of MSCs into CAFs in breast cancer [88]. Tissue-resident MSCs and those recruited from distant tissues and organs can interact with

cancer cells and be transformed to CAFs. Quiescent stellate cells can also transform into CAFs when activated and contribute to the CAF population in the liver and the pancreas [82, 83]. Epithelial cells within the vicinity of cancer cells can undergo EMT and become CAFs under fibrotic conditions [89]. This means that epithelial-derived cancers can end up with a huge population of CAFs driving tumor progression. Endothelial cells can also undergo EndMT and become CAFs [90]. Both transformed epithelial cells and endothelial cells express CAF markers including S100A4 [89, 90]. Through a transdifferentiation process, cells such as adipocytes and pericytes can become CAFs [91, 92]. It is therefore plausible to speculate that all cells that are within the vicinity of cancer cells and those that end up at the tumor site via circulation can potentially be transformed into cells that will eventually promote tumor growth such as CAFs. We are just beginning to get a clear picture of the components of the TM and functions in tumor initiation and progression and detailed mechanistic studies are likely to reveal interesting information.

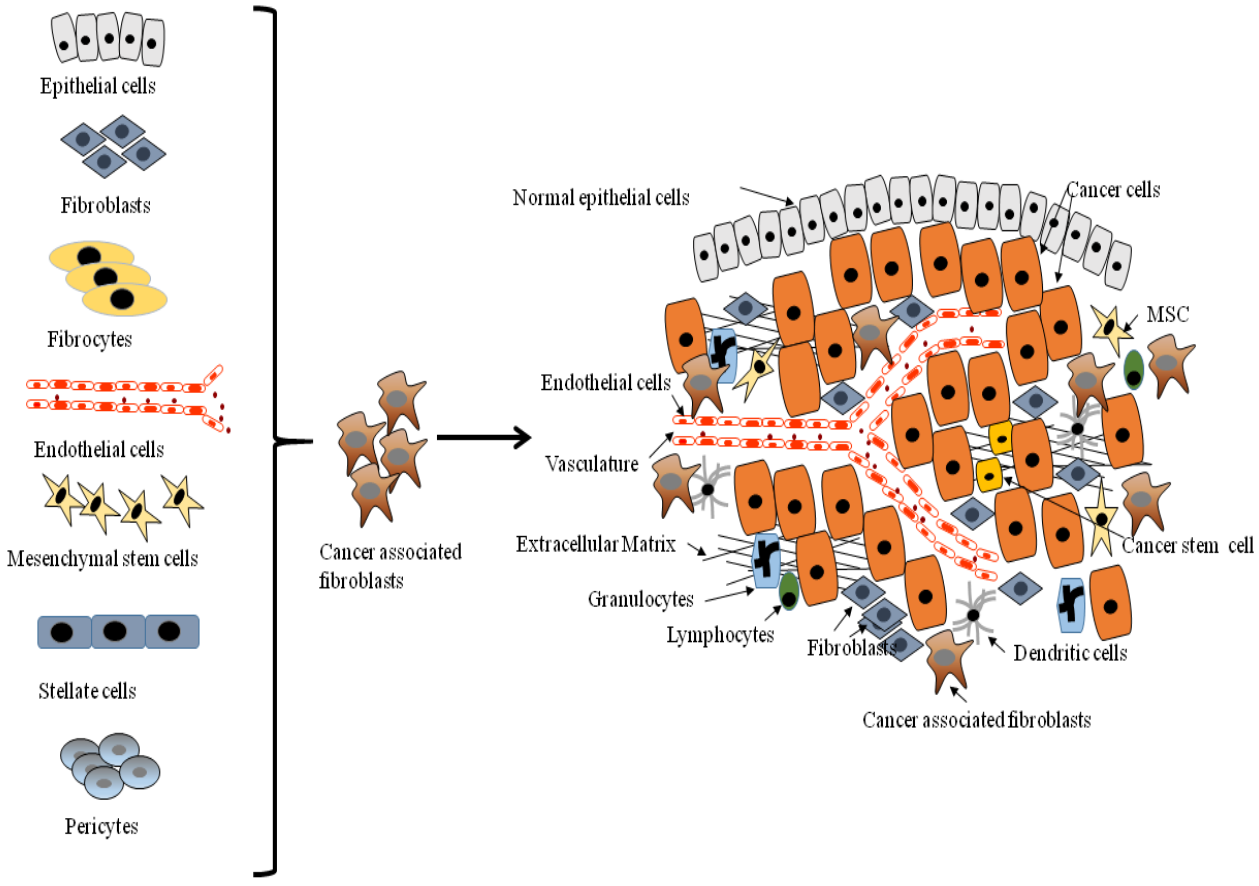

Figure 1. Cancer-associated fibroblasts can be derived from different cellular sources. Fibroblasts and stellate cells can be activated through various processes to become CAFs; mesenchymal stem cells and fibrocytes are recruited to the tumor via circulation; epithelial cells and endothelial cells undergo epithelial to mesenchymal transition and endothelial to mesenchymal transition, respectively, to become CAFs. Furthermore, pericytes and adipocytes are known to undergo transdifferentiation to become CAFs. Figure is adapted from our earlier publication, Senthebane et al, 2017 [18].

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It is now accepted that CAFs show heterogeneity with distinct subsets of cells displaying different phenotypes and functions within the TM [28, 29, 38, 47, 93]. Furthermore, CAFs heterogeneity is also dependent on the stage of tumor development [93, 94]. Whilst normal fibroblasts are generally considered genetically stable, the same cannot be said about CAFs. The process of transformation, the generation of reactive oxygen species (ROS) and the hypoxic conditions within the tumor can result in DNA alterations in CAFs as well, with CAFs co-evolving with cancer cells as the tumor develops [29, 95, 96]. Although rare, alterations to the genetic material of CAFs or stromal cells have been found in different cancers [97, 98]. Several available techniques including the use of CRISPR-Cas9 technology and tracing experiments can be used to determine if genetic alterations occur in CAFs as it does in cancer. It is plausible to speculate that as the tumor evolve so does the cells associated with it such as CAFs. Our study clearly demonstrate that previously anti-cancer activity of MSCs is diminished over time and 'transformed' cells eventually become pro-tumorigenic [18]. In addition, the synthesis of the ECM over time by both CAFs and cancer cells result in combinatorial ECM which is pro-tumorigenic than normal ECM [17]. Clearly, more research and focussed analysis of the TM components is needed, especially the tumor-associated cells.

Given their possible cellular origin, it is not surprising that CAFs display great phenotypic heterogeneity. Different CAFs subsets have been identified within the TM and are spatially distributed throughout the tumor [29, 97]. Recent characterisation of CAFs has identified specific biological markers for specific subsets of CAFs [24, 99]. In addition, no CAF marker is expressed by all CAFs. Early studies identified markers such as α-SMA, fibroblast activation protein-alpha (FAP-α or FAP) and PDGF receptor-β (PDGFR-β) to be expressed by different subsets of CAFs with none being expressed by all CAFs [24, 100, 101]. To be useful, a combination of these markers is normally used during CAFs characterisation.

Among the markers, α-SMA has proven useful in the identification of CAFs as well as a marker for smooth muscle cells and pericytes [29]. Senthebane and colleagues used both vimentin and α-SMA as markers to study cancer cell-derived TGF-β-mediated transformation of MSCs to CAFs *in vitro* [18]. Over time, both markers expression increased significantly in MSCs co-cultured with cancer cells. Cancers in which CAFs express elevated levels of α-SMA include breast, pancreatic and liver cancers [83, 102]. However, several other cells including normal fibroblasts, smooth muscle cells, cardiomyocytes and pericytes also express α-SMA. Mostly involved in maintenance

of cellular cell structure, α-SMA is also involved in the migration and contraction of cells. Another CAF marker vimentin is expressed highly by CAFs in breast and prostate cancers [55, 103]. We recently shown that vimentin can be induced via TGF-β-mediated transformation of MSCs [18]. Biological functions of vimentin include promotion of migration and maintenance of cellular structure and integrity [104-106]. In contrast to α-SMA and vimentin, desmin is mostly downregulated in CAFs (agreeing with our analysis of TCGA data, see Figures ahead) and is also expressed by fibroblasts, muscle cells and pericytes [42, 107]. Caveolin-1 is a scaffolding protein expressed in CAF subpopulations as well as cells such as endothelial cells, fibroblasts and adipocytes. Low expression of caveolin-1 is used as a marker of a CAF subpopulation undergoing metabolic reprogramming and promoting tumorigenesis [108]. In contrast, elevated levels of caveolin-1 are observed in CAFs with the propensity to promote metastasis [109, 110]. This clearly demonstrates the challenges involved in sorting and isolating of CAFs, a necessary step to their characterisation, with huge ramifications to their therapeutic targeting. Recently, CD10 and G-protein-coupled receptor 77 have been shown to be highly expressed in CAFs and are involved in promoting cancer stemness and resistance to chemotherapy in breast cancer cells [38]. Illustrating the challenges faced by any CAFs-targeted therapies, CD10 and GPR77 are also expressed in bone marrow-derived stromal cells and polymorphonuclear neutrophils, respectively [38, 111].

S100A4, sometimes referred to as fibroblast-specific protein (FSP), is expressed by fibroblasts within tumors and display serine protease activity, allowing it to remodel the ECM [112]. Fibroblasts expressing S100A4 are known to protect cancer cells via ECM production. Cells expressing S100A4 are known to be highly malignant and display a propensity for migration [113]. S100A4 is highly expressed in CAFs in breast cancers, for example [114]. This marker is also expressed by other cells including cells undergoing EMT, macrophages and normal fibroblasts [112, 114, 115]. PDGFR-β is a CAF marker that has been targeted with kinase inhibitors [116]. PDGF receptor signaling inhibition with Imatinib was shown to abrogate malignant progression of cervical lesions [116]. CAFs found in colorectal and cervical cancers express high levels of PDGFR-β [116, 117]. Macrophages have been shown to cause immune suppression through the expression of fibroblast activation protein-a (FAP-α) [118]. FAP-α is expressed in many human cancers and is highly expressed in CAFs [118, 119].

In summary, CAFs are a heterogeneous population of cells clearly demonstrating their diverse cellular origin and have been shown to have many functions within the solid tumor. A major challenge facing scientists today is the identification of reliable cell surface markers that can be used for therapeutic targeting. New data demonstrating that CAFs function is dependent on location within the tumor amplify the challenge faced [28, 29]. Irrespective of cell of origin, tumor stage and location within the tumor, recent studies emphasize the need to identify cancer-specific CAF markers or CAF subsets markers for use in diagnosis and anti-cancer targeting.

3.0 The expression of CAF markers in cancer

Given that the burden of cancer worldwide is on an upward trend, new diagnostic, prognostic biomarkers and treatment strategies are needed [2, 120]. Whilst anti-cancer strategies directed at cancer cells have resulted in significant success, durable cancer treatment can only be a result of both anti-cancer and anti-stromal strategies. The characterisation of CAFs phenotypic and functional heterogeneity has revealed potential treatment strategies aimed at ablating or re-educating CAFs to control tumor development and progression. Below I evaluate the expression of CAF markers in several cancers. I utilised the publicly available The Cancer Genomic Atlas (TCGA) (http://cancergenome.nih.gov.) and Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn.) databases to evaluate the expression of several CAF markers in tumor samples compared to normal samples.

3.1 Ethics and Approval

The publicly available The Cancer Genome Atlas (TCGA) and GEPIA databases were used in this analysis. This study does not contain any human or animal participation.

3.2 Bioinformatic Analysis: CAF markers RNA-seq analysis based on TCGA and GEPIA data

Two online databases, The Cancer Genome Atlas and GEPIA were used in the present analysis. The mRNA expression levels of ACTA2, S100A4, vimentin, desmin, FAP, PDGFR-β, CD10 and caveolin-1 in cancer tissues versus normal tissues of different cancers were analysed by searching both TCGA and GEPIA databases.

3.3 Differential expression of CAFs Markers in tumor tissues

This study accessed the publicly available TCGA and GEPIA databases and evaluated CAF markers mRNA expression in tumor tissues and paired normal tissues. Overall, our analysis revealed a differential expression of CAF markers in different cancer types. Collectively, this analysis reveals the selective expression of CAF markers, with each cancer type displaying its own pattern of expression. This demonstrates that the specific TM present within different tumors influence stromal cell gene expression. In addition, the origin of CAFs within the TM may influence marker expression. This analysis suggests that a combination of CAF markers may be needed to identify CAFs in different cancers. Both significantly low and high expression of CAF markers can be useful in the identification of CAFs or their subsets in different cancers.

3.3.1 Colon Cancer

Colorectal cancer has been reported to contribute about 10.2 % of diagnosed cancers and causes approximately 9.2 % of all cancer deaths annually [1, 121, 122]. The global incidence of colorectal cancer continues to increase unabated, with patients' survival varying greatly between countries. Thus the understanding of the biology and mechanism of progression of colorectal cancer is needed [123]. Bioinformatic analysis shows that FAP-α and CD10 expression was significantly upregulated in colon adenocarcinoma patients' samples compared to corresponding adjacent normal tissues (Figure 2). On the other hand, ACTA2, vimentin, desmin and caveolin-1 expression was significantly downregulated in tumor samples versus normal samples as shown below (Figure 2).

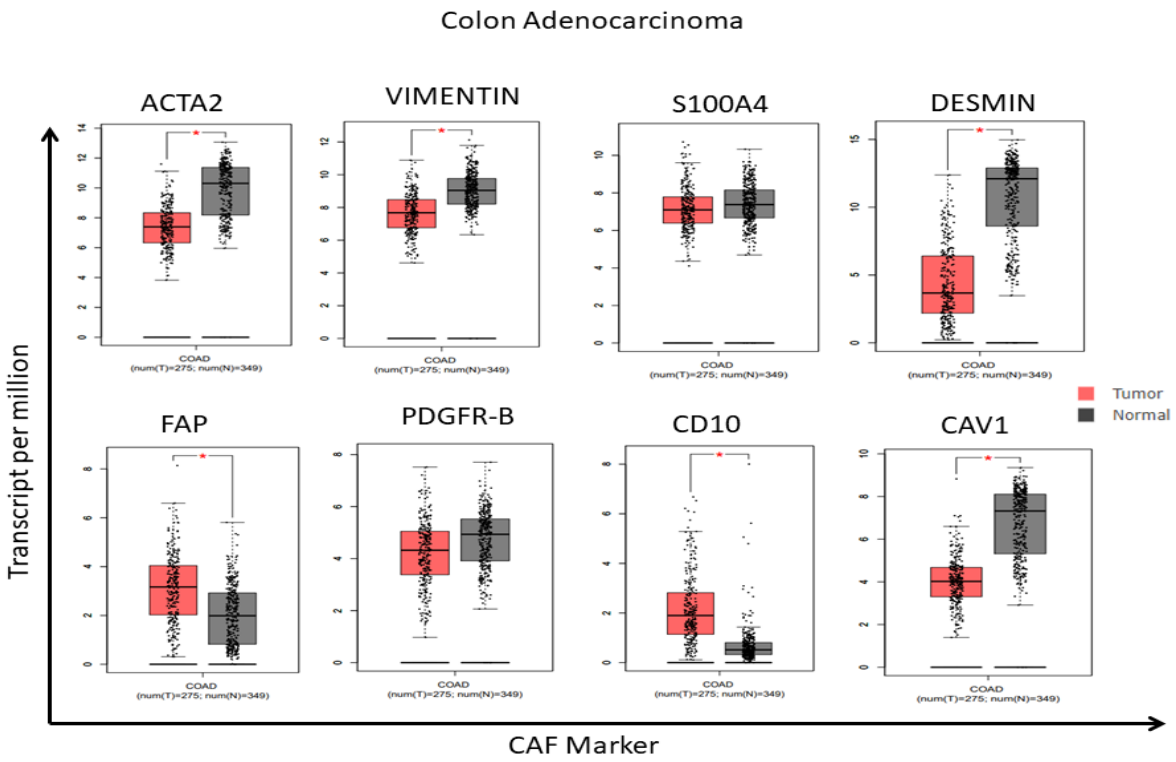

Figure 2. Cancer-associated fibroblast markers gene expression profiles in colon adenocarcinoma (COAD). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in colon adenocarcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA COAD samples n = 275; normal = 349.

3.3.2 Breast Cancer

Breast cancer is the second leading cancer diagnosed annually, with its incidence thought to be 11.6 % of all total cases [1, 2]. Breast cancer accounts for 6.6 % of total cancer deaths annually [1]. Some of the risk factors for breast cancer include family history of the cancer, inherited mutations in genes such as *BRCA1* and *BRCA2* [1, 2]. Bioinformatic analysis show that with the exception of FAP-α expression, which was significantly upregulated, all other analysed CAF markers were significantly downregulated in breast invasive carcinoma tissues compared to corresponding normal samples (Figure 3).

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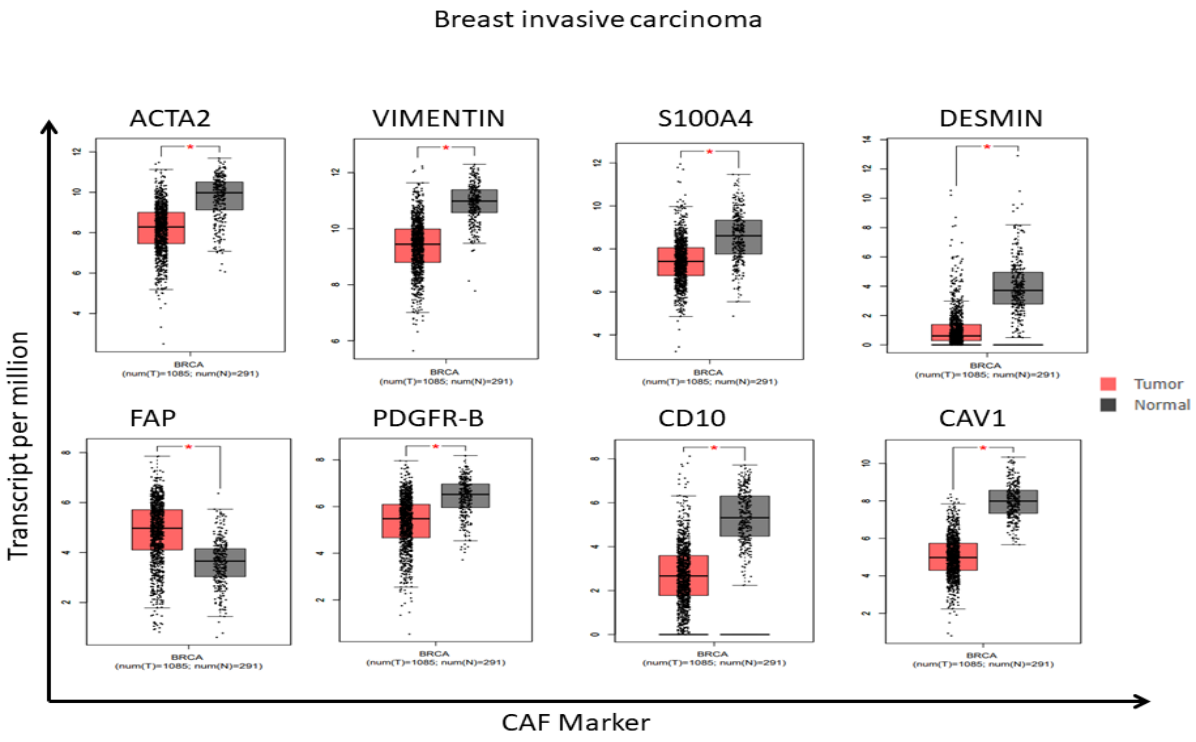

Figure 3. Cancer-associated fibroblast markers gene expression profiles in breast invasive carcinoma (BIRC). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in breast invasive carcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA BIRC samples n =1085; normal = 291.

3.3.3 Skin Cutaneous Melanoma

Malignant melanoma develops from melanocytes, pigment-containing cells. Most melanomas occur in the skin but can also occur in the intestines and mouth. Some melanomas originate from moles consisting of mutant melanocytes that have undergone senescence [124, 125]. Skin cutaneous melanoma is reported to be responsible for the majority of skin cancer deaths worldwide [126]. Several studies have identified the importance of CAFs in melanoma growth and progression [126-128]. TCGA data analysis shows that only vimentin expression was significantly upregulated in skin cutaneous melanoma samples compared to normal samples (Figure 4). The expression of α-SMA, desmin and PDGFR-β was significantly reduced in skin cutaneous melanoma samples compared to normal samples (Figure 4).

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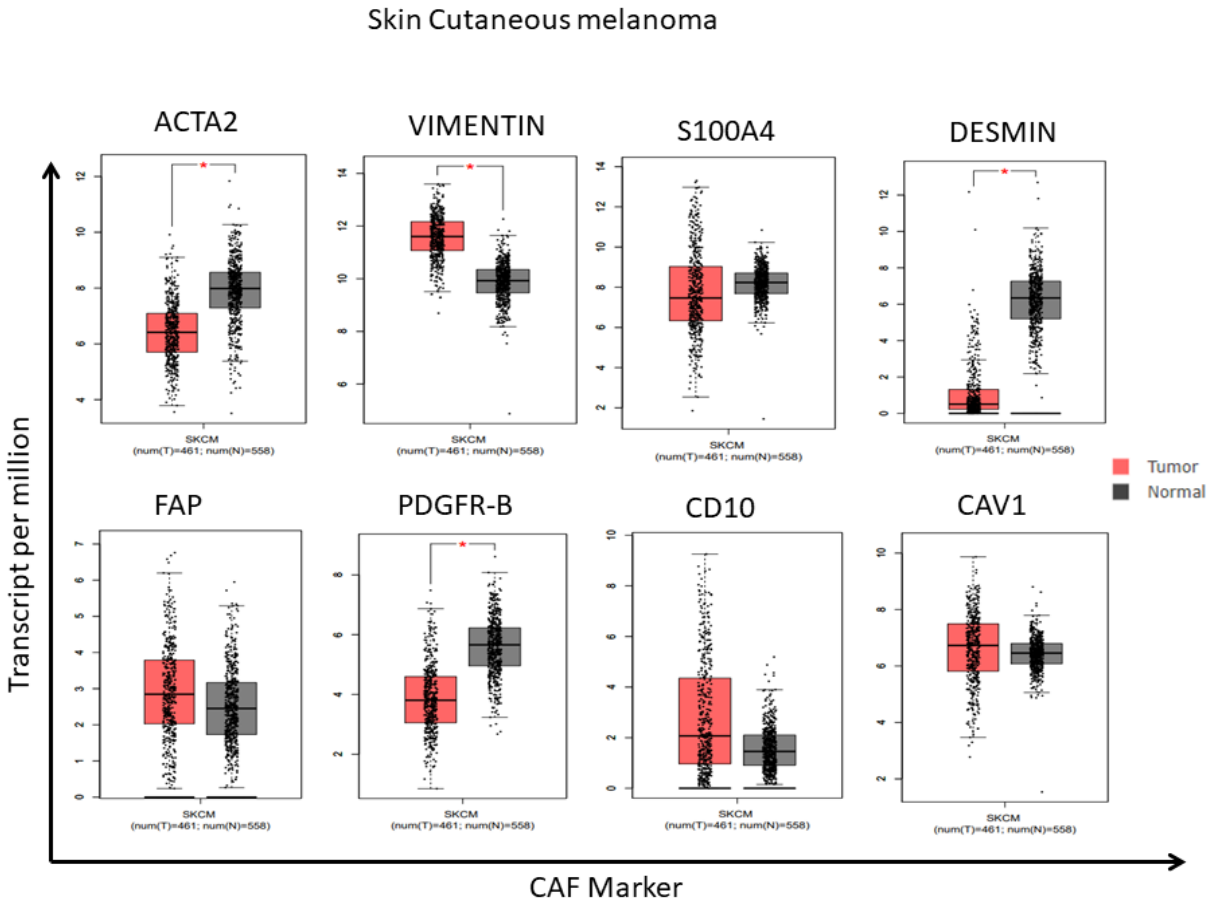

Figure 4. Cancer-associated fibroblast marker gene expression profiles in skin cutaneous melanoma (SKCM). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in skin cutaneous melanoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA SKCM samples n = 461; normal = 558.

3.3.4 Lung cancer

Lung cancer is the most diagnosed cancer in the world, with its incidence reported to be 11.6 % of the total cases [2]. Globally, lung cancer causes the most cancer deaths, accounting for 18.4 % of cancer deaths [2]. Some the main risk factors include exposure to tobacco, smoke and asbestos [1, 122, 129, 130]. With the exception of FAP expression, which was significantly upregulated, the expression of other CAF markers was significantly downregulated in TCGA lung adenocarcinoma samples compared to normal samples (Figure 5). In lung squamous cell carcinoma, with the exception of FAP expression, which was unchanged, the expression of other CAF markers was significantly downregulated in tumor tissues compared to normal tissues (Figure 6).

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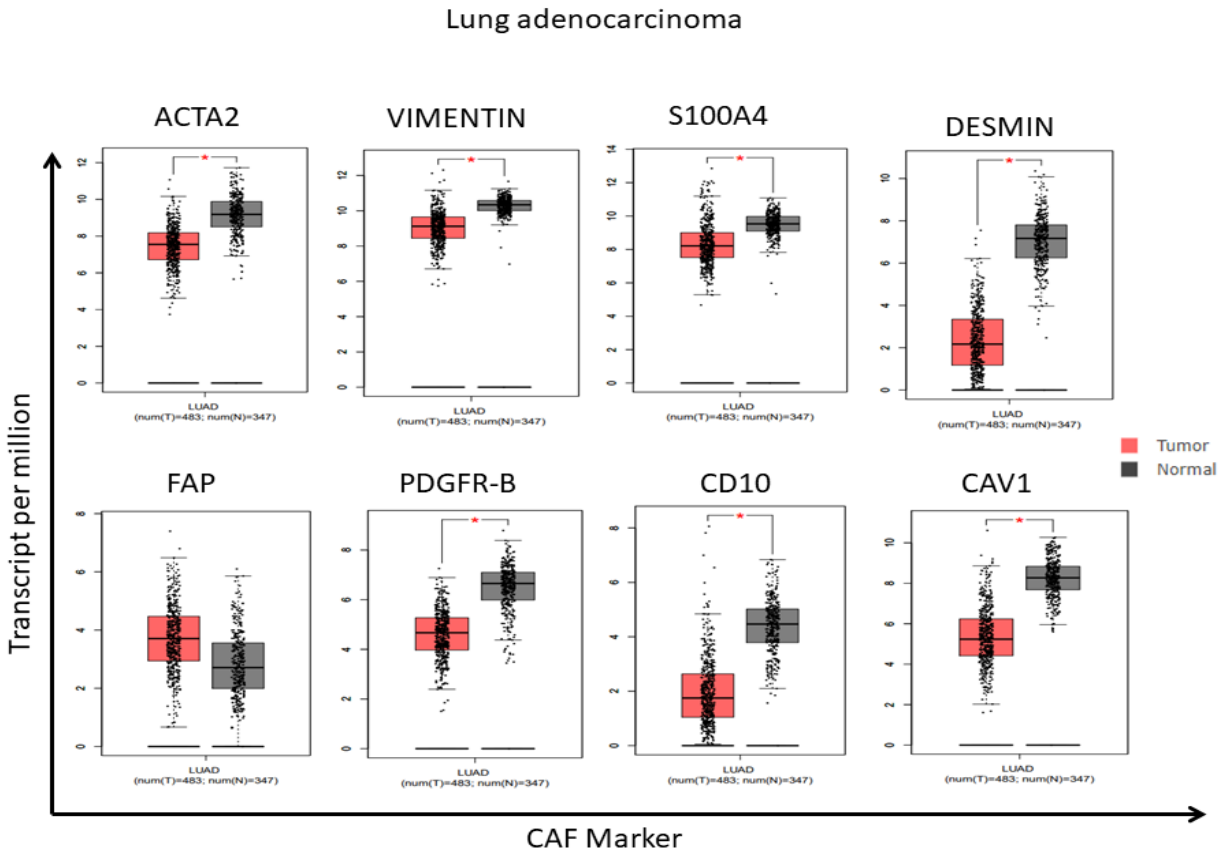

Figure 5. Cancer-associated fibroblast markers gene expression profiles in lung adenocarcinoma (LUAD). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in lung adenocarcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA LUAD samples n = 483; normal = 347.

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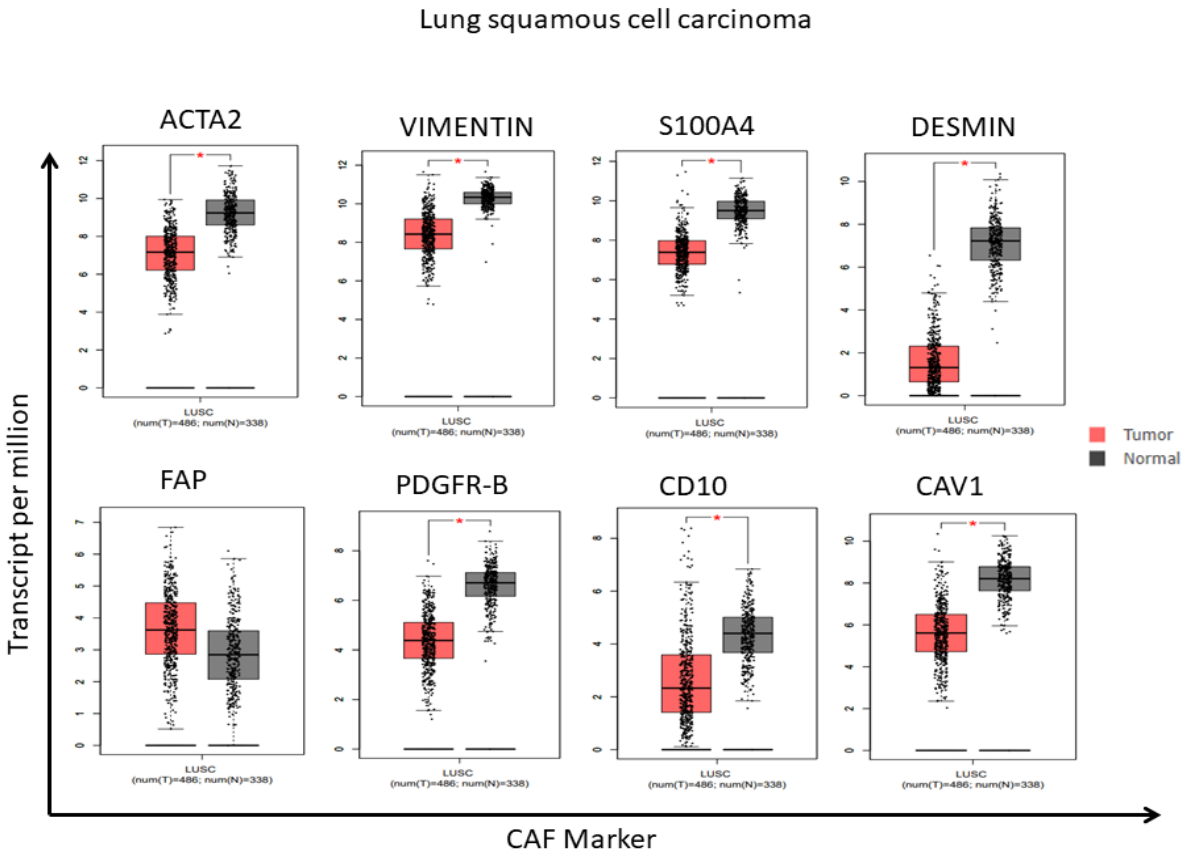

Figure 6. Cancer-associated fibroblast markers gene expression profiles in lung squamous cell carcinoma (LUSC). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in lung squamous cell carcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA LUSC samples n = 486; normal = 338.

3.3.5 Prostate Cancers

The second most diagnosed cancer in men is prostate cancer and can be cured if detected early [131]. Once the disease reaches the castration-resistant prostate cancer, the cancer becomes resistant to treatment [132-135]. CAFs have been identified in prostate cancer and have been implicated in cancer cell aggressiveness through metabolic alterations and mitochondrial transfer [136]. Using the TCGA database samples, bioinformatic analysis revealed that with the exception of FAP and CD10 expression which was unchanged, ACTA2, vimentin, S100A4, desmin, PDGFR-β and caveolin-1 expression was significantly downregulated in tumor samples compared to normal samples (Figure 7).

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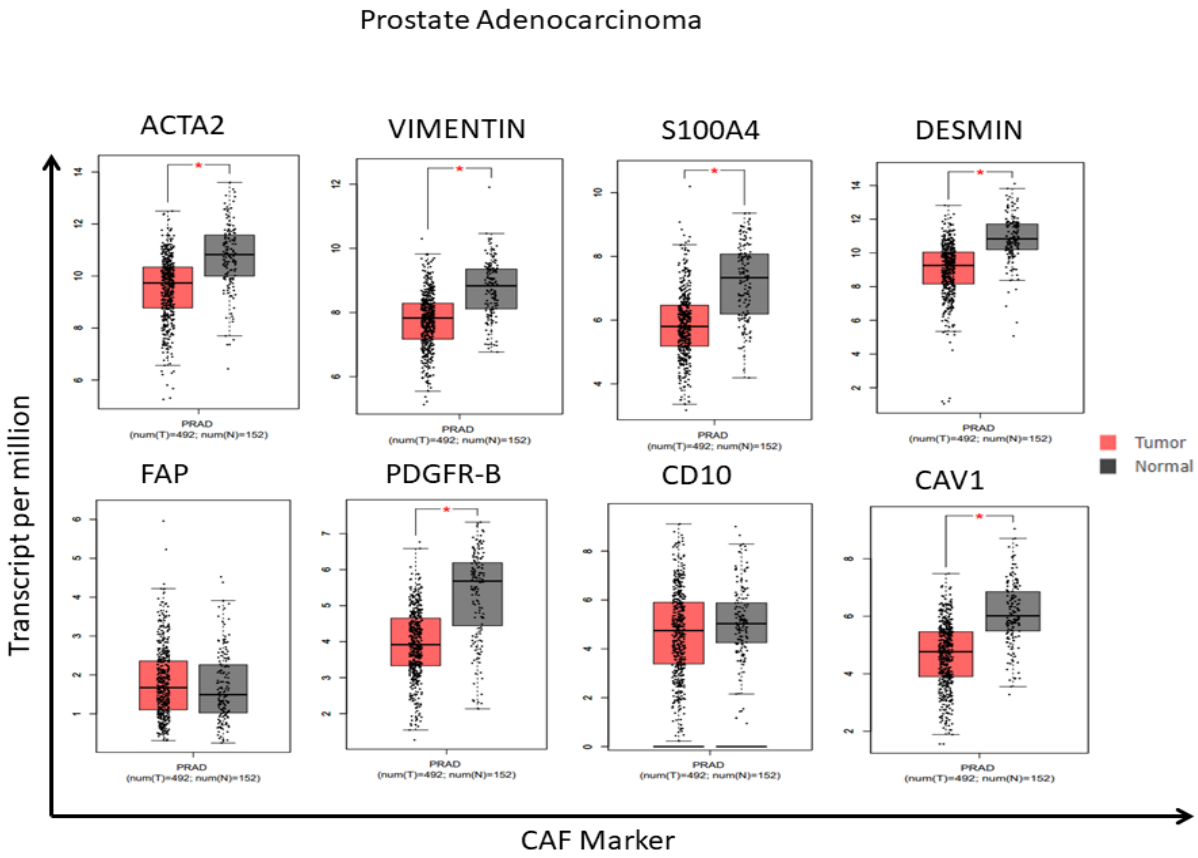

Figure 7. Cancer-associated fibroblast markers gene expression profiles in prostate adenocarcinoma (PRAD). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in prostate adenocarcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA PRAD samples n = 492; normal = 152.

3.3.6 Pancreatic Cancer

Pancreatic adenocarcinoma is one of the most common and deadly cancers worldwide [137]. The expression of several CAF markers was evaluated as shown below. This study show that with the exception of desmin expression which was unchanged, the expression of ACTA2, vimentin, S100A4, desmin, FAP, PDGFR-β, CD10 and caveolin-1 was significantly upregulated in TCGA pancreatic adenocarcinoma samples compared to normal samples (Figure 8).

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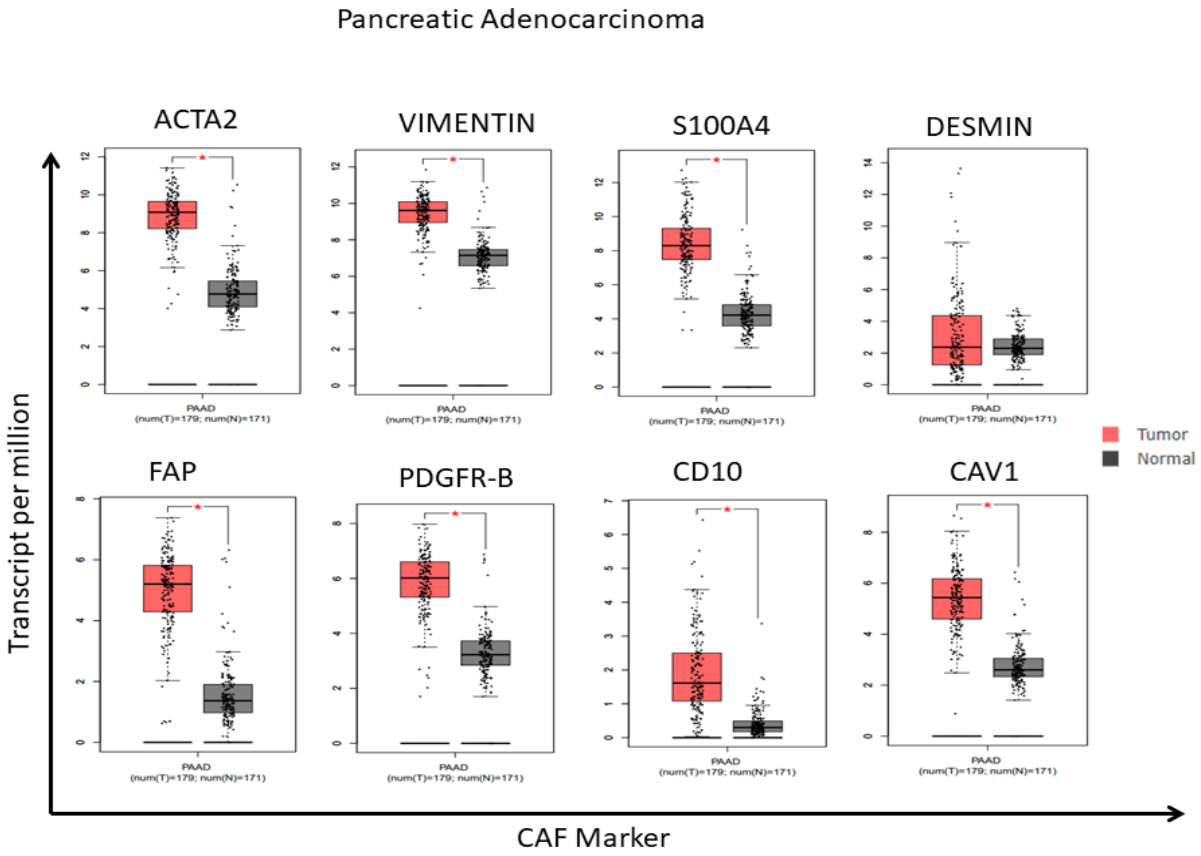

Figure 8. Cancer-associated fibroblast markers gene expression profiles in pancreatic adenocarcinoma (PAAD). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in pancreatic adenocarcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA PAAD samples n =179; normal = 171.

3.3.7 Esophageal cancer

Esophageal cancer malignancy is high and it has a poor prognosis [130, 138, 139]. Novel molecular targets are definitely required for durable cancer treatment. Based on bioinformatic analysis, FAP and CD10 expression was significantly upregulated in esophageal carcinoma samples compared to normal samples (Figure 9). In addition, ACTA2 and desmin expression was significantly downregulated in tumor samples versus normal samples (Figure 9).

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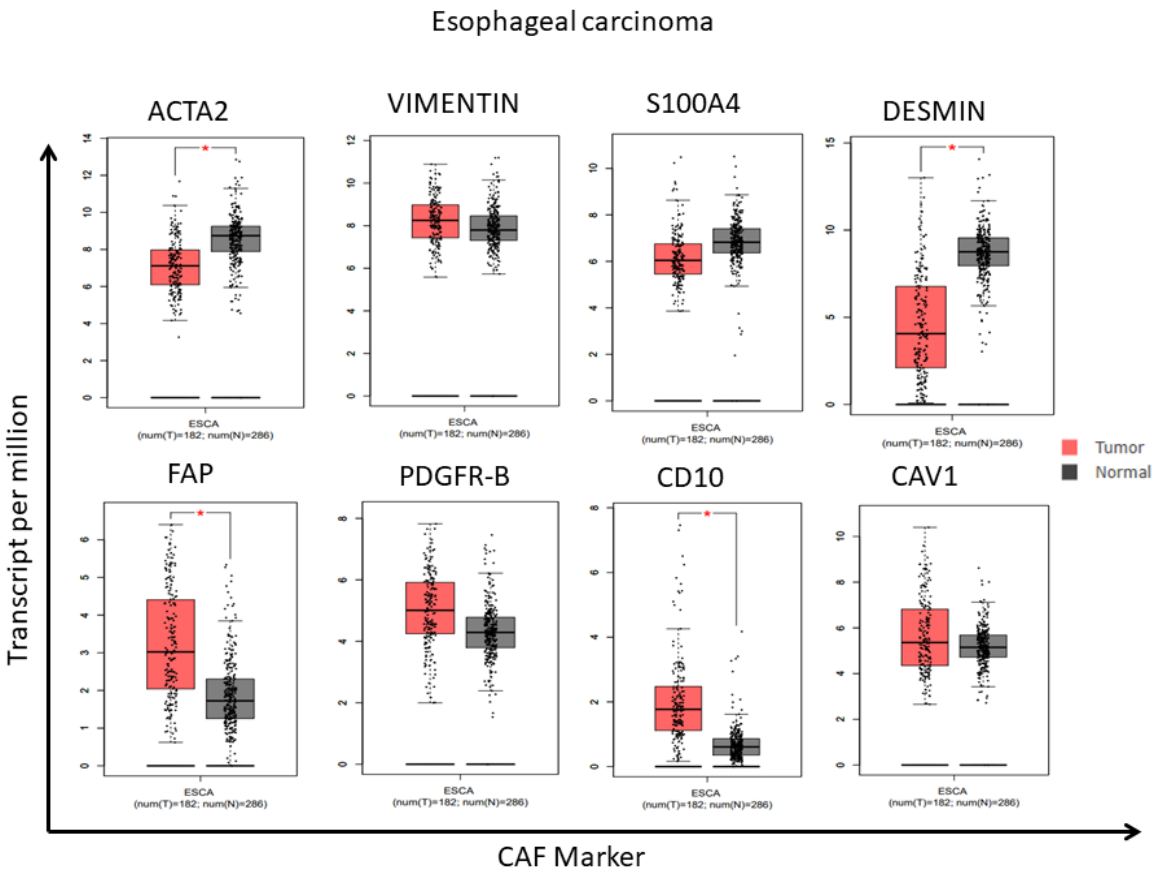

Figure 9. Cancer-associated fibroblast markers gene expression profiles in esophageal carcinoma (ESCA). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in esophageal carcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA ESCA samples n =182; normal = 286.

3.3.8 Glioblastoma Multiforme

Glioblastoma multiforme, also referred to a simply glioblastoma, is one of the fastest growing known cancer and starts in the glial cells [140]. Another name given to this cancer is grade IV astrocytoma. Several studies have shown the involvement of stromal cells in the development and progression of glioblastoma multiforme [141-144]. Bioinformatic analysis of glioblastoma multiforme tissues revealed that ACTA2, vimentin, S100A4 and caveolin-1 expression was significantly upregulated in tumor samples compared to normal samples (Figure 10).

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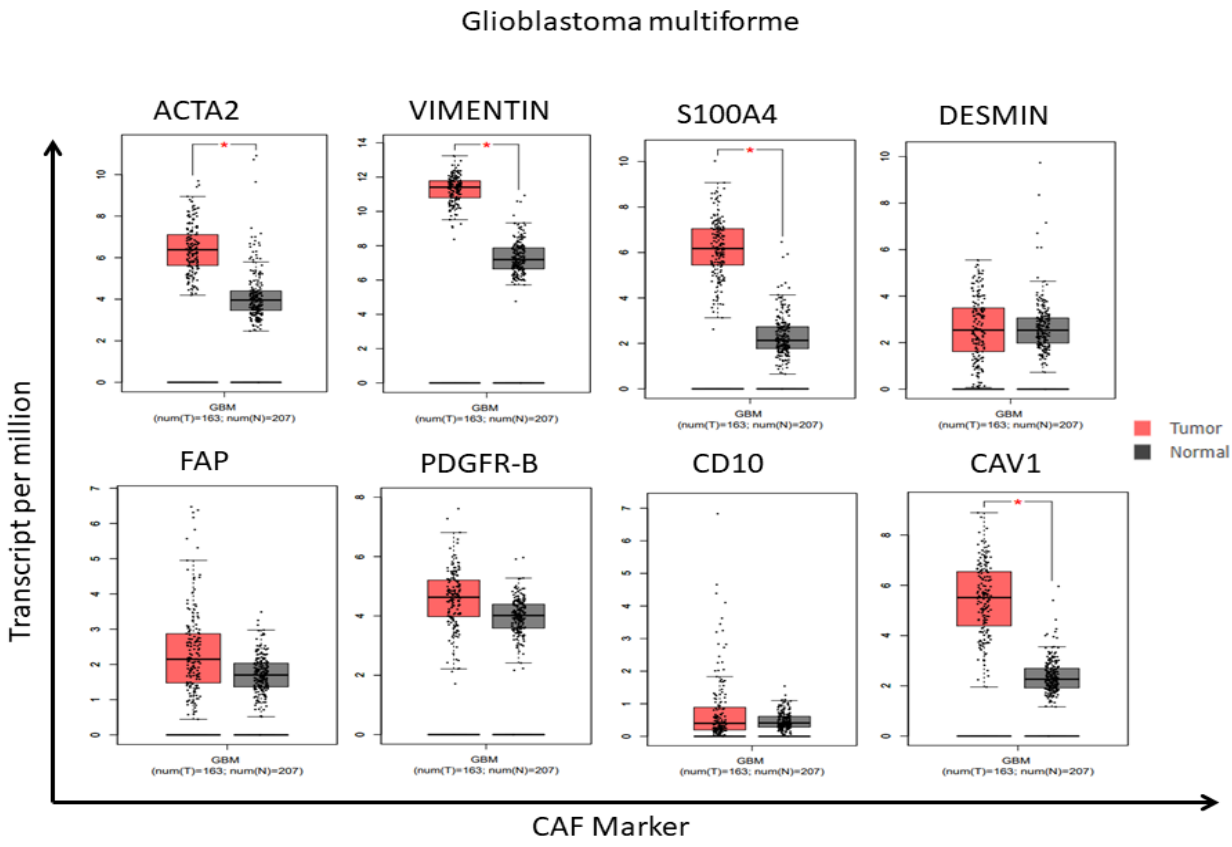

Figure 10. Cancer-associated fibroblast markers gene expression profiles in Glioblastoma multiforme (GBM). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in glioblastoma multiforme tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA GBM samples n = 163; normal = 207.

3.3.9 Kidney renal clear cell carcinoma

Kidney renal clear cell carcinoma is identified as having malignant epithelial cells with clear cytoplasm, compact acinar growth and a dense vasculature [145-148]. Several studies have shown the involvement of CAFs in renal clear cell carcinoma progression [149, 150]. Bioinformatic analysis of kidney renal cell carcinoma samples revealed that ACTA2, vimentin, FAP and caveolin-1 expression was significantly upregulated in tumor samples versus normal samples (Figure 11). As expected, desmin expression was significantly downregulated in tumor samples (containing CAFs) versus normal samples (Figure 11).

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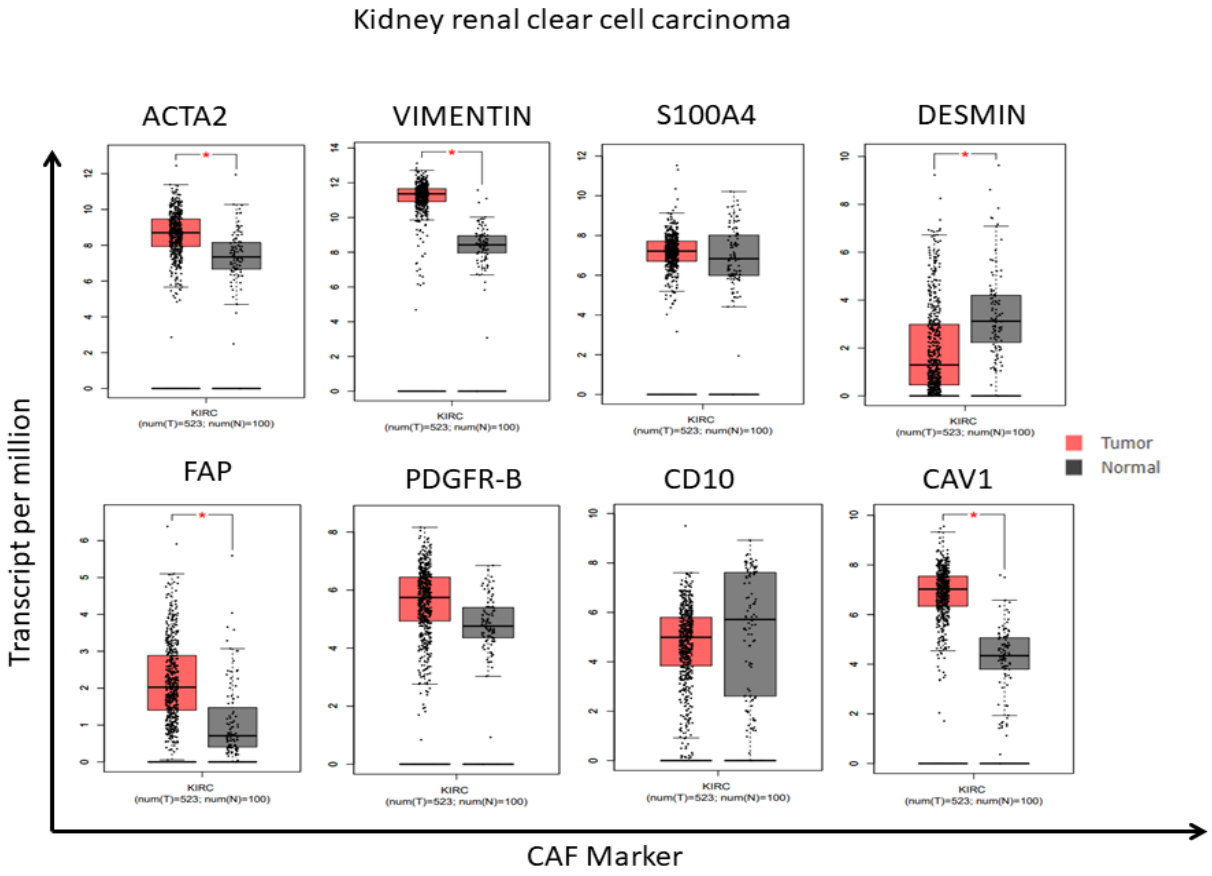

Figure 11. Cancer-associated fibroblast markers gene expression profiles in kidney renal clear cell carcinoma (KIRC). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in kidney renal clear cell carcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA KIRC samples n = 523; normal = 100.

3.3.10 Brain lower grade glioma

This brain cancer originates from two types of brain cells referred to as astrocytes and oligodendrocytes [151-154]. Although considered the slowest of brain tumors, lower grade gliomas can arise in healthy and young individuals [155-158]. This study shows that vimentin and caveolin-1 expression was significantly upregulated in brain lower grade glioma samples compared to normal samples (Figure 12). To confirm previous reports on downregulation of desmin in CAFs, this study shows that desmin expression is downregulated in tumor samples (containing CAFs) versus normal samples [107] (Figure 12).

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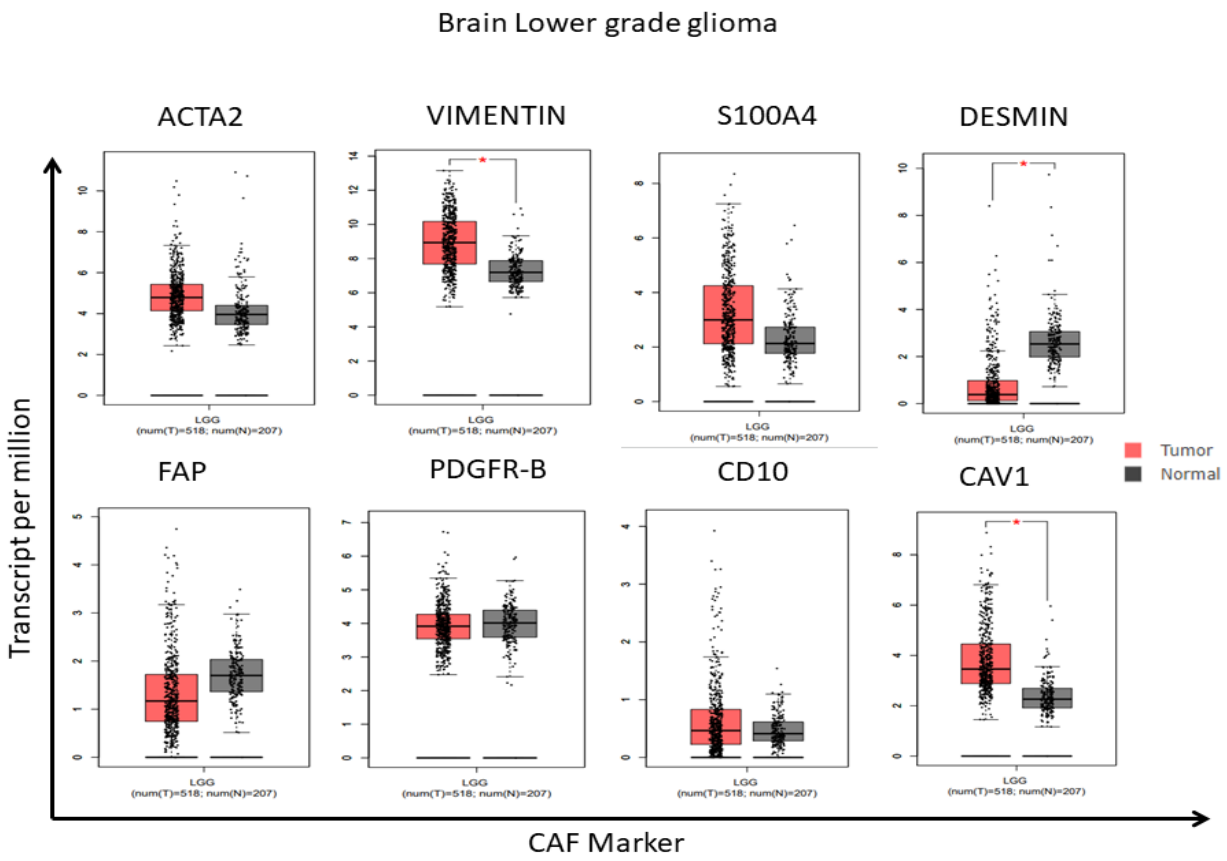

Figure 12. Cancer-associated fibroblast marker expression profiles in brain lower grade glioma (LGG). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in brain lower grade glioma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA LGG samples n = 518; normal = 207.

3.3.11 Liver hepatocellular carcinoma

Liver hepatocellular carcinoma is one of the most vascularised tumor types, with reports linking CAFs to enhanced tumor angiogenesis and invasion [159, 160]. Other studies link CAFs to induction of stem-cell like behaviour in cancer cells, leading to chemoresistance and metastasis [161, 162]. Below, the expression of CAF markers in liver hepatocellular carcinoma versus normal samples based on TCGA samples was evaluated. This study shows that vimentin, S100A4, PDGFR-β, CD10 and caveolin-1 expression was significantly upregulated in tumor samples compared to adjacent normal tissues (Figure 13). Desmin, as expected, is downregulated in tumor samples versus normal tissues (Figure 13) [107].

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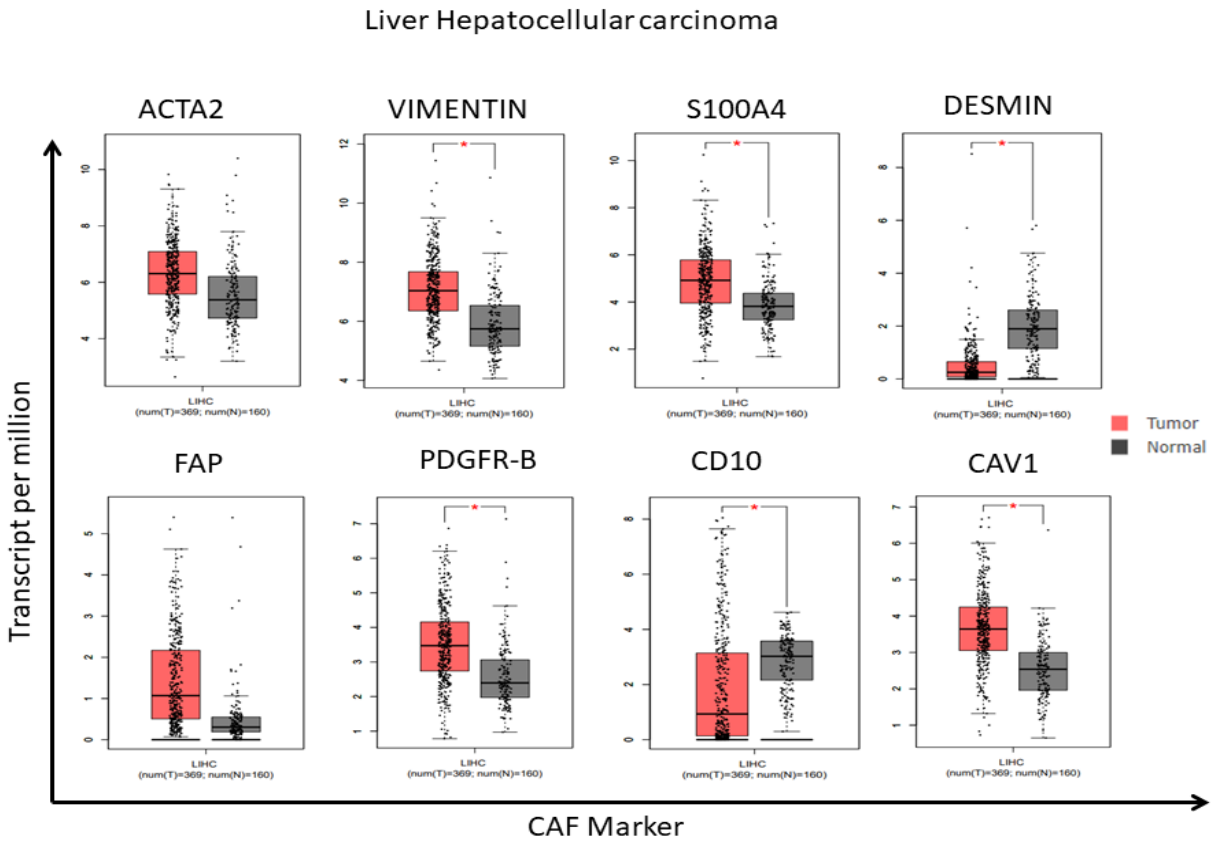

Figure 13. Cancer-associated fibroblast markers gene expression profiles in liver hepatocellular carcinoma (LIHC). The differential expression of CAF markers ACTA2, Vimentin, S100A4, Desmin, FAP, PDGFR-β, CD10 and Caveolin 1 in liver hepatocellular carcinoma tissues and paired normal tissues (Box plot) based on TCGA/GEPIA database. Data is based on TCGA LIHC samples n = 369; normal = 160.

4.0 Cancer-associated fibroblasts and Carcinogenesis

Data from several studies illustrate the supporting role of TM components in tumor progression, metastasis and formation of new tumors [18, 41-43, 69]. Whilst initially being prohibitive of tumor growth, we demonstrated that over time cells within the TM promote tumor growth via the release of growth factors and deposition of ECM [17, 18]. Several other studies confirmed that normal fibroblasts show inhibitory effects on cancer cell growth *in vitro* [163, 164]. The expression of PTEN in stromal cells was shown to be necessary for this inhibition effect on epithelial tumors [165]. Several growth factors and cytokines, including VEGF, SDF-1, TGF-β and IL-6 have been shown to be necessary in the transformation of normal stromal cells into cancer-supporting cells [18, 166, 167]. In addition, conditions within the TM such as hypoxia and ROS within the TM milieu also contribute to the conversion of normal cells to pro-tumorigenic cells [168, 169]. Through the expression and secretion of growth factors and cytokines and their receptors, CAFs impact cancer cell-associated processes such as inflammation, angiogenesis,

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migration, invasion, chemoresistance and immune evasion (Figure 14) [79, 170-173]. Erez and colleagues demonstrated that normal fibroblasts can be induced to express inflammatory genes by carcinoma cells [174].

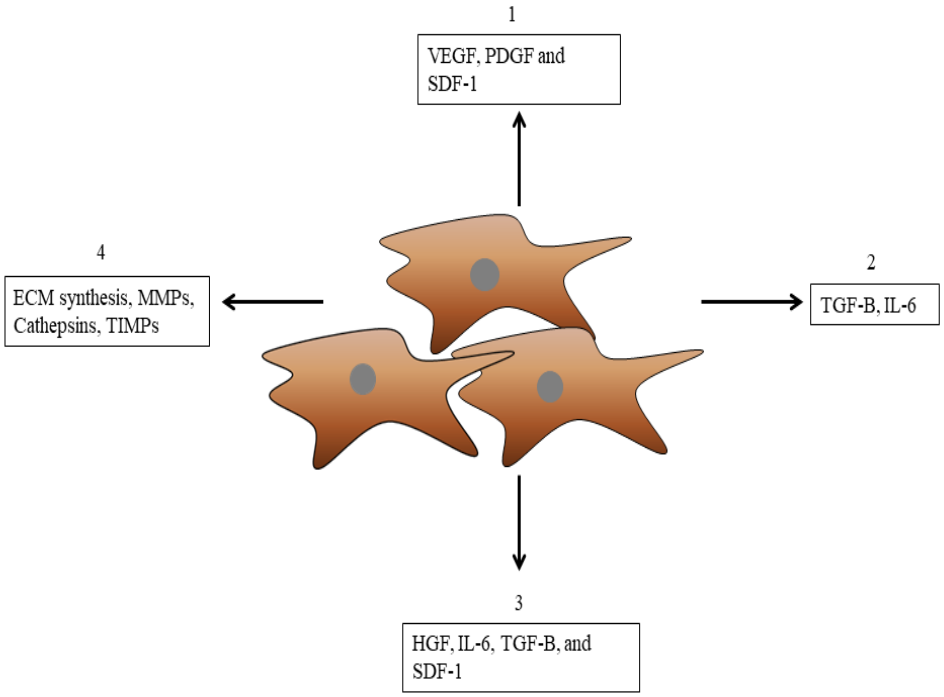

Figure 14. Effect of CAFs on tumor cells, other stromal cells and the ECM within the TM. CAFs synthesise and secrete the ECM, MMPs and various factors, impacting on cancer cell processes. Most of the secreted factors are growth factors and cytokines including HGF, FGF, TGF-β, IL-6, IL-1, COX-2, VEGF, HIF1-α, PDGF and SDF-1 and impact tumor processes such angiogenesis (1), chemoresistance (2), proliferation (3) and ECM remodelling (4).

In addition, miRNAs are also thought to be involved in transformation of normal fibroblasts into CAFs. miRNAs are delivered to their target cells via exosomes, allowing miRNAs to induce and transform local and distant fibroblasts [175, 176]. A recent study by Fang and colleagues demonstrated that exosomal delivered miRNA-1247 from cancer cells induce the transformation of fibroblasts within lung pre-metastatic environments, thereby promoting metastasis [177]. Mitra and colleagues also demonstrated that cancer cells reprogram fibroblasts to CAFs via the release of miRNAs in ovarian cancer [178]. Pang and co-workers also showed that cancer cell-derived miRNA-155 was involved in the transformation of normal fibroblasts into CAFs in pancreatic cancer [179]. It is important to note that the involvement of miRNAs is bi-directional with stromal cells also affecting cancer cells via the release of micro-RNAs [180, 181]. The hypoxic conditions of the TM result in the generation of ROS. Toullec and co-workers demonstrated that ROS within the TM induce the expression of hypoxia inducible factor 1-α

(HIF1-α) and CXC-chemokine ligand 12 by stromal fibroblasts, allowing the cells to have enhanced metabolism and migratory capabilities [182].

Albrengues and colleagues showed that there is an epigenetic switch that drives the transformation of normal fibroblasts into CAFs [183]. Leukamia inhibitory factor, a member of the IL-6 superfamily was shown to initiate the epigenetic switch leading to the activation of the JAK-STAT signaling [183]. The continuous activation of the JAK-STAT signaling leads to CAFs promoting cancer cell invasive behaviour. Several other studies have shown the importance of the JAK-STAT signaling in the maintenance of the CAF phenotype [184-186]. The continuous interaction between CAFs and cancer cells mean that during tumor progression CAFs also change, with CAFs demonstrating heterogeneity both at phenotype and function level [187-189].

The growth and transformation of normal epithelial cells is driven partly by CAFs [190]. Olumi and colleagues demonstrated that CAFs and not normal fibroblasts were responsible for the transformation and cancer initiation and growth of prostatic epithelial cells [190]. Kuperwasser and colleagues also demonstrated that TGF-β from CAFs was necessary for tumor formation from epithelial cells a result that was in contrast to the use of normal fibroblasts [191]. In addition, Shekhar and colleagues demonstrated that normal fibroblasts inhibited tumor growth and the tumorigenic transformation of epithelial cells [192]. Implantation of tumor cells and CAFs together allowed enhanced tumor growth compared to co-implantation of tumor cells and normal fibroblasts [193]. Several studies have shown the involvement of both cancer cell-derived and CAF-derived TGF-β and heat shock factor-1 in driving tumor cell growth and metastasis [18, 187, 194, 195]. Using both esophageal and breast cancer cells, we demonstrated that both CAFs and cancer cells released TGF-β which promoted both transformation of fibroblasts in addition to promoting tumor growth [18]. Several cancer cells have been shown to express TGF-β receptors on their cell surfaces, supporting the notion that cancer cells respond to both autocrine and paracrine TGF-β signaling [171, 196].

Besides releasing growth factors, CAFs also influence tumor growth through the release of enzymes such as MMPs and urokinase-type plasminogen activator (uPA) [197-199]. Although further research into the role of CAFs into tumorigenesis is required, there is some evidence that CAFs induce epithelial cell transformation [200]. To sustain tumor growth, new blood vessels are

formed and these supply all the nutrients required by cancer cells as well as remove toxic substances from the tumor [201]. CAFs release SDF-1 which has been shown to recruit endothelial progenitor cells, leading to formation of new blood vessels within the TM [114]. CAFs are known to release several other angiogenic factors such as PDGF-C, VEGF-A, and secreted frizzled-related protein-2 (SFRP2) [41]. Through the synthesis of ECM proteins and generation of ECM stiffness, CAFs also influence blood vessel formation and also the flow of blood through the tumor [17, 202].

Most early-stage epithelial tumors have a basal lamina that acts as a barrier between the tumor and vascular system [203, 204]. This results in early-stage tumors lacking proper supply of nutrients and removal of toxic substances. Migration and invasion of tumor cells into the surrounding tissues induce angiogenesis as well [205]. The induction of angiogenesis is coupled to infiltration of leukocytes, proliferation and activation of fibroblasts as well as increased deposition of ECM proteins [206]. Depending on the tumor type, stromal components and site in the human body, vascularisation can take different forms and patterns [204, 207-209]. In addition, the balance of expression of anti-angiogenic factors and pro-angiogenic factors will ultimately play a key role in determining both formation and pattern of blood vessels within the tumor [208, 210]. Ultimately, pro-angiogenic factors and signaling are eventually upregulated during tumor formation, leading to aberrant and dysregulated formation of blood vessels [205]. CAFs together with infiltrating leukocytes, macrophages and other stromal cells such as pericytes are known to be the major sources of pro-angiogenic factors such as VEGFA, PDGFC, FGF2, Osteopontin and MMPs (Table 1, below) [211-213].

For blood vessels to be formed, there has to be the right tumor or TM elasticity and stiffness [18, 202]. Whilst CAFs synthesise the TM ECM, enzymes released by CAFs such as MMPs, hydroxylases and lysyl oxidases influence both ECM synthesis and degradation and therefore control biophysical properties of the TM [206, 214-216]. Growth factors such as PDGFC act on CAFs in an autocrine manner to induce secretion of FGF2 as well as Osteopontin [116, 217].

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Table 1. Several angiogenic factors are produced by CAFs, CAMs and CANs and influence vascularisation within the TM.

Angiogenic Factor	Cellular source	Effect on vascular system	Reference
VEGFA	CAFs, CAMs, CANs	Pro-angiogenic, recruits other cells such as myeloid cells, ECM production	[24, 218, 219]
PDGFC	CAFs	Pro-angiogenic	[116, 217, 220]
FGF	CAFs, CAMs, CANs	Pro-angiogenic	[221, 222]
CXCL12	CAFs, CAMs	Pro-angiogenic, recruits monocytes, endothelial cells	[114, 223, 224]
CSF3	CAFs	Pro-angiogenic	[225, 226]
Collagen	CAFs	Pro-angiogenic	[227-229]
Fibronectin	CAFs	Pro-angiogenic	[15, 230]
Osteopontin	CAFs	Pro-angiogenic	[231-233]
MMPs	CAFs, CAMs, CANs	Pro-angiogenic, creates space for blood vessels formation	[234-237]

As the tumor grows in size, cancer cells migrate and invade surrounding tissues. When cancer cells breach the basement membrane they enter into circulation, travel to distant tissues and organs and eventually extravasate into new tissues, a process called metastasis. It is important to note that only a few cancer cell survive the arduous journey to new tissues and organs, but once there, these cancer cells colonize and form new tumors, metastases [238, 239]. Grum-Schwensen and colleagues demonstrated that tumors without stromal cell-derived mts1 protein do not metastasize, demonstrating the importance of stromal cell in tumor growth and spread [240]. Several studies have shown that beside stromal-derived growth factors, several cytokines are also released by stromal cells and aid cancer cell metastasis [241-244]. IL-6 has received a lot of attention and has been shown to help cancer cell metastasize to the bone [245]. Chang and colleagues showed that IL-6 and its downstream signaling cascades such as JAK-STAT are involved in breast cancer tumorigenesis and metastasis [246]. CAF-derived SDF1 has been

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shown to aid breast cancer cells home to the bone and aid in adaptation to this new environment [247, 248]. The release of stanniocalcin-1(STC1) by CAFs drives colon cancer metastasis [117]. TGF-β has been implicated in many cellular processes and Yu and colleagues demonstrated that TGF-β can induce EMT in cancer cells [249]. Both TGF-β and hepatocyte growth factor (HGF) have been shown to promote invasiveness in esophageal cancer [250, 251].

By releasing huge amounts of MMPs as well as synthesising the ECM, CAFs can remodel the TM and allow cancer cells to migrate and invade surrounding tissues. Increase in collagen levels within the TM has been shown to promote cancer cell invasiness [252, 253]. Degradation of the ECM by CAF-derived MMPs can create highways through which cancer cells can migrate to other tissues and organs [17, 81]. In addition, ECM stiffening is enhanced via activation of YAP1 in CAFs and has been shown to allow cancer cell invasion and formation of tumor blood vessels [67]. Goetz and colleagues demonstrated that CAF-driven biomechanical remodelling of the TM can allow migration and invasion of cancer cells [109]. Once cancer cells reach their new environment, it has to be remodelled to suit their needs or the cancer cell adapt to the new conditions. As postulated by Paget in the 'seed and soil' theory, the new microenvironment must allow cancer cells to flourish [254]. Kaplan and colleagues suggested that a pre-metastatic environment must be rich in ECM proteins such as fibroblast-derived fibronectin [255]. In addition, stromal cell-derived factors including TGF-β and SDF1 within the pre-metastatic regions may act as attractants to cancer cells [255, 256]. Resident fibroblasts within the pre-metastatic regions promote blood vessel formation allowing tumors to grow [256, 257]. It is plausible to suggest that these fibroblasts and any other stromal cells associated with metastatic cancer cells are resident cells within the colonised regions.

5.0 The role of CAFs in therapy resistance

There are two possible ways through which cancer cells can be resistant to therapy. Firstly therapy resistance can be intrinsic. The expression of several transporter proteins such as the ABC proteins and other genetic alterations can influence drug uptake and export at the cellular levels. Secondly, tumors are always evolving and this can result in previously responsive tumors to become irresponsive. The TM has emerged as a contributor to therapy resistance via the actions of stromal cells and the ECM. The versatile IL-6 cytokine has been implicated in resistance to chemotherapy in lung cancer [258]. Whilst it's understandable that cancer cells can

develop therapy resistance, CAFs have also been reported to be resistant to several drugs including gemcitabine in pancreatic cancer [259]. Communication between CAFs and cancer cells also includes exosomes which transport several factors and miRNAs from CAFs to cancer cells [259].

The EMT process is used by cancer cells to transform and reduce the expression of many cellular membrane proteins such as drug transporters [260]. The net effect of reduced drug transporter expression is reduced drug intake, ultimately leading to therapy resistance. EMT is a process activated by several signaling pathways and occurs in normal events such as embryonic development. Unfortunately, it also occur during neoplastic conversion of cells as well as fibrosis [261, 262]. Cells undergoing EMT gradually loose epithelial cell junction proteins and begin to synthesise more vimentin, becoming more migratory, invasive and chemoresistant [261, 262]. Several studies have shown enhanced vimentin, Snail and ZEB1 expression in cells that are chemoresistant [263-265]. Zheng and colleagues demonstrated that although EMT is not necessary for metastasis, it induces development of chemoresistance in pancreatic cancer [266]. In pancreatic cancer, resistance to gemcitabine is associated with EMT [263, 267, 268]. Poor survival of pancreatic patients has been associated with increased EMT program that cause impaired response to chemotherapy [269, 270]. Even more sinister is the seemingly ability of CAFs to uptake and accumulate high concentrations of drugs within the TM, resulting in reduced amount of drugs eventually reaching cancer cells [271]. Chemotherapy can kill cancer cells via production of ROS. CAFs have been shown to abrogate ROS production and therefore prevent death of cancer cells when exposed to chemotherapy [272]. Several survival pathways such as MEK-ERK and PI3K-Akt are known to be activated in cancer cells via the action of CAF-derived HGF and cause cancer cell resistance to RAF inhibitors [273]. In elaborate experiments, Senthebane and colleagues demonstrated that CAF-derived TGF-β play a role in breast and esophageal cancer cells resistance to paclitaxel and cisplatin [18]. Thus the CAF secretome play a huge role in development of therapy resistance in cancer cells.

The presence of cancer stem cells (CSCs) within the TM is still debatable but several studies have shown that these stem-like cells are able to resist therapies [274-278]. Several studies have demonstrated that CAFs subsets express drug transporter proteins such as ABC transporters and also provide a protective environment to CSCs within the TM [38, 279, 280]. CAF-derived cytokines such as IL-6 are responsible for maintenance of the CSC phenotype [281]. Microvesicles from CAF also deliver micro-RNAs to generate CSCs in breast cancer [282].

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Overall, studies have demonstrated that CAFs or their subsets promote therapy resistance in cancer cells via various mechanisms from accumulating large amounts of drugs, release of protein factors, mi-RNAs-laden exosomes to providing physical barriers to therapy. The combined targeting of these CAFs or their subsets together with cancer cells may offer durable treatment solutions for many cancers.

6.0 Cancer-associated fibroblasts and other stromal cells interactions

The interaction between TM components is through cell to cell adhesions, release of growth factors and cytokines and indirectly through exosomes. In addition, cells interact with the ECM via surface receptors such as integrins. Crosstalk between stromal cells is inevitable given the compact nature of most solid tumors. The most abundant immune cells within the TM are the macrophages, referred to as cancer-associated macrophages (CAMs) or tumor-associated macrophages (TAMs). As reported by Comito and colleagues CAFs and TAMs work together to promote tumor progression in prostate cancer [283]. Communication between the two types of cells occur via release of CXCL14 by CAFs, resulting in recruitment of TAMs to the tumor site and subsequent differentiation [283]. In turn, M2 TAMs are known to activate CAFs and therefore further promote tumorigenic growth. Hashimoto and colleagues demonstrated that CAFs derived from bone marrow MSCs promote macrophage invasiveness and transformation and in turn the resulting TAMs can prompt the proliferation of CAFs [284]. By working together these CAFs and TAMs can promote tumorigenic growth of neuroblastoma [284]. Myeloid cells within tumors can increase the expression of S100A8 in response to IL-6 released by CAFs in colon cancer [39]. Myeloid cells within tumors can also differentiate into suppressor cells linked to suppression of immunity [39]. For example, circulating myeloid-derived suppressor cells are recruited to tumors via release of fibroblast activation protein by CAFs and these cause suppression of immunity in hepatic cancer [75].

CAFs are known to express FAS ligand (FasL) and this is known to cause apoptotic death of CD8-positive T cells [285]. Furthermore, CAFs express programmed cell death 1 ligand 2 (PD-L2) which cause the functional inactivation of T cells [285]. Our study and several others have shown that CAFs secrete huge amounts of TGF-β which has been suggested to cause immunosuppression and can induce transformation of immune cells into immune suppressing cells [18, 74, 286]. Recently, Mariathasan and colleagues provided further evidence of the

involvement of TGF-β in abrogating antitumor immunity in bladder cancer [287]. CAFs attract and sequester CD8-positive T cells and this prevents T cells from binding to and killing cancer cells [288]. The net effect of all this is suppression of anti-tumor activity of immune cells. Removal of FAP-positive CAFs was shown to reactivate the anti-tumor activity of immune cells of T cells [289]. Overall, CAFs are more likely to promote tumorigenic growth through their effect on immune cells within the TM. Several growth factors are known to be sequestered by the ECM and these include vascular endothelial growth factor-A (VEGFA) and TGF-β. Through production of matrix metalloproteases (MMPs), CAFs can degrade the ECM and cause enhanced levels of free growth factors within the TM [43]. Thus through recruiting endothelial cells in addition to releasing VEGFA, CAFs promote tumor vascularisation [43]. The interaction of CAFs and other cells therefore creates a tumor environment that promotes immune evasion, inflammation and vascularisation.

As reported by Senthebane and colleagues, CAFs and other TM components can also display anti-tumorigenic effects especially during the early stages of tumor development [18]. Our data revealed that normal fibroblast-derived ECM limits cancer cell proliferation and migration compared to an ECM from fibroblasts co-cultured with cancer cells [17]. Further evidence of the involvement of CAFs or their normal counterparts in anti-tumorigenic behaviour comes from studies of breast cancer. Brechbuhl and colleagues reported two subsets of CAFs in breast cancer, with one subset expressing CD146 and conferring sensitivity to tamoxifen whilst the CD146- subset confers tamoxifen resistance [77]. Removal of CAFs expressing α-SMA from pancreatic ductal adenocarcinoma (PDAC) results in acceleration of cancer and reduced survival [49, 51]. With this in mind, novel therapeutic strategies aimed at CAFs have to be selective and cognisance of the CAFs phenotypic and functional heterogeneity. Mere targeting CAFs for removal based on presumed pro-tumorigenic behaviour will be detrimental and can lead to fatal disease. CAFs subsets must be identified and only targeted therapy used. In addition, it might be helpful to re-educate or re-direct the pro-tumorigenic CAFs into anti-tumorigenic CAFs. To be able to do this, it is important that specific markers for anti-tumorigenic and pro-tumorigenic CAFs be identified to distinguish the two.

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7.0 Advances in therapeutic targeting of CAFs

7.1 CAF-directed therapies

It has long been recognised that manipulation of CAFs functions, especially tumorigenic promotion part, have therapeutic value in cancer treatment. In theory targeting CAFs appear easy since they are the major stromal component of the tumor. In addition, CAFs have been described as genetically stable, making them a better target than cancer cells in cancer immunotherapy [290]. In practise however, major challenges need to be overcomed before this promising avenue is utilised in cancer treatment. Firstly, targeting CAFs will have a negative effect on normal tissue and other components of the TM. For example, the depletion of CAFs can result in less ECM production, creating highways through which cancer cells escape and metastasize to other tissues and organs. Secondly, the removal of CAFs itself suffers from the lack of specific markers that can be used to achieve that. Thirdly, and probably most challenging is the existence of CAFs subsets displaying phenotypic and functional heterogeneity. To overcome this requires the identification of more than one specific markers of each subset that can be used for targeting that subset.

Several approaches have been devised to target CAFs within the TM. Firstly, the activation and trans-differentiation of stromal cells into CAFs can be targeted and inhibited. Since CAFs influence both tumor cells and stromal cells via synthesis and secretion of growth factors and cytokines, inhibition of this synthesis and secretion is under intense scrutiny, with the aim of inhibiting CAF function. Secondly, CAFs normalisation through the use of several molecules has been tried. For example, all-trans-retinoic acid (ATRA) can be used to induce quiescence in CAFs or activated fibroblasts/stromal cells, preventing aberrant secretion of growth factors and cytokines. Whilst CAFs are pro-tumorigenic, they can be used as carriers of drugs to kill cancer cells. Together with other cells such as cancer-associated macrophages (CAMs), MSCs and pericytes, CAFs can carry anti-cancer viruses and apoptosis-inducing ligands. Several studies including our recent publication have demonstrated that MSCs can be transformed into CAFs [18, 76, 132, 291, 292]. Senthebane and colleagues demonstrated the influence of the ECM in tumor growth and chemoresistance [17]. Importantly, the presence of ECM proteins including type I collagen and fibronectin was shown to affect drug delivery to cancer cells, with the knockdown of both ECM proteins showing increased drug-induced cancer cell death [17]. Previous studies implicated signalling pathways such as the MEK-ERK and MMPs in regulating ECM synthesis [214, 215]. Ablation of stromal ECM can therefore be used to increase cancer

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cell sensitivity to anti-cancer drugs. Direct targeting of CAFs or their subsets is still challenging, with difficulties in identification of markers to use to identify the CAFs. Currently, immunotherapy, use of immunotoxins and DNA vaccines can be used to target CAFs, with the duly still out on the effectiveness of such therapy.

Senthebane and colleagues utilised both vimentin and α-SMA as markers to identify MSC-derived CAFs recently [18]. Other studies have shown that α-SMA only identifies a specific subset of CAFs [49, 293, 294]. Ozdemir and colleagues described that the removal of α-SMA-positive CAFs in pancreatic ductal carcinoma (PDAC) was linked to decreased angiogenesis [49]. The same authors observed that whilst angiogenesis decreased there was increased hypoxia within solid tumors leading to increased EMT and the presence of CSCs [49]. Several lung and colon cancer animal models have shown that removal of FAP from within solid tumors is associated with decreased tumor growth [295]. Santos and colleagues demonstrated that a pre-clinical FAP inhibitor, PT630, can inhibit the growth of tumors as well as stromagenesis in lung and colon cancers [296]. Similarly, removal of FAP in PDAC also reduced tumor growth [297]. Ostermann and colleagues developed a monoclonal antibody against FAP which they conjugated to maytansinoid and this treatment has been used in pancreas and head and neck cancers where it has shown its effectiveness [290]. In addition, elaborate experiments by Loeffler and colleagues using a mouse DNA vaccine against FAP resulted in ablation of CAFs and enhanced drug uptake by tumors [298]. The DNA vaccine induced a CD8+ T cells to kill a large part of the CAFs expressing FAP. Further evidence for the utility of the DNA vaccine against FAP-positive CAFs was provided by Reisfeld [299]. The utility of CAR T cell treatment for solid tumors is still to be proven. Several reports however show that targeting FAP-positive CAFs using CAR T cells results in antitumor activity [300-302]. However, CAFs are not the only cells expressing FAP. Bone marrow-derived MSCs are also known to express FAP [303]. Thus it is possible that anti-tumor CAR T cells will also target other cells. Whilst reports show that CAR T cells targeting FAP-positive CAFs are able to kill cancer cells in lung and pancreatic cancers [302], Roberts and colleagues demonstrated that CAR T cells killed bone marrow-derived stem cells and can cause cachexia and anaemia [304].

Increased knowledge and analytical tools has enabled scientists to identify new and better surface markers for CAFs. For example, Su and colleagues were able to characterise tumorigenic CAF subsets based on the expression of CD10 and GPR77 [38]. Used together with FAP and α-SMA,

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these new surface markers are likely to define specific CAF subsets leading to their killing. The same authors reported reduced cancer cell stemness when GPR77 was blocked [38]. Several strategies are being developed to target cellular sources of CAFs. Senthebane and colleagues demonstrated that it is possible that MSCs are transformed into CAFs through their interaction with cancer cells [18]. Thus targeting MSCs may prevent the accumulation of CAFs in tumors, reducing pro-tumorigenic cells within the tumor. Removal of pro-tumorigenic support is likely to reduce tumor growth and metastasis. Several clinical trials have been undertaken to target CAFs sources with the duly still out on their effectiveness.

Re-education of activated CAFs has been suggested as a strategy to direct CAFs from being pro-tumorigenic to anti-tumorigenic. Inactivation of CAFs can induce quiescence with the resulting CAFs or fibroblasts dividing slowly and releasing normal levels of growth factors and other factors. Akin to quiescent satellite cells in muscle, these re-educated CAFs can attain a tumor suppressive phenotype. Induction of quiescence in pancreatic stellate cells in PDAC through the use of ATRA revert the activated cells to normal fibroblasts and arrests tumor growth [305]. The mechanism of action of ATRA involve inhibition of the versatile Wnt-β-catenin signaling cascade [305]. Inactivated pancreatic stellate cells also release sequestered CD8+ T cells allowing infiltration into PDAC resulting in tumor growth arrest [288]. Carapuca and colleagues showed that coupling ATRA, a vitamin A analogue, and gemcitabine can be effective at treating PDAC in animal models through inhibition of several pathways including Wnt-β-catenin and Hedgehog signaling [306]. Sherman and colleagues demonstrated that global reprogramming of the stroma through the use of calcipotriol, a vitamin D receptor ligand, and gemcitabine resulted in reduced inflammation and ECM synthesis in PDAC tumors [307]. Reduced ECM synthesis allowed better delivery of gemcitabine into the tumor leading to tumor regression [307]. Both ATRA and calcipotriol are at pre-clinical stage of investigations. Thus depending on the tumor type, different strategies from ablation of CAFs to normalisation of activated CAFs may be undertaken to achieve better cancer treatment. This provides a new avenue of cancer treatment that focus not just on cancer cells but on the stromal component as well. Combinations of strategies focussed on cancer cells and stromal cells may offer durable cure for cancer treatment.

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7.2 Targeting signaling pathways activated in CAFs and their downstream effectors

One of the remaining challenges to CAFs ablation and normalisation is the huge heterogeneity observed in many tumors, meaning some CAFs subsets will remain unaltered by treatment. Instead of targeting the CAFs, several approaches have been developed to target signaling pathways activated in CAFs and factors released by tumor and stromal cells. Tumor cells and stromal cells release huge amounts of factors during tumor initiation and progression [17, 18, 308]. Senthebane and colleagues demonstrated that TGF-β released by tumor cells and transforming MSCs can be involved in the transformation of stromal cells into potential CAFs [18]. The same study also show that once transformed, activated CAFs release increased levels of the same growth factor, TGF-β, which is involved in tumor growth and development of chemoresistance [18]. One signaling cascade that has been studied in detail in different cellular processes is the IL6-JAK-STAT pathway [167, 309, 310]. Sanz-Moreno and colleagues showed that Oncostatin M, a member of the IL-6 superfamily, activates STAT3 signaling and drive ECM remodelling [311]. ECM remodelling allows cancer cells to invade surrounding tissues, escape and metastasize to other sites [311]. A detailed description of inhibition of the IL-6-JAK-STAT signaling pathway as well as the TGF-β signaling is given below.

Pietras and colleagues demonstrated that the reduction of fibroblast growth factor 2 (FGF2) and fibroblasts growth factor-7 (FGF7) in animal models of cervical cancer via Imatinib-mediated inhibition of platelet-derived growth factor receptor slowed cancer cell division and disrupted angiogenesis [116]. The authors showed that targeting CAFs can act in complement to conventional therapeutic strategies and improve the management of cancers that are difficult to cure. Research by Anderberg and colleagues further showed that platelet-derived growth factor-CC induces the expression of osteopontin in CAFs, leading to tumor growth acceleration [217].

The chemokine SDF1, exclusively produced by FAP-positive CAFs, binds to its receptor CXCR4 resulting in suppression of immunity within the TM through prevention of CD8+ T cell infiltration [289, 297, 312]. Several inhibitors of SDF1-CXCR4 interactions have been developed and these can reactivate the anti-tumor immunity by enhancing the infiltration of CD8+ T cells into the TM [297]. Inhibition of SDF1 and CXCR4 interactions include the use of inhibitors such as AMD3100 and may enhance the anti-tumor effects of monoclonal antibodies against

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PDI/PDL1 in pancreatic duct adenocarcinoma [313]. Another strategy under consideration to control CAF-derived factors includes inhibition of protein synthesis. Inhibition of protein synthesis through the use of SOM230, an inhibitor of protein synthesis in α-SMA-positive CAFs, resulted in reduced levels of several molecules [314]. Indeed, inhibition of protein synthesis in CAFs led to less ability of cancer cells to resist chemotherapy in a PDAC model [314].

7.2.1 Targeting the IL-6-JAK-STAT signaling in cancer

It has been shown that the IL-6-JAK-STAT3 is abnormally activated in several cancers, with enhanced activation of the pathway linked to poor patients' survival [315-317]. Within the TM, the IL6-JAK-STAT3 signaling has been shown to be responsible for cancer cell invasive and metastatic behaviour. In addition, the IL-6-JAK-STAT3 signaling represses immunological response to tumors. Anti-cancer agents or inhibitors against members of the IL-6-JAK-STAT3 have been approved by the FDA and the EMA, whilst others are still under investigations.

Several pathological conditions display high levels of IL-6 and increased activation of the IL-6-JAK-STA3 including rheumatoid arthritis as well as many cancers [318, 319]. Mutations in genes of several JAK-STAT pathway members activate the pathway in many neoplasms. Increased IL-6 in circulation and within the TM is a result of the JAK-STAT pathway being constitutively activated [315, 320, 321]. Besides CAFs, multiple other cells have been shown to produce IL-6 within the TM, from pericytes, immune cells and even tumor cells [322-324]. Activation of STAT3 by IL6 in tumor cells results in expression of proliferation and survival genes including cyclin D1 and BCL2-like protein 1 (BCL-xL), respectively [325]. Since both CAFs and tumor cells show activation of IL6-JAK-STAT signaling, the description given below and the targeting of the IL-6-JAK-STAT signaling can therefore be applied to both CAFs and tumor cells to achieve durable cancer treatment. IL-6 activated STAT3 can induce VEGF, MMPs and TGF-β expression, promoting angiogenesis, invasion and development of therapy resistance, respectively [325-327]. Besides direct effects on cancer cells, IL6 and JAK-STAT signalling influence the behaviour of stromal cells including CAFs, CAMs, TANs, effector T cells and killer cells [328-333]. By affecting both CAFs and immune cells, the IL6-JAK-STAT signalling contributes to the suppression of the immune response in the TM.

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The importance of IL6 in TM is underscored by its various effects on tumor cell and stromal cell survival, proliferation and invasiveness [328, 334]. Two IL6 signaling are known: the classical IL6 signaling pathway which involves IL6 binding to IL6 receptor on the cell surface and interacts with transmembrane protein gp130; the trans-signaling pathway whereby IL6 binds to a soluble form of IL6 receptor and then interacts with gp130. Importantly, although similarities exists in the ways in which both signaling pathways regulates cell behaviour, the trans-signaling pathway controls the recruitment and activation of stromal cells [335, 336]. Activation of the IL-6 signaling results in activation of mostly JAK1 and JAK2, which then phosphorylate members of the STATs family [309, 337]. Of the STATs proteins, STAT3 is the most studied and has been linked with tumor progression and suppression of immune system [326, 338]. Activation of STATs proteins is regulated by PIAS proteins, suppressor of cytokine signaling (SOCS) proteins, phosphatases and miRNAs [339-342].

IL6 levels are increased in cancers including breast, lung, colorectal, oesophageal, ovarian and prostate cancers [343-347]. Several pre-clinical studies utilising models and patient samples have demonstrated the critical roles of circulating IL6 in tumor development [12, 348, 349]. For example, IL6 enhances CSC proliferation in breast cancer [348]. In addition, IL6 is known to promote epithelial to mesenchymal transition and metastasis in breast cancer [350, 351]. Consequently, IL6 levels in circulation have been used as prognostic indicators in patients' survival and can predict response to therapy [352-355]. Several studies utilising models and patients samples have demonstrated the critical role played by CAF- and tumor-derived IL-6 cancers including breast, colorectal, oesophageal, lung and skin cancers [348, 356-358]. Aberrant levels of STAT3 activation have been shown in many cancers [359, 360]. Besides being involved in tumor progression, several studies have shown that STAT3 can promote therapy resistance [361, 362].

Several strategies have been developed to target the IL-6-JAK-STAT signaling pathway (Figure 15). Siltuximab for example, targets IL-6 directly and whilst Tocilizumab targets the IL-6 receptor. Siltuximab has shown efficacy against several solid tumors including lung and prostate cancers [363, 364]. Siltuximab have been shown to reduce the levels of STAT3 and other signaling cascades such as MEK-ERK in tumors [365, 366]. Tocilizumab is used in patients with rheumatoid arthritis and has efficacy against colorectal and pancreatic cancers [356, 367].

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Inhibitors of JAKs include Pacritinib, Ruxolitinib and Tofacitinib and these have shown varied efficacy against cancers such as colitis, myelofibrosis, liver, pancreatic and ovarian cancers [368-373]. STAT3 inhibitors demonstrated antitumor activities and promoted apoptosis against several cancer cells [374-379].

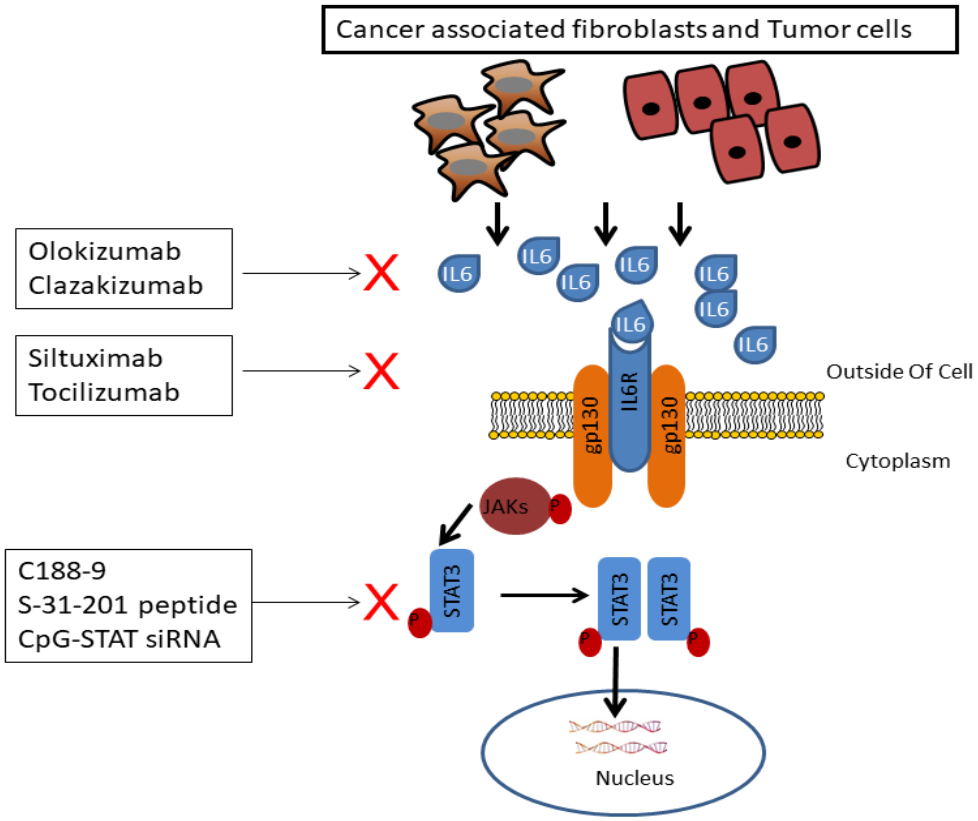

Figure 15. Some of the strategies targeting both cancer-associated fibroblast- and tumor cell-derived IL-6-JAK-STAT signaling pathway are indicated. X – Blocking of signaling step.

7.2.2 Targeting the Cancer-associated fibroblast-derived TGF-β signaling pathway in cancer

Several reports document the lack of cancer patients' response to therapy being associated with TGF-β signaling in CAFs and CAMs [80, 380-385]. In normal cells and during early stages of tumor development, the TGF-β signaling display anti-tumor functions, with reports of cancer cell cycle arrest and induction of apoptosis [18, 80, 386]. Our study demonstrated that as tumors develop, TGF-β from both stromal cells and tumor cells participate in the transformation of normal fibroblasts and MSCs into CAFs and thus contributes to further tumor development, metastasis and therapy resistance (Figure 16, below) [18, 78, 387]. Thus, depending on the stage of tumor development, TGF-β signaling can have both tumor-promoting and tumor-suppression functions. Targeting this pleiotropic signaling cascade is therefore difficult, with

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further research required to determine the specific members of the pathway to target as well as the right doses. Importantly, the effects of inhibition of this signaling cascade on both cancer cells and stromal components must be further investigated. The elucidation of possible biomarkers that can point to the usefulness of potential inhibitors during and after treatment must be determined. In their elaborate study, Mariathasan and colleagues demonstrated that a combination of TGF-β signaling blockade and anti-PD-L1 repressed TGF-β signaling in stromal cells, leading to enhanced tumor suppression [381]. Importantly, the authors demonstrated the need to combine treatment strategies to attain durable cure in cancer. Several drugs targeting TGF-β are under trial and these include fresolimumab (NCT02581787).

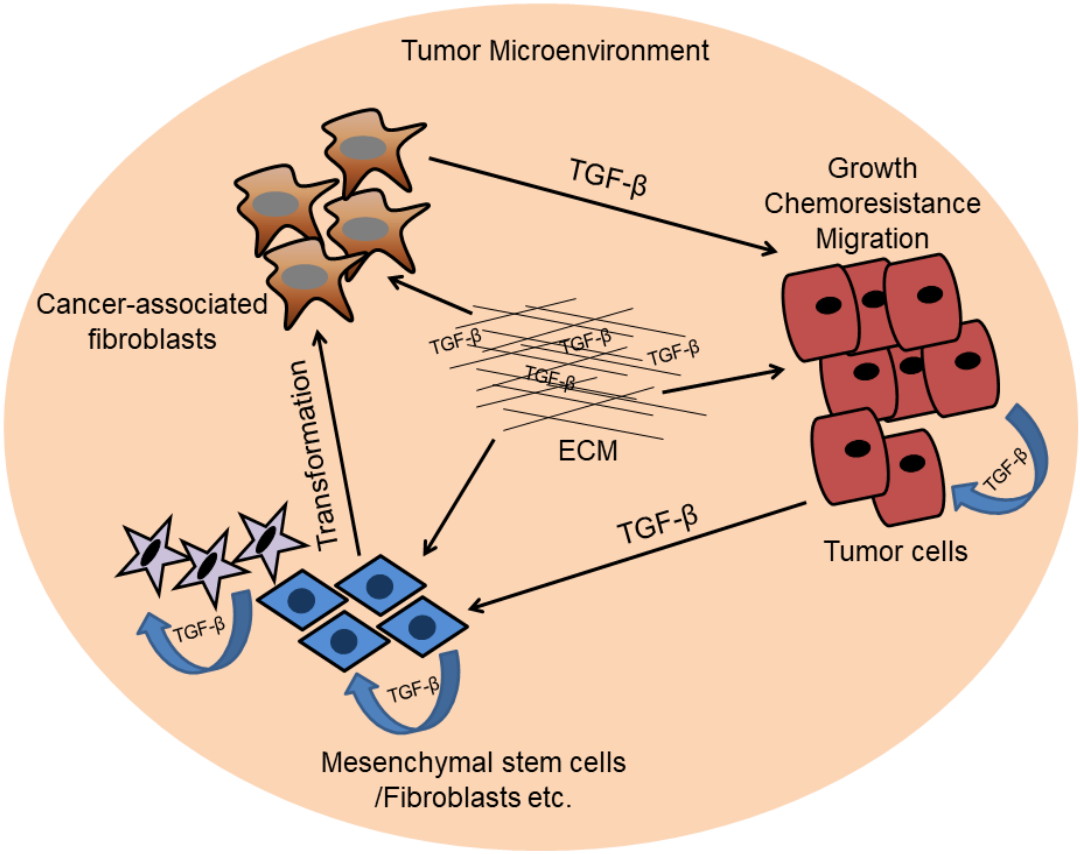

Figure 16. Both tumor and stromal cells secrete TGF-β into the TM milieu. TGF-β and other growth factors can be sequestered by the ECM. Increased TGF-β within the TM leads to transformation of MSCs and fibroblasts into CAFs. Increased CAF- and tumor-derived TGF-β levels cause increased tumor growth, chemoresistance and metastasis. Figure adapted from [18].

7.3 Targeting CAF-derived ECM proteins and associated signaling

CAFs are the principal cells responsible for synthesising the ECM [388-392]. In normal tissue, fibrillar collagens, fibronectin, hyaluronan, tenascin C are deposited in large amounts to make the

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ECM. Increased synthesis of ECM proteins result in desmoplastic reactions and these are known to drive tumor growth [393]. Besides inducing desmoplastic reactions, increased ECM synthesis creates a barrier for the delivery of drugs to cancer cells [18, 66]. In elaborate *in vitro* experiments, we demonstrated that the presence of an ECM increased the resistance of breast and oesophageal cancer cells to several chemotherapeutic agents [17]. Whilst it is plausible that reduction in ECM synthesis in CAFs and other stromal cells such as macrophages is an appealing strategy, improper ECM synthesis can create 'highways' through which cancer cells may metastasize [17, 18, 394]. Increased amounts of both collagen and hyaluronan in tumors can result in compressed vascular networks, inadvertently reducing the flow of drugs to cancer cells [215, 395]. Targeting both collagen and hyaluronan production by both CAFs and macrophages can allow drugs to reach cancer cells [395]. Inhibition of collagen through the use of halofuginone has been shown to reduce desmoplasia, impacting tumor progression [396].

Enzymatic degradation of ECM proteins such as collagen via MMPs occurs during ECM remodelling. The use of MMPs as an anti-cancer therapy has largely failed to materialise [397]. For a start there is so much overlap in MMP activities and indiscriminate degradation of ECM proteins can have a negative effect during treatment [397]. Currently several MMPs inhibitors are under investigations in many cancers [398]. Deciphering the exact MMPs activities and their specific targets can aid in the development of novel use of MMPs in cancer treatment [214, 399, 400]. Hyaluronan can be depleted through the use of recombinant hyaluronidase enzyme to allow drugs to reach cancer cells [401, 402]. Targeting hyaluronic acid via the use of PEGPH20 is still under investigations (NCT01453153). New clinical trial data (HALO-109-301) show that when used together with gemcitabine and nab-paclitaxel in patients with advanced pancreatic cancer, PEGPH20 is promising [403]. Caution however must be heeded as the resulting expansion of the vascular system can result in invasion and metastasis of cancer cells. A combination of the removal of ECM proteins during treatment can enhance patients' survival, demonstrated in PDAC by Hingorani and colleagues [404]. *In vitro* work by Senthebane and colleagues demonstrated that removal of both collagen and fibronectin from ECM resulted in increased apoptosis in oesophageal cancer cells [17]. Antibodies have been used to target fibronectin to reduce vascularisation and tenascin C to prevent metastasis [405, 406]. Targeting Tenascin C together with chemotherapy improves the survival of glioma patients [406]. Inhibition of signaling pathways perturbed in TM such as the IL-6-JAK-STAT and sonic hedgehog cascade can aid in reducing CAFs and their secreted factors, resulting in better therapy

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response [407]. For example, IPI-926, an inhibitor of Hedgehog pathway, together with Gemcitabine has been shown to influence resistance to chemotherapy in PDAC [408]. Currently most stromal-directed therapy is still in its infancy and removal of any stromal elements must be studied carefully. Stromal cells and their products such as the ECM are needed for normal tissue architecture and homeostasis [17, 18, 214, 409]. Any stromal-directed therapy will have to work in combination with tumor-directed therapy to achieve durable cancer treatment.

7.4 Targeting CAF- or stromal-induced Angiogenesis

Given the diverse cells and mechanisms through which tumor vasculature is induced and develops, inhibition of tumor angiogenesis is challenging. Whilst angiogenesis inhibition has been successful in some cases, partial to total failure has also been reported in some studies [410-417]. Studies demonstrated that tumor angiogenesis is regulated by several factors and mechanisms and does not solely dependent on VEGF-A signaling [411, 417, 418]. Several studies have also shown the existence of tumor growth requiring no angiogenesis [419, 420]. Angiogenesis-independent tumor growth is also achieved through the action of immune cells such as macrophages and neutrophils [421-423]. Coupling anti-angiogenesis specific therapy to strategies that disrupt any compensatory factors and signaling from cells such as macrophages and neutrophils offer a better potential at inhibiting angiogenesis in tumors [424-426]. Blockage or elimination of both macrophages and neutrophils that confer VEGF-A-independent angiogenesis to tumors has been shown to enhance tumor response to VEGF-A specific therapy [427]. Kaneda and colleagues demonstrated that inhibition of PI3K signaling, highly expressed in myeloid cells, successfully inhibited angiogenesis in cancer treatment [428]. Caution must be taken however, as several studies have shown that inhibition of angiogenesis may enhance the ability of tumor-associated cells to promote tumor growth [410, 429, 430]. Crawford and colleagues demonstrated that some tumors can overcome angiogenesis inhibition through upregulation of PDGF-C [220].

8.0 CAFs as delivery vehicles of Therapeutic agents

As described by Miao and colleagues, CAFs can be used to delivery anti-tumor drugs or nanoparticles and cause cancer cell death via apoptosis [431]. It has also been shown that fibroblasts within a tumor can scavenge and accumulate therapeutic drugs, resulting in increased

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drug concentrations within tumors [271]. Senthebane and colleagues demonstrated that MSCs can be transformed into CAFs and thus are a major source of CAFs found in tumors [18]. The authors and others demonstrated that although MSCs initially demonstrate anti-tumor behaviour they are easily transformed into tumor-supporting cells (CAFs) when in contact with cancer cells [432, 433]. Due to their likelihood of being found within tumors, MSCs have been suggested as drug-delivery vehicles or can be manipulated to secrete anti-tumor factors [433]. Amniotic MSCs have been suggested to deliver therapeutic agents to tumors [434]. Several clinical trials are under way on the use of MSCs in gene therapies for different cancers [435-437]. Overall, the use of MSC-based gene therapies requires further investigations as Senthebane and colleagues demonstrated. The authors' results show that MSCs can be pro-tumorigenic or anti-tumorigenic depending on tumor stage [18, 432]. Other studies support this dual-effect of MSCs [438-440].

Of late CAFs are now being used as a stromal indicator of the disease stage during diagnosis and as an indicator of tumor response to treatment strategies. Tsujino and colleagues demonstrated that the number of myofibroblasts within TM can be used as a clinical biomarker of disease relapse in colorectal cancer [65]. Surowiak and colleagues showed that the presence of CAFs within breast cancer tissue is a poor prognostic factor [441]. Contrasting data on the prognostic value of CAFs in tumors may be due to CAFs heterogeneity as well as co-evolution of CAFs with tumor cells during tumor progression [77, 442].

9.0 Perspectives and Conclusion

Several lines of research are being initiated to evaluate the effectiveness of many therapeutic drugs on CAFs. Epigenetic drugs including histone deacetylase (HDAC) inhibitors are under investigation for their effect on several signaling pathways such as the JAK-STAT pathway in both cancer cells and CAFs [443]. These epigenetic drugs are being evaluated on their potential to prevent CAFs generation and increase in abundance within tumors [444]. Another appealing strategy include the use of normal fibroblasts in cancer treatment or the reversion of activated CAFs to normal fibroblasts [445].

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Many questions remain to be answered regarding the origin of CAFs or their subsets as this can influence CAF-directed therapeutic strategies adopted during cancer treatment. It is hoped that as new information becomes available, new markers and signaling pathways specific only to CAFs or their subsets can be identified. The identification that MSCs, beside fibroblasts, can be a source of CAFs might explain CAFs heterogeneity and could be the reason why several CAFs subsets are observed in tumors [18]. If different cells contribute to the CAFs subsets observed in tumors, which cell(s) of origin gives rise to pro-tumorigenic CAFs and which cell(s) gives rise to anti-tumorigenic CAFs? Based on data revealed by Senthebane and colleagues it appears despite different cell(s) of origin, stromal cells may start as anti-tumorigenic but are transformed through several secreted factors to become pro-tumorigenic [18]. Whether different cell types contribute to different subsets require further investigations. In addition, the identification of specific markers for different subsets can allow retrospective determination of cell of origin as well as the development of specific anti-tumorigenic therapies against these CAFs subsets. Stromal cells can also co-evolve with tumor cells. Is tumor cell heterogeneity also partly driven by different CAF subsets? Epigenetic regulation of CAFs must also be investigated to allow development of drugs targeting epigenetics of CAFs [443]. Many clinical trials done for different candidate drugs have focussed on targeting cancer cells and up to now no trial has been done on candidate drugs targeting CAFs.

One major challenge faced by scientists during the development of novel cancer therapies has been the absence of adequate cancer models that recapitulate the TMs as seen *in vivo* to use in preclinical studies. This has prevented the proper understanding of tumor cell-stromal cells interactions as well as cell-matrix interactions. For example, very few available cancer models include cells such as CAFs, CAMs and CANs. As shown by recent reports, addition of ECM proteins to cancer models as well as the development of tumor spheroids and organoids promises to reveal more about tumor initiation and development than the use of cancer cells in *in vitro* experiments. New advances including microfluidic technology will allow the development of what is known as 'human organs on chips'. With the ability to change parameters as required during tumor development as well as potential additions of several cells including CAFs, these new cancer models will potentially reveal accurate information about tumor initiation and development. In addition, microfluidic technology as applied to tumor development will also allow collection of samples at specific times with ease.

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Definitions

Endothelial to mesenchymal transition – The process through which endothelial cells are transformed into mesenchymal cells. This is achieved through the loss of endothelial properties and gaining of mesenchymal properties.

Epithelial to mesenchymal transition – The process through which epithelial cells are transformed into mesenchymal cells. This is achieved through the loss of epithelial properties and gaining of mesenchymal properties.

Extracellular Matrix – Fibrous proteins secreted by stromal cells including fibroblasts, mesenchymal stem cells, pericytes and its main functions is to provide structural support and biochemical cues to surrounding cells. The ECM accumulates growth factors, cytokines and chemokines and these in turn influence tumor and stromal cell behaviour.

Desmoplasia – the resulting state of tissue after a response to an injury and includes fibrosis as stromal cells synthesis huge amounts of ECM proteins

Matrix Metalloproteases – A large family of zinc-containing protease enzymes referred to as endopeptidases and are responsible for degrading ECM proteins such as fibronectin, collagens and laminins.

Tumor microenvironment – Includes all cellular and non-cellular components of the environment surrounding/within a tumor and includes all stromal cells, blood vessels and the ECM. Stromal cells include CAFs, CAMs, CANs, pericytes and other immune cells. The TM provides the 'theatre' within which tumor cells can survive and tumors develop and eventually spread.

Stromal cells- includes all cells found within the TM and act to support tumor cells by secreting tumor promoting growth factors, cytokines, chemokines and ECM proteins.

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