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Molecular Communication between Tumor-Associated Fibroblasts and Head and Neck Squamous Cell Carcinoma

George Leef[1] and **Sufi Mary Thomas**[1,2]

[1]Department of Otolaryngology, University of Pittsburgh and University of Pittsburgh Cancer Institute

[2]Department of Pharmacology and Chemical Biology, University of Pittsburgh and University of Pittsburgh Cancer Institute

Abstract

Over the past few decades, it has become increasingly clear that the lethality of cancers depends on more than the malignant cells themselves. The environment those malignant cells are exposed to is just as important a determinant of their behavior. Head and neck squamous cell carcinoma (HNSCC) is both common and deadly. It is the 6th most frequently occurring cancers, and prognosis is still generally poor. Recent evidence indicates that activated fibroblasts residing within the tumor stroma play a significant role in promoting the aggressive spread often seen in head and neck cancer. Tumor associated fibroblasts (TAFs) have also been implicated in facilitating angiogenesis and suppressing the normal anti-tumor function of immune cells. Studying the signaling molecules involved in these processes will facilitate the development of promising targets and inhibitors to prevent tumor-associated fibroblasts from exerting their reinforcing effects on the tumor. In this article, we review the recent literature on the signals used in tumor associated fibroblast communication, with a focus on potential therapeutic targets. Further, we highlight the lead candidates for TAF-targeted therapeutic interventions. Future anticancer strategies may achieve better results than current approaches by targeting the support cells in tumor stroma in addition to the cancerous cells.

Keywords

Fibroblasts; Head and Neck Cancer; tumor stroma; invasion; proliferation

Introduction

In recent years it has become apparent that tumors are complex structures formed from mutually supporting parts. The malignant cells do not grow in isolation; rather they communicate with and are supported by stromal cells. Therefore, a full understanding of tumor progression requires studying the tumor stroma in addition to the malignant parenchymal cells. One of the main elements of the stroma, and a major contributor to the extracellular environment of solid tumors, is the tumor associated fibroblast (TAF). In many

Correspondence: Dr. Sufi Mary Thomas, University of Pittsburgh, 200 Lothrop Street, W947 BST, Pittsburgh, PA 15213, USA. Tel.: +1-412-383-5403; fax: +1-412-647-2080, smt30@pitt.edu.

different types of cancer, the secretion of factors by TAFs correlates with poor prognosis [1], leading to the idea that TAFs could be the targets of new drugs to interrupt the supportive relationship between stroma and tumor cells.

Soluble factors secreted by TAFs have been implicated in the progression of tumors in many different organs, including breast and pancreas [1]. While some of the factors identified in tumor-stroma communication are similar among cancer types, others are unique; suggesting that the best drug targets might be specific to particular cancers. For example, hepatocyte growth factor (HGF) and insulin-like growth factor 1 (IGF1) have been implicated in prostate cancer, while the cytokine CXCL12 has been implicated in breast cancer [1]. Transforming growth factor beta (TGFβ), however, has been identified as a key mediator in prostate, breast, and pancreatic cancer [1]. In order to design the optimal therapeutic agent for any given malignancy, it is necessary to study the communication between stroma and parenchyma in that cancer.

Head and neck cancer is a malignancy that is both common and deadly. Oral cancer is the 11th most common type of cancer worldwide, and laryngeal cancer is the 20th most common [2]. If all head and neck cancers are counted together, they are the 6th most common neoplasm in the world [3]. Survival is still less than 50% for head and neck cancer, and this has not improved over the last four decades [2, 4]. When detected early, survival is much better (75% at 5 years), but the majority of patients present with advanced metastatic disease at diagnosis [3]. The tendency of head and neck squamous cell carcinoma (HNSCC) to invade and metastasize aggressively plays a major role in its morbidity and mortality.

Several reports suggest that TAFs play a significant role HNSCC progression. Expression profiles of fibroblasts from cancer free oral mucosa, dysplastic epithelium, and malignant epithelium are all reliably different from each other [5]. TAFs are also frequently found in the lymph node metastases of HNSCC tumors [6]. It is unclear whether TAFs migrate to distant sites along with the cancer cells, or if the cancer cells recruit new TAFs upon arrival in the lymph node. In either case, TAFs are a critical part of HNSCC tumor progression [6]. Various studies have implicated TAFs in promoting HNSCC metastasis [7, 8], invasion [9, 10], angiogenesis [11, 12], immune escape [11, 12], and proliferation [13, 14]. Lack of TAFs or TAF-produced factors significantly impairs the ability of HNSCC cells to engage in all of these processes [9–14]. The purpose of this review is to provide an overview of the signaling mechanisms triggered by TAFs reported to influence HNSCC tumor progression (Figure 1). The molecular interactions between the tumor and stromal fibroblasts are complex. A comprehensive compilation of TAF-tumor signaling is important to fully grasp the mechanisms contributing to tumor progression and to facilitate the development of potent therapeutic strategies to reduce the morbidity and mortality caused by HNSCC. The promise of targeting fibroblasts is illustrated in a study where inhibition of the fibroblast growth factor receptor (FGFR) reduced growth of HNSCC tumors transplated into mice, possibly due to a reduction in the number of murine fibroblasts within the tumor mass [15].

HNSCC tumors arise at multiple sites in the head and neck region including tongue, floor of the mouth, pharynx, and larynx. There may be significant heterogeneity in the signaling pathways used by different types of HNSCCs and their associated fibroblasts. Some of the molecules discussed in this paper have been implicated in the progression of HNSCC arising from various sites, while most have only been studied in HNSCC tumors from a specific site. When selecting molecules for further development as drug targets, it may be helpful to pick out molecules which are implicated in HNSCC across all sites. It is also important to note that some studies used patient derived TAFs, while others used transformed normal fibroblasts. Although exposure to HNSCC cells can induce a TAF-like phenotype in normal fibroblasts [7], there has not yet been a study rigorously comparing the behavior of

transformed normal fibroblasts and TAFs. Although studies using primary TAFs might more closely reflect the situation *in vivo*, further studies comparing the phenotypes of primary TAFs vs. human fibroblast derived from other sources such as foreskin are required. Table 1 lists the source of the fibroblasts used in various reports examining molecules involved in promoting HNSCC tumor progression. In this review, we will we discuss the molecules implicated in transforming normal fibroblasts or mesenchymal stem cells into TAFs and the impact of these signaling molecules (listed in Table 2) on invasion/metastasis, proliferation, angiogenesis, and immune escape by HNSCC cells.

Induction of TAF phenotype

TAFs are distinct from normal fibroblasts (NFs) from cancer-free patients in a variety of ways. Normal fibroblasts are quiescent but maintain tissue architecture by secreting extracellular matrix (ECM) components [1]. If damage occurs to the surrounding tissue, paracrine signals trigger fibroblast activation facilitating wound healing. They begin to express α-smooth muscle actin, increase production of ECM components, and begin proliferating [1, 16]. After wounds heal, reactive fibroblasts undergo apoptosis (some may also revert to quiescence), but TAFs retain their activated phenotype [1]. This has led to the characterization of tumors as “wounds that do not heal” [16].

TAFs can originate from either normal fibroblasts in the immediate vicinity of the tumor or from circulating bone marrow-derived mesenchymal stem cells (MSCs) [17]. MSCs have been found to contribute a significant number of cells to the tumor stroma [17–19]. Once they arrive in the tumor periphery, the MSCs are exposed to factors secreted from the cancer cells, which induce differentiation into TAFs [20]. So far little work has been done to investigate what factors drive the MSC to TAF transformation, but exposure to exogenous transforming growth factor beta (TGFβ) has been found to partially mimic the effects of direct exposure to cancer cells [20].

Recent reports also suggest that cancer cells are capable of transforming normal fibroblasts into TAFs. Co-culture of normal fibroblasts with cancer cells has been found to produce specific changes in gene expression patterns of fibroblasts [12]. Treatment of normal fibroblasts with interleukin-1 beta (IL-1β) or TGFβ causes them to recapitulate these changes in gene expression [12, 21]. Furthermore, IL-1β or TGFβ inhibition reduced the gene expression changes induced by co-culturing fibroblasts with HNSCC cells [12, 21].

It appears that the TAFs themselves may play a role in the induction of TAF phenotype, helping to transform their normal fibroblast neighbors or newly arrived MSCs. TGFβ-1 has been identified in expression profile assays as a molecule whose production is substantially upregulated in TAFs as compared to normal fibroblasts [22]. TGFβ-1 is the most effective form of TGFβ in inducing the TAF phenotype in normal fibroblasts and MSCs [20, 21]. It appears that the transformation of fibroblasts to TAFs can start a positive feedback loop; each fibroblast that is converted into a TAF starts producing TGFβ-1 and influencing other normal fibroblasts and MSCs in turn transform into a TAF phenotype.

In summary, tumor cells secrete TGFβ and IL-1β, inducing TAF phenotype in local fibroblasts. The cancer cells could also co-opt MSCs by exposing them to TGFβ as they migrate into the damaged area. Blocking TGFβ or IL-1β might therefore be very useful in preventing the production of tumor-supporting TAFs.

The Role of TAFs in Tumor Invasion

HNSCC is known for its tendency to invade local structures aggressively and metastasize to distant sites. In fact, the majority of patients diagnosed with advanced non-metastatic

disease will go on to develop metastases in spite of treatment [23]. Once the disease becomes metastatic, there are no good treatment options. Local/regional invasion of vital structures in the neck is also a cause of substantial mortality, since it can be difficult or impossible to obtain clear margins around the tumor in a surgical resection. Therefore there is great interest in developing strategies to mitigate the invasive and metastatic potential of HNSCC.

TAFs are reported to produce a number of pro-invasive molecules, including brain-derived neurotrophic factor (BDNF), hepatocyte growth factor (HGF), insulin-like growth factor 2 (IGF2), bone morphogenic protein 4 (BMP4), and chemokine ligand 7 (CCL7) [7, 9, 10, 24, 25]. In addition, TAFs are capable of directly facilitating invasion/metastasis through the production of proteases that can help digest the extracellular matrix including matrix metalloproteases [1–3, 26–28]. Production of these factors by the TAFs appears to be induced by signals from the cancer cells, especially tumor necrosis factor alpha (TNFα) and interleukin-1 alpha (IL-1α) [9, 10]. Furthermore, TAFs produce factors that encourage production of TNFα and IL-1α by the HNSCC cells [29]; it appears that the TAFs and the HNSCC cells communicate with each other in a mutually reinforcing cycle. Table 3 summarizes the molecules reported to be involved in tumor-TAF cross-talk.

Brain derived neurotrophic factor (BDNF) is one of the invasion promoting signals produced by HNSCC-TAFs but not normal oral fibroblasts [7]. BDNF exerts its effects by promoting an epithelial-mesenchymal transition (EMT), thereby facilitating metastasis [7]. Cancer cells exposed to BDNF changed their gene expression profile to one characteristic of cells undergoing EMT, specifically an increase in vimentin and a decrease in E-cadherin expression [7]. BDNF production by TAFs is theorized to be driven by exposure to HNSCC-produced TNFα [7]. Although this has not yet been proved rigorously, it is suspected because TNFα up-regulation in the tumor accompanies BDNF up-regulation in the stroma [7]. Furthermore, anti-TNFα antibody infliximab significantly inhibits TAF-induced invasion by HNSCC cells [28]. TNFα blockers such as infliximab and etanercept have met with success in clinical trials [30, 31], but they have not yet been tested in head and neck cancer. Given the significant role of TNFα in HNSCC invasion, infliximab and etanercept may be useful in preventing HNSCC metastasis.

In co-cultured TAFs and HNSCC cells, BDNF production is increased by the TAFs, while TrkB (a receptor for BDNF) is up-regulated by the cancer cells [7]. In addition, IL-1β was found to be increased in the fibroblasts, and TNFα in the cancer cells. These cytokines were suggested as possible regulators of BDNF and TrkB, but the exact mechanism remains unclear. TrkB and BDNF are being investigated as potential drug targets. Inhibitors of TrkB have already been developed and met with some success in cell culture models [32]. Furthermore, down-regulation of TrkB has been linked to reduced tumor growth in a murine xenograft model of HNSCC [33]. Blocking the interaction of BDNF and TrkB could potentially reduce rates of metastasis.

Hepatocyte growth factor (HGF) is a pro-invasive molecule produced by activated TAFs and binds to the MET receptor on the cancer cells, triggering enhanced invasion through the basement membrane [9, 21, 25, 34]. The HGF/MET signaling pathway is already being extensively targeted in anti-cancer research [25, 35]. Production of HGF by TAFs may be regulated by exposure to HNSCC-secreted IL-1α [9, 10]. Stromal-derived factor 1 (SDF-1) also induces invasiveness, and like HGF, it is upregulated in fibroblasts exposed to IL-1α [9]. A recombinant IL-1 receptor antagonist called anakinra has been used successfully to treat inflammatory conditions, such as rheumatoid arthritis [31]. Anakinra could potentially be used to inhibit IL-1 signaling between tumors and fibroblasts. Inhibitors of SDF-1 signaling have been found useful in preventing metastasis in a mouse model of breast cancer

[36] and they also extended survival in a mouse model of leukemia [37], but these inhibitors have not yet been tested in HNSCC.

TAF-secreted insulin-like growth factor 2 (IGF2), bone morphogenic protein 4 (BMP4), and CCL7 have also been found to promote HNSCC invasion [10, 24]. Neutralizing antibodies to these molecules abrogated the pro-invasive effect, which confirms the involvement of these mediators [10, 24]. CCL7's role in metastasis was confirmed by the fact that its receptor, CCR7, was found to be substantially upregulated in HNSCC cells with higher metastatic tendencies [38]. It has not yet been determined what factors the tumor cells secrete to encourage IGF2 and BMP4 production; however some inducers of CCL7 expression are known. IL-1α, but not vascular endothelial growth factor (VEGF), produced by the cancer cells was determined to be specifically responsible for stimulating CCL7 secretion from TAFs [10]. However, exposure to both VEGF and IL-1α further increased CCL7 secretion compared to IL-1α alone.

Other chemokines of the CXCL and CCL families are also overproduced when fibroblasts are exposed to tumor cell factors and some of these, such as CCL2 (monocyte chemotactic protein-1) have also been found to enhance invasion by HNSCC cells [9, 26, 34, 39]. SDF-1 (CXCL12), which was mentioned before, is also a member of this family [26]. So far only CXCL12 has been targeted for pharmacotherapy, but the success of these experiments should encourage efforts at blocking CCL7, CCL2, and other molecules in the CCL and CXCL families.

Matrix metalloproteases (MMPs) degrade components of the ECM including collagens, fibronectin and laminin [40]. Collagen I produced by TAFs interacts with the α2β1 integrin on the HNSCC cells, inducing production of MMP 2 [26]. Expression of membrane type 1 matrix metalloproteinase by TAFs has been reported in HNSCC [26–28]. Western blotting of TAF lysates showed elevated expression of membrane type 1 MMP (MT1-MMP) as compared to normal mucosal fibroblasts [28]. Further, HNSCC cells promote MMP secretion from TAFs via expression of extracellular matrix metalloprotease inducer (EMMPRIN) [41]. EMPIRIN is a glycoprotein reported to function as a cell adhesion molecule and a paracrine inducer of MMP expression. MT1-MMP cleaves EMPIRIN from the cell surface releasing a 22 KD fragment that mediates expression of MMP-2 from fibroblasts [42]. Normal gingival fibroblasts activated by exposure to HNSCC cells showed up-regulation of MMPs 1–3, along with tissue inhibitors of metalloproteinases 1 and 3 (TIMPs 1 and 3) [27]. Expression of TIMP 1 and 3 in HNSCC tissue was observed in TAF's via immunohistochemistry [43]. Inhibition of specific MMPs produced in the tumor and in the stroma has the potential to achieve antitumor effects.

Interactions between TAFs and Immune Cells

Less work has been done in this area, but there is evidence that TAFs secrete arachidonic acid derivatives that can impair immune surveillance [11, 12]. IL-1β secretion by tumor cells induces production of COX2 [11, 12] and microsomal PGE synthase 1 by TAFs, both of which are involved in synthesis of prostaglandin E2 (PGE2) [11]. Increased PGE2 in the tumor microenvironment functions to suppress immune attack [11]. It is thought that PGE2 accomplishes this through its effects on CD4 (helper) and CD8 (killer) T cells; PGE2 reduces the proliferation of both types of T cells and alters their production of cytokines [44]. In addition to its role in inflammation, PGE2 promotes angiogenesis by inducing endothelial cell growth, tumor migration and proliferation [11]. As a result of these properties, COX2 activity in the stroma is correlated with worse tumor grade in various cancers, but specifically in HNSCC [45]. These results suggest that COX2 inhibitors should have value as anti-cancer agents, but more specific inhibition of microsomal PGE synthase

might be an even better line of attack [11]. These studies help to explain the long-established anti-cancer activity of COX2 inhibitor celecoxib [46], which is known to be active against many tumors [46] including oral squamous cell carcinoma [47]. Inhibitors of microsomal PGE synthase have been created [48], but have not yet been tested for efficacy against HNSCC.

Interestingly, TAFs also produce cytokines which are known to have a pro-immune effect. CCL7 and SDF-1 (CXCL12) have been found to enhance the activity and migration of T cells [49, 50], which are a pivotal cell type for immune defense against malignancies. It seems counterintuitive that TAFs would secrete both immune stimulating and immune suppressing mediators, but since fibroblast activation is a normal part of the wound repair process, it makes sense that activated fibroblasts would produce mediators to stimulate an immune response at the site of damage.

TAFs also secrete Monocyte Chemotactic Protein 1 (MCP1) [39], and thus may play a role in attracting tumor associated macrophages (TAMs) to head and neck cancers. In several types of cancer, TAMs have been found to mature predominantly into type 2 macrophages, which tend to support tumor growth by favoring angiogenesis, remodeling, and repair [34, 51]. Furthermore, a high level of macrophage infiltration into HNSCC tumors is associated with more aggressive disease [34, 52]. Therefore TAFs may play an additional role in facilitating tumor progression by attracting monocytes, which the tumor cells then co-opt.

Angiogenesis

TAFs are reported to induce angiogenesis in HNSCC via COX2-mediated production of PGE2 [11, 12]. In addition, HGF [53], CXCL12/SDF-1 [54], and BMP4 [55] secreted by TAFs have documented angiogenic properties. Although it has not been confirmed in HNSCC, TAFs have also been shown to express vascular endothelial growth factor (VEGF), a well-known angiogenic signal in transgenic models and human breast carcinoma [56, 57]. Therefore, TAFs may be involved in neovascularization through an array of molecules that promote angiogenesis. Since TAFs produce pro-angiogenic factors besides VEGF, they may be also involved in “evasive resistance”, a phenomenon where tumors develop resistance to VEGF inhibitors by exploiting alternative angiogenic pathways [58]. Targeting pro-angiogenic factors produced by TAFs could complement existing anti-angiogenic therapies based on inhibiting VEGF signaling.

Proliferation/Mitotic Activity

Several TAF-secreted factors have been linked with increased proliferation of HNSCC cells including PGE2, keratinocyte growth factor (KGF), and activin A [11, 13, 14]. Oral cancer TAFs have been found to produce substantially higher levels of KGF than normal fibroblasts [13]. Furthermore, inhibition of KGF with blocking antibodies abrogated TAF-induced HNSCC mitosis and viability [13]. Although inhibitors targeting the KGF receptor were developed a few years ago and have shown promise against breast cancer in *in vitro* studies [59], these agents have not yet been tested in HNSCC. The utility of blocking KGF is somewhat dubious, however, since KGF seems to stimulate the growth of normal keratinocytes just as strongly as it stimulates the growth of malignant keratinocytes [60].

Activin A, which plays a role in regulating the HNSCC cell-cycle through its effects on SMAD-family proteins [61], is produced at a much higher levels by TAFs than normal resting fibroblasts [14]. Further, activin A knockdown with siRNA reduced TAF-induced tumor growth [14]. Inhibitors of activin A have been developed and have met with some success in certain cancers, such as multiple myeloma [62]. Further studies on the effects of targeting activin A in HNSCC are warranted.

Conclusions and Future Directions

TAFs and HNSCC cells engage in molecular communications facilitating tumor progression through a variety of mechanisms. TAFs secrete factors including CCL7 and HGF [9,10, 21,25], that induce HNSCC invasion. TAFs also encourage tumor cell proliferation via KGF, activin A, and PGE [11, 13, 14]. Although the role of TAFs in angiogenesis and immune escape are less-well studied, TAFs produce prostaglandin E2, which encourages tumor angiogenesis and interferes with T cell mediated cytotoxicity [11]. Molecular networks involved in tumor-stroma communication will likely be areas of active research in the near future. As the communication between tumor and reactive stroma is more fully elucidated, more potential drug targets will become apparent.

For the present, however, some of these targets look very promising in the near term, while others might take years of research to reach clinical application. The molecular targets which may be most useful are those for which clinically tested inhibitors already exist. TNFα inhibitors such as adalimumab and etanercept have already been developed and tested in cancers including head and neck [30, 31]. Further, inhibitors of prostaglandin synthesis (COX2 inhibitors), c-Met, IL-1, and activin A are also currently available and could be used to target the tumor associated stroma [25, 31, 46, 62]. In all likelihood, several of these approaches will need to be combined with more traditional medical and surgical management in order to achieve maximum anti-tumor effects.

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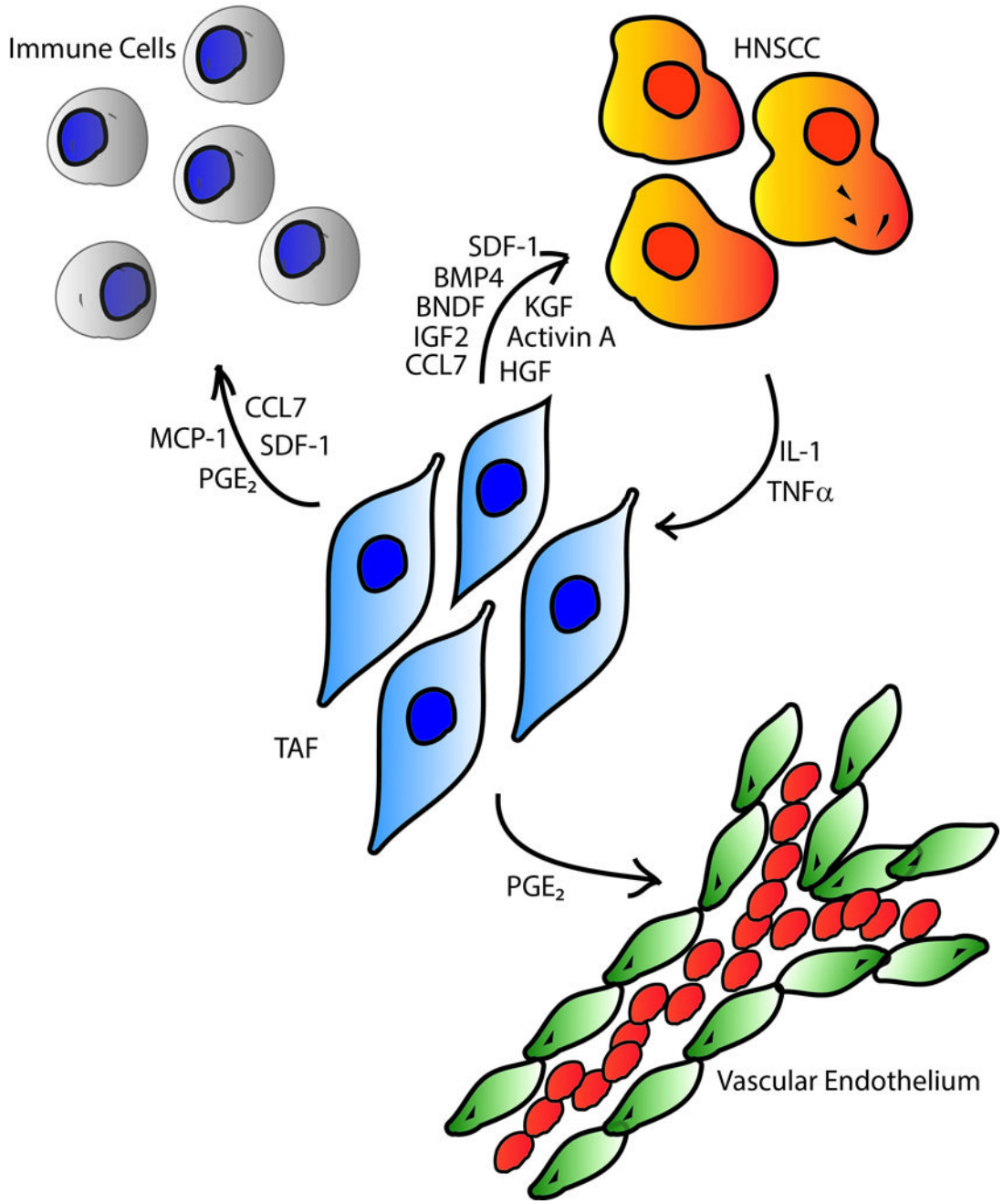

Figure 1.
Schematic showing the paracrine factors involved in TAFs-mediated tumor progression. Arrows point from the cell that secretes the mediator to the cell it acts upon.

Table 1

Origin of the fibroblasts used in studies reviewed in this article

Secreted Factor	Source of fibroblasts	Reference
Gene expression study	Patient derived oral SCC	[5]
BDNF	Cancer-free human oral fibroblasts activated by exposure to oral SCC	[7]
HGF	Cancer-free human oral fibroblasts activated by exposure to oral SCC	[9]
CCL7	Patient derived oral SCC	[10]
PGE2	Cancer-free human dermal fibroblasts activated by exposure to pharyngeal or tongue SCC	[11]
IL-1β	Cancer-free human oral fibroblasts activated by exposure to oral SCC	[12]
KGF	Patient derived oral SCC	[13]
Activin A	Patient derived lingual SCC	[14]
TGFβ	Cancer-free human oral fibroblasts activated by exposure to oral SCC	[21]
TGFβ	Patient derived HNSCCs, various locations	[22]
BMP4	Patient derived lingual, tonsilar and laryngeal SCC	[24]
HGF	Patient-derived lingual, tonsillar and laryngeal SCC	[25]
MMPs	Patient derived lingual and pharyngeal SCC	[26]
MMPs	Cancer-free human oral fibroblasts activated by exposure to oral SCC	[27]
MMPs	Patient derived oral and pharyngeal SCC	[28]
MMPs	Human gingival fibroblast from cancer free subjects	[29]

Table 2

Molecular signals, categorized by the mechanism they use to facilitate tumor progression

Molecule	Invasion	Proliferation	Angiogenesis	Immune	Reference
TNFα	x				[7, 29]
IL-1α	x				[9, 10]
IL-1β		x	x	x	[12]
CCL7	x				[10]
SDF-1	x		x		[9]
BDNF	x				[7]
Collagen I	x				[29]
HGF	x		x		[9, 21]
IGF2	x				[24]
BMP4	x		x		[24]
MMPs	x				[26–28]
PGE2		x	x	x	[11]
KGF		x			[13]
Activin A		x			[14]

Table 3

Pro-invasive signaling – molecules are categorized by which compartment secretes them and which compartment reacts to them.

	Stroma → Cancer	Cancer → Stroma	Reference
BDNF	x		[7]
HGF	x		[9, 21]
SDF-1	x		[9]
IGF2	x		[24]
BMP4	x		[24]
CCL7	x		[10]
Collagen	x		[29]
TNFα		x	[7]
IL-1α		x	[9, 10]