Extracellular Matrix in Chronic Inflammation

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Bidirectional communication between cells and their microenvironment has a key function in normal tissue homeostasis and for disease initiation, progression and patient's prognosis at least. The extracellular matrix (ECM), as an element of all tissues and cellular microenvironment, is a frequently overlooked component in implication in pathogenesis and progression of several diseases. In inflammatory microenvironment (IME) different alterations affect ECM resulting from remodeling processes which progressively induce cancer initiation and the passage toward a tumor microenvironment (TME). Indeed, it is demonstrated that altered ECM components interact with a variety of surface receptors triggering intracellular signaling that, in turn, affect cellular pathways. Supporting this concept, new studies have offered exciting clues about the function of decellularized ECM (dECM) and its components, as active participants in cancer and inflammation diseases evolution, once matched it with other cellular elements. Research results support the notion that the ECM, rather than acting as a passive element, is an active participant in promotion of chronic inflammatory and cancer initiation. Particularly it highlights the different effects of ECM components alterations in both disease and the correlation between chronic inflammation and cancer initiation. In conclusion, it soughts to explore the employment of dECM models as a tool to prevent cancer initiation. Indeed, reporting some of the data obtained in cancer research, it reflects about the employment of dECM models to investigate the short-circuits contributing to create distinct IME, representing, thus, a potential tool to avoid the progression toward a malignant lesion.

Keywords: chronic inflammation ; cancer ; extracellular matrix

1. Introduction

1.1. ECM as More Than a Physical Support: ECM Major Components, Properties and Functions

The extracellular matrix (ECM), typically situated in large intercellular spaces of connective tissue, consists of a voluminous meshwork of fibrous proteins, mainly represented by collagens, glycosaminoglycans (GAGs), proteoglycans (PGs) and matricellular proteins with different physical and biochemical properties. These components are combined between them with different ratio giving rise to distinct structures with different properties and functions.

Two basic forms of specialized ECM can be distinguished: basement membranes (BM), a thin network of highly crosslinked glycoproteins, and the loose fibril-like interstitial matrix (IM). BM, produced by epithelial, endothelial and stromal cells, is mainly composed of collagens, laminins, fibronectin (FN) and linker proteins such as nidogen and entactin, which connect collagens with other protein components. This composition makes BM structure more compact and less porous than IM. Indeed, IM, which is produced primarily by stromal cells, is rich in fibrillar collagens, proteoglycans, and various glycoproteins, such as tenascin C and FN. It contributes greatly to the tensile strength of tissues thanks to its charged and hydrated structure [1][2]. Nevertheless, some specialized ECM structures combine features of both forms of ECM, BM and IM, such as the reticular fibers network of secondary lymphoid organs [3][4]. In each existing version, ECM is not merely intercellular filling, but represents a bioactive element with multiple functions related to its physical, biochemical and biomechanical essential properties in cell behavior regulation [1][5]. ECM's physical properties, molecular architecture, rigidity, porosity, insolubility, spatial arrangement and orientation allow the function of ECM: to shape and maintain the form of tissue and organ integrity. It also functions as a barrier and anchorage site, and has both a negative and positive influence on cell migration [1]. Its biomechanical properties are mainly related to the fibrous protein content, such as type collagen I, which provides tissue with tensile strength and resistance to deformation [6].

1.2. ECM-Cells Interplay

Cells can sense all mechanical and biochemical properties of ECM through cell surface and transmembrane receptors. These receptors bind cells to the ECM components and transmit mechanical and chemical signals from ECMs to cells. Integrins are typical matrix receptors which mediate ECM and cell communication. Their function is to connect their

extracellular domain with matrix molecules and interact with actin cytoskeleton, through their cytoplasmic tails, thus regulating cell adhesion and motility [7][8][9]. Integrins can be activated through two different mechanisms, either inside-out or outside-in signaling [6]. Indeed, biochemical signals coming from intracellular space can induce conformational changes in the integrin extracellular domain. These changes facilitate ECM ligand binding through the promotion of talin and kindlin recruitment to the cytoplasmatic tails. Regarding the outside-in signaling in ECM, ligands bind to the extracellular domain of integrin and contribute to the recruitment of talin and kindlin to their cytoplasmatic tail. Talin molecules connect the actin cytoskeleton to the integrin and the activation signaling induces conformational alterations that lead to the intracellular recruitment of scaffolding proteins, such as focal adhesion kinase (FAK), which promote cell signaling. The integrin-ECM ligand linkage stimulates FAK/SRC complex assembly at the tails of integrins, recruiting various downstream effectors which activate Pl3K/Akt and Ras/MEK/ERK pro-survival signaling [10].

For biomechanical properties, cells can sample them and tune intracellular signaling pathways through a process termed mechano-transduction [11]. As it turns out, the elasticity of ECM (which can range from soft and compliant to stiff and rigid) helps to coordinate how a cell senses and perceives external forces and stimuli [12][13], providing major environmental cues that affect cell behavior [14][15]. Cells use actomyosin contractibility to remodel the ECM and to sense its material properties or stiffness while integrins, DDr receptors and FAKs mediate cells response [6].

1.3. ECM Deposition

Fibroblasts are the main producers of ECM components, whether in physiological or pathological conditions. These cells, once activated, become myofibroblasts, secrete ECM components, and, exerting contractile functions, thus confer mechanical alterations of three-dimensional spatial topology of the ECM. Myofibroblasts originate from different cell types and combine phenotypic and functional features of both fibroblasts and smooth muscle cells. Their activation is triggered by several pro-inflammatory factors, among which transforming growth factor β (TGF-β) represents the most important one [13]. The balance of activation and the ensuing inactivation of myofibroblasts is essential to keep physiological conditions and to preserve ECM homeostasis, especially during tissue regeneration and wound repair. Under pathological conditions, indeed, sustained inflammatory stimuli and ensuing TGF-β production by immune cells and tumor cells, alter myofibroblasts' activation/inactivation equilibrium, causing its hyperproliferation and overactivation which are signatures of fibrosis and the regulated stroma formation in cancer [16][17].

1.4. Degradation of ECM and MMPs Activity

The ECM components are normally cleaved and degraded by pericellular target-specific remodeling and degrading enzymes. Among them, various proteases such as soluble and membrane-bound metalloproteinases (MMPs), disintegrin and metalloproteinases (ADAMs), disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), cathepsins, bone morphogenic protein1 and Tolloid-like proteinases, as well as hyaluronindase and heparanase, are mainly involved. MMPs are of outstanding importance in ECM remodeling, and are crucially involved in cancer progression more than the other ECM-degrading enzymes [18]. The MMP family comprises 28 members and, depending on their type, these can have gelatinolytic and collagenolytic activity toward the ECM. MMPs' proteolytic activity is triggered by an activation cascade through which it is secreted as zymogens (pro-MMPs) without biological activity and kept inactive until the disruption of the interaction between the conserved cysteine in the propetide domain and the zinc ion bound to the catalytic domain. The activation cascade can include endogenous inhibitors, such as the case of MMP-2 which requires a tissue inhibitor of metalloproteinases (TIMP)-2 to be activated by MMP-13. TIMPs are a protein family which, forming a complex with their own N-terminal domain and chelating the catalytic zinc ion in the active center of MMP, function as natural MMPs inhibitors. Nevertheless, TIMPs can also interact with their C-terminal domain with the hemopexin domain of MMPs and thereby activate them [19].

The several MMPs are stringently regulated from transcriptional to post-translational level to maintain their expression and activity limited in spatio-temporal distribution and activity. This regulation process is frequently lost in many cancers [20]. Nevertheless, metabolic conditions also influence MMPs' activity, such as in hypoxia conditions. In particular hypoxia-inducible factor (HIF)-1 increases the degrading action of MMP-1 and MMP-9 [21].

MMPs exert different molecular functions. They can cleave the insoluble ECM components into soluble fragments, can activate or inactivate soluble proteins and can release soluble ectodomains of membrane-bound proteins as autocrine or paracrine signals [22]. Among MMPs, MT1-MMP, also known as MMP-14, exhibits the highest value of substrate specificity, cleaving the interstitial collagen I, II and III while activating MMP-2, and can also indirectly promote cleavage type IV [23]. Other membrane-bound MMPs, such as MMP-15, can cleave type I collagen while MMP-16 is able to cleave type III collagen and both can also activate pericellular pro-MMP-2. [24][25]. Nevertheless, MMPs' activity is not limited to the degradation of ECM components.

1.5. ECM Dynamics under Pathological Conditions

Consistent with the numerous cell biological functions in which the ECM participates, ECM remodeling and degradation are processes that need to be tightly regulated. Not surprisingly, pathological conditions, such as inflammation and cancer, and the breaking of the balance of tissue homeostasis of both processes, cause alterations in the composition and properties of ECM. Thus, despite multiple regulatory mechanisms, ECM dynamics can go awry when activities of ECM remodeling proteins are deregulated, resulting in devastating consequences, manifested in various human diseases. Many ECM features are mostly related to development of disease, such as the interconnection between the different properties of ECM. Indeed, when the ECM stiffness increases due to a pathological condition, its biochemical properties change and, vice versa, cells can perceive the variation and changing the kind of force exerted on ECM. This feature explains why stiff linearized cross-linked collagen bundles promote cell migration, whereas the presence of a denser network of stiff cross-linked matrix fibers, instead, impedes migration unless matrix MMPs are simultaneously activated [26]. The reciprocity represents another important feature of cell-ECM interaction and is involved in the development of disease [27]. Cells constantly act on ECM to modify one or more of its properties, creating, breaking down, rearranging and realigning ECM components. Instead, any changes in the ECM as a result of cellular activities will in turn influence adjacent cells and modify their behavior [1][28][29].

2. Role of ECM in IME

2.1. The Immune Microenvironment and ECM Components Interactions

The immune microenvironment is strongly influenced by ECM features, while many immune type cells have a key role in ECM deposition and remodeling processes, in both homeostasis and pathological conditions.

Inflammation is a multifactorial network of chemical signals which initiate and maintain the host response aimed to heal the injured tissue. The inflammation process involves primary cell players, such as neutrophils, monocyte-macrophages, mast cells (MCs) and T lymphocytes. These cells produce cytokines, chemokines, growth factors and proteases which support the proliferation of epithelial cells, as well as the production and remodeling of ECM by fibroblasts [30].

Fibroblasts have key role in restoring the ECM homeostasis during inflammation and also exhibit a crucial crosstalk with the immune system. Despite the fact that the process through which immune cells mediate the resolution of inflammation is tightly regulated and self-limiting, this can be hampered leading to abnormalities. Indeed, the profile of cytokines and chemokines persisting at the inflammatory site is decisive for the development of chronic diseases which provoke ECM alteration [31]. In inflamed tissue, infiltrating cells release cytokines such as tumor necrosis factor α (TNF-α), interferon gamma (IFN-γ) and TGF-β, which influence both ECM turnover and protease secretion by tissue-resident cells, thus modulating the expression of a wide range of ECM molecules. On the other hand, the aberrant expression of ECM components can influence immune cell activation, differentiation and survival. Therefore, the remodeled ECM of inflamed tissue influences the perpetuation of inflammatory response and its chronicization.

2.2. ECM Damaging and Remodeling during Chronic Inflammation

Tissue damage and the alteration of tissue architecture are common features of chronic inflammation disease, such as inflammatory bowel disease (IBD), and are mainly related to immune components' activity which activate different MMPs [32]. During inflammatory process, MMPs activity increases and promotes ECM degradation, releasing into circulation its cleaved components. Shimshoni et al. in 2020 [33] provided interesting insights into ECM remodeling during inflammation. The study was conducted on murine models of IBD, in which the ECM dynamic was monitored during intestinal inflammation. They conducted a comparative analysis of matrix structure, stiffness, and composition of a healthy ECM, IBD ECM and ECM of an IBD pre-symptomatic state. The results revealed that in a clinical pre-symptomatic state of IBD, the ECM displayed unique signatures distinct not only from the healthy one, but even from the IBD ECM in the course of full-blown-disease pathology [33]. Thus, the analysis of ECM identified unexpected pre-symptomatic states with its own unique ECM, resulting from progressive changes of the ECM features. Furthermore, the study demonstrated that this progressive change in ECM was related to an increased activity of remodeling enzymes, especially basement membrane degrading gelatinases, which are mediated by the sub-clinical infiltration of immune cells bearing remodeling enzymes in the epithelium [33].

2.3. Key Immune Cells Driving ECM Remodeling during Chronic Inflammation

Neutrophils are the first effectors during inflammation recruited by damage-associated molecular patterns (DAMPs) whose concentration can be altered by ECM components or ECM fragments. Sustained neutrophil recruitment incites the

production of pro-inflammatory cytokines and chemokines, promoting angiogenesis and degrading the ECM. In the course of inflammation, neutrophil extracellular traps (NETs) are important sources for ECM-degrading enzymes, such as serine proteases, which function to ingest pathogens, as well as to cleave ECM, aiding in migration [34].

Proceeding along the inflammation process, once spent, neutrophils secrete many chemoattractant cytokines, such as CCL-2 (MCP-1), CCL-3 (MIP1α), CCL-4 (MIP-1β), CCL-5, TSP-1, IL-1, IL-6, and TNF-α [35][36], which recruit monocytes in situ and induce them to differentiate into mature macrophages and dendritic cells. At the initial stage, the stimulation of most macrophages mediated by IFN-γ, TNF-α and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) induces them to polarize toward a pro-inflammatory M1 phenotypic state, which is responsible for the clearance of the inflammation site from pathogens, dead neutrophils and dead tissue. IL-4, IL-10, IL-13 and TGF-β induce, instead, the M2 anti-inflammatory phenotype to encourage wound healing and stimulate fibroblast migration, proliferation and angiogenesis.

2.4. ECM-Derived Fragments as Modulators of Chemotactic Activity for Immune Cells

ECM bioactive fragments can exhert chemotactic activity for inflammatory cells such as those derived from collagen types I and IV, elastin, fibronectin, laminins, entactin/ nidogen, thrombospondin and hyaluronan [37]. Interesting to note, Senior et al., demonstrated that the chemotaxis dose response curves to ECM fragments can be comparable to those obtained with formyl met-leu-phe (fMLP) and the complement anaphylatoxin C5a which are classic chemoattractants [38].

ECM fragments' chemotactic activity is mediated by several cell surface receptors, such as the 67-kDa protein on the neutrophil surface, also called high affinity laminin receptor. These receptors mediate chemotaxis to fragments of type IV collagen, laminins and elastin [37]. Nevertheless, the same ECM component can be recognized by more than one receptor involved in stimulating responses and, moreover, the same ECM component can be split into fragments with opposite activities.

2.5. Alterations in ECM Components Affect Immune Cells' Activity

ECM-derived fragments and alterations of some molecules, besides exerting chemotactic activity, may also activate immune cells, fostering the inflammatory response [39]. These effects are generally mediated by the Toll-like receptors (TLRs) family, which recognize conserved products (such lipopolysaccharides) defined as pathogen-associated patterns (PAMPs), as well as molecular DAMPs [40]. The activation of TLRs triggers innate immune response which, in turn, also influences the adaptive response. Several fragments of the ECM function as activators, such those derived from interstitial matrix, such as tenascin C isoform, the small leucin-rich proteoglycan biglycan [41], fibronectin [42], heparan sulphate [43][44] and HA [45].

2.6. ECM-Fragments Influence Gene Expression of Inflammatory Cells

The interaction between inflammatory cells and ECM components has effects on inflammatory cell gene expression [37]. Indeed, fragments derived from ECM cleavage stimulate monocytes/macrophages to product cytokines and proteases. For instance, low molecular weight fragments of HA increase the MMP-12, PAI-1 [46][47] and stimulate the production of several cytokines, such as macrophage inflammatory 1- α (MIP-1α), MIP-1β, MCP-1,KC, IL-8, and IL-12 by macrophages [48][49][50], while fragmented fibronectin provokes an increase in monocyte/macrophage secretion of proteases, such as MMP-9/gelatinase B, MMP-12/macrophage elastase and pro-inflammatory cytokines [51][52][53].

3. From Chronic Inflammation to Cancer

3.1. Main Inflammatory Pathways Correlated with Tumorigenesis and Colitis-Associated Cancer

The inflammatory process, besides contributing to the transformation of malignant clones even allows their outgrowth in tumor mass [54]. Indeed, cytokine receptors signaling in mutated cells offer a great contribution in the induction of pro-survival pathways, promoting the survival rate of mutated clones [55].

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) represents a protein complex key orchestrator of innate immunity and inflammation, and has emerged as a key tumor promoter [56]. Once activated in inflammatory cells, NF-kB regulates cell cycle mediators (cyclin D1, c-Myc), anti-apoptotic (c-FLIP, survivin, Bcl-XL) and adhesion molecules (ICAM-1, ELAM-1, VCAM-17), proteolytic enzymes such as MMP-9 and uPA and pro-inflammatory cytokines (such as TNF-α, IL-1, and IL-6), which, altogether, contribute to inflammation-related tissue damage and tumor development and progression [57]. NF-kB, indirectly, through TNF-α production which acts as a potent mutagen, contributes to tumor initiation, inducing ROS release and promoting DNA damage [58], while encoding antiapoptotic regulators, ensuring the

survival and proliferation of tumorigenic cells [56]. Moreover, NF-kB may trigger tumor initiation and progression, enhancing angiogenesis through the expression of vascular endothelial growth factors (VEGF), cyclooxygenase 2 (COX-2) and IL-8 [59]. NF-kB activation is often correlated with tumor-associated inflammation in colitis-associated colon cancer (CAC) [60].

STAT3 activation in IBD, mediated through the interaction between IL-6 with its membrane bound receptor (IL6R), enhances the expression of antiapoptotic factors, causing CD4 T cell resistance and thus promoting the perpetuation of chronic intestinal inflammation [61]. An important role in colonic inflammation and tumorigenesis is attributed even to COX-2. Indeed, elevated expression of COX-2 was detected in IBD patients and in colitis-associated neoplastic tissue [62]. COX-2 may trigger tumor development, likely inducing the expression of antiapoptotic factor STAT3 and increasing levels of MMPs, as well as promoting the migration of malignant cells [63]. As demonstrated in colon cancer cell line CACO-2, programmed to constitutively express COX-2, an increased invasiveness compared with the parental CACO-2 was detected, along with the activation of MMP-2 and increased RNA levels for membrane-type 1 matrix metalloproteinase (MT1-MMP) [64].

The effect of COX-2 in IBD and CRC is mediated by Prostaglandin E2 (PGE_2) acting through specific cell surface receptors (EP), which include four subtypes, EP1, EP2, EP3, EP4, among which the first is proposed as a mediator of PGE_2 role in colon carcinogenesis [65]. The cancer-promoting effect of PGE_2 involves CXCL1 and nuclear hormone receptor peroxisome proliferator-activated receptors (PPARs) [66][67]. CXCL1 is a proangiogenic chemokine which sustains microvascular endothelial cell migration and tube formation to support tumor growth and invasion [66]. PPARs are a downstream target of the COX-2/PGE_2 pathway, and its activation can induce COX-2 expression in colonic cancer cells.

3.2. ECM Deposition in TME

In TME, as well as in a physiological context, the major producers of ECM components are stromal cells, which, in this scenario, are recruited and orchestrated by tumor cells through their production of pro-fibrotic growth and inflammatory factors, such as TGF-β, fibroblast growth factor (FGF)-2, platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) [68]. Notably, TGF-β that is a key regulator of myofibroblast differentiation, in that within the ECM it is bound to FN, and connected to the fibrillar meshwork of the ECM through the complex TGF-β-binding protein (LTBP) and the latency-associated protein (LAP). Mechanical tension along the ECM fibrils and partial proteolysis of LAP provokes the release and the activation of TGF-β. Once free to act, TGF-β promotes the differentiation of fibroblasts into more contractile so-called cancer-associated fibroblasts (CAFs), which, increasing tension, foster the release of TGF-β1 in an autocatalytic manner [69][70]. CAFs originate predominantly from tissue resident or bone marrow-derived fibroblasts [71], but also from mesenchymal cells and other cells which have undergone epithelial to mesenchymal transition (EMT) [72]. CAFs exert a variety of tumor promoting functions and, producing several growth factors, chemokines, and owing to their different origin attract other cells, such as endothelial and immune cells to tumor mass and orchestrate their joining the TME [71].

3.3. Tumorigenic Alterations in ECM Composition

ECM dramatically changes in its composition and relative abundance at the primary site of tumor [73]. These alterations also have consequences for ECM biophysical and biochemical properties, which influence tumor development. Indeed, since ECM components can present both tumor-suppressing and tumor-promoting properties, their alterations during the tumorigenic process can promote one aspect or the other [18]. For instance, as Bohaumilitzky et al. reviewed in a study from 2017, HA, depending on its molecular weight, can act as a tumor suppressor or a tumor promoter [74]. The most frequent tumorigenic alteration of ECM is the increased amount of fibrillar collagen [75], which, instead, has a tumor-promoting effect. In physiologic conditions, the collagen fibers which surround the normal epithelial structures are curly and smooth while, during tumor development, a variable number of the fibers progressively become denser, aligned and stiffer. The increase in parallel orientation in collagen fibers increases their density and concentration, stiffening the ECM. In addition, collagen may undergo post-translational modifications inside and outside the cell, enhance protein complexity, alter 3D organization and, also, affecting matrix interaction with other molecules and cellular receptor, influence ECM degradation [76]. These post-translational modifications affect collagen precursors, procollagens, through various mechanisms, such as the hydroxylation of lysin residues or glycosylation. Modified procollagens form triple helices and are further processed extracellularly by proteases to create collagen fibrils [18]. Collagen fibrils are covalently cross-linked by the action of extracellular ECM-modifying enzymes, such as lysyl oxidases (LOX) and LOX-like proteins (LOXLs). Post-translational modifications or dysregulations of LOX and LOXLs' activity provoke morphological changes which improve tumorigenesis and tumor progression. Indeed, collagen cross-linking and the ensuing increase of ECM stiffness influence tumor cell motility, improve the recruitment of stromal cells and are associated with poor prognosis [77]. Notably, matrix stiffness provokes an increase in tension which induces integrin clustering, phosphorylation and activation of FAK.

Once activated, FAK may promote RAS-mediated phosphorylation of ERK, which can control migration, invasion, proliferation and cell differentiation, myosin contraction and the induction of transcription programs [78].

3.4. Tumorigenic ECM and Its Remodeling Influence on Immune Cells within Tumor Mass

Cancer and immune cells' migration is frequently guided by gradients of surface-bound molecules, such as the ECM, through a phenomenon termed haptotaxis [79]. Given increased expression of fibronectin and collagen in tumor stroma, as previously discussed, and since immune cells encounter the tumor mass on their route of immunological surveillance, it is reasonable to assume that haptotactic response can enhance immune cell invasion in tumor stroma [6]. Nevertheless, cells migrate faster in stiffer substrates and their persistent migration can be directed up a stiffness gradient, through a process termed durotaxis [80], which could explain why stiffer tumors show a higher infiltration of immune cells. Once immune cells meet desmoplastic ECM, they are kept in an immunosuppressive state [81] which fosters tumor progression [82]. Macrophage polarization is critical for the switch from pro-inflammatory to anti-inflammatory signaling. However, an imbalance in this phase contributes to tumorigenesis. Macrophages polarized towards the M1 phenotypic state are associated with tumor-suppressive functions, such as supporting CD8+ [83] cytotoxic T-cell activity. Macrophages polarized towards the M2 state are anti-inflammatory and associated with tumor-promoting functions such as ECM remodeling, angiogenesis, stimulating cancer cell proliferation and metastasis. Indeed, in the later process of inflammation, macrophages are favorable for tumor progression and often contribute into the process. Monocyte-derived macrophages within the tumor stroma, which differentiate in M2 phenotype, are indicated as TAMs. These cells release in tumor stroma several cytokines and interleukins (ILs), among which is IL-10, which inhibits the expression of major histocompatibility complex (MHC) and co-stimulatory molecules inducing immune suppression and TGF-β release [82]. This latter one, instead, attracts Tregs and other cells of adaptive immune system, such as the myeloid suppressor cells, which collaborate to inhibit the attack of CD8+ -T-cells and natural killer (NK) cells to the tumor mass [84][85]. Tregs, in turn, secrete TGF-β, supporting the activation of ECM-tethered TGF-β and thus reinforcing the tumor supportive action [86].

The role of TAMs is well investigated for their interaction with CAFs. TAMs and CAFs can activate and recruit each other in a similar manner to that observed in normal macrophages and tissue fibroblasts. Indeed, CAFs secrete bFGF, inducing M2 polarization, while M2 cells release TGF-β, provoking fibroblast reprogramming to a tumor-promoting CAF state [87]. It has been demonstrated in an orthotopic CRC model that the recruitment of TAMs to the tumor site regulates several ECM-associated genes, which established key characteristics of the TME. The high remodeling activity mediated by tumor cells and CAFs, as previously pronounced, results in the release ECM components which can act as inflammatory stimuli, creating an inflammatory tumor environment [88].

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