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Review

Cancer-associated fibroblasts (CAFs) and plaque-associated fibroblasts (PAFs): Unraveling the cellular crossroads of atherosclerosis and cancer

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ABSTRACT

Atherosclerosis is a complex process involving various cells and molecules within the atherosclerotic plaque. Recent evidence suggests that plaque-associated fibroblasts (PAFs), also known as atherosclerosis-associated fibroblasts (AAFs), might play a significant role in the development and progression of the disease. The microenvironment of the atherosclerotic plaque, resembling the tumor microenvironment (TME), includes various cellular populations like plaque-associated macrophages (PAMs), plaque-associated neutrophils (PANs), vascular smooth muscle cells (VSMCs), myeloid-derived suppressor cells (MDSCs), and PAFs. Similar to cancer-associated fibroblasts (CAFs) in tumors, PAFs exhibits a wide range of characteristics and functions. Their interactions with endothelial cells, smooth muscle cells, and other stromal cells, including adventitial fibroblast precursors, significantly influence atherosclerosis progression. Moreover, the ability of PAFs to express various markers such as alpha-SMA, Desmin, VEGF, and GFAP, highlights their diverse origins from different precursor cells, including vascular smooth muscle cells, endothelial cells, glial cells of the enteric nervous system, adventitial fibroblast precursors, as well as resident and circulating fibrocytes. This article explores the molecular interactions between

Abbreviations: PAFs, plaque-associated fibroblasts; AAFs, atherosclerosis-associated fibroblasts; TME, tumor microenvironment; PAMs, plaque-associated macrophages; PANs, plaque-associated neutrophils; VSMCs, vascular smooth muscle cells; MDSCs, myeloid-derived suppressor cells; CAFs, cancer-associated fibroblasts; Alpha-SMA, Alpha-smooth muscle actin; VEGF, vascular endothelial growth factor; GFAP, Glial fibrillary acidic protein; ECM, extracellular matrix; MMPs, multiple metalloproteinases; PDGF, platelet-derived growth factor; SCF, stem cell factor; PDGF-D, plateled derived growth factor-D; TGF-β, Transforming growth factor-β; FAP, Fibroblast activation protein; FAP, Fibroblast activation protein-alpha; FSP-1, Fibroblast-specific protein-1; TCGA, the cancer genome atlas; FGF, fibroblast growth factors; CXCL5, C-X-C motif chemokine 5; IGF, insulin-like growth factors; ADAM, A disintegrin and metalloproteinases; β-FGF, Beta-fibroblast growth factor; BFGF, basic fibroblast growth factor; SDF-1, Stromal cell-derived factor 1; PDGFRα, plateled derived growth factor receptor alpha; GREM1, Gremlin1; ISLR, immunoglobulin super family containing leucine-rich repeat; BMP, bone morphogenic protein; L1CAM, the L1 cell adhesion molecule; LDLs, low-density lipoproteins; EndMT, endothelial mesenchymal transition; Sca1, stem cell antigen-1; MMT, macrophage-to-myofibroblast transition; AIT, adaptive intimal thickening; PIT, pathological intimal thickening; PME, plaque microenvironment; DKK1, Dickkopf-related protein 1; IPH, intra-plaque hemorrhage; BMAL1, basic helix-loop-helix ARNT-like protein 1; FSP1;, fibroblast-specific protein 1; COL1A1, Collagen Type 1 Alpha 1 Chain; DCN, Decorin; MYOCD, Myocardin; ACTA-2, smooth muscle actin alpha-2; MyH11, Myosin Heavy Chain-11; KLF4, Krüppel-like Factor 4; CNN1, Calponin 1; EMT, epithelial-to-mesenchymal transition; Tregs, regulatory T cells; IL-6, interleukin-6; TNF-α, Tumor necrosis factor- alpha.

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PAFs, cells associated with atherosclerosis, and other stromal cells. It further examines the role of PAFs in the development and progression of atherosclerosis, and compares their features with those of CAFs. The research suggests that studying tumor-associated fibroblasts can help understand fibroblast subpopulations in atherosclerotic plaque. Identifying specific subpopulations could provide new insight into atherosclerosis complexity and lead to the development of innovative drugs for medical intervention.

1. Introduction

In recent decades, remarkable revolutions have taken place in the field of medicine. In oncology, recent research has increasly focused on the tumor microenvironment (TME), shifting the traditional view of cancer as a tumor cell-centric disease to a more complex model. According to the “seed and soil” theory, the TME primarily consists of a unique extracellular matrix that includes mesenchymal stromal cells, various immune cell types, blood vessels, and other noncellular components surrounding the tumor cells [1]. Interestingly, the predominant elements within the TME are not tumor cells themselves, but rather mesenchymal stromal cells and different types of fibroblasts, both of which have significant tumorigenic effects [2]. Among the various stromal cells present in the TME, cancer-associated fibroblasts (CAFs) play a crucial role [3]. CAFs are essential in various aspects of tumorigenesis, tumor progression, tumor immunity, metastatic potential, therapeutic response, and drug resistance [4].

In particular, metabolic dysregulation in CAFs promotes increased production of extracellular matrix components, leading to hyalinizing fibrosis, immune evasion, and chemotherapy resistance [5,6]. Tumor metaplasia, historically recognized by pathologists as a markers of a cancer aggressiveness, is now largely understood as a consequence of complex tumor-host interactions, especially between activated fibroblasts within the TME and cancer cells in aggressive tumors [7].

Collectively, these findings underscore the importance of unraveling the cellular composition of the atherosclerotic plaque and investigating the intercellular interactions within its microenvironment. Such efforts are essential prerequisites for gaining a deeper understanding of the pathobiology of atherosclerosis and devising more effective strategies to combat this intricate disease.

Recent studies have highlighted the dynamic and functionally active roles of fibroblasts in atherosclerosis, particularly in plaque progression. Notably, PAFs share significant similarities with CAFs, including their roles in extracellular matrix remodeling, secretion of cytokines, and interactions with immune cells [8,9]

In this article, we explore the emerging role of PAFs in the development and progression of atherosclerosis. We also compare the microenvironment of the atherosclerotic plaque to that of cancer, highlighting potential shared features.

We aim is to challenge the traditional lipid- or smooth muscle cell-centric view of atherosclerosis by proposing a new perspective that places PAFs at the centre of plaque dynamics. PAFs may play a dual role, either contributing to plaque stabilization or promoting its progression toward instability, with relevant consequences on human health. This study aims to move beyond a descriptive comparison of PAFs and CAFs by analyzing the functional relevance of their shared biological behaviors. We propose that both fibroblast types act as central orchestrators in their disease microenvironments, modulating immune responses, promoting ECM remodeling, and exhibiting remarkable phenotypic plasticity. Through this lens, we explore how understanding CAF biology can inform novel therapeutic approaches in atherosclerosis, including strategies targeting specific fibroblast subpopulations to promote plaque stabilization or limit progression.

2. Fibroblasts: origin and function in health and disease

Fibroblasts play a crucial role in producing and remodeling extracellular matrix-rich connective tissues, supporting essential organ functions during development, in health, and in disease states [10]. They are a family of mesenchymal cells involved in tissue homeostasis, and exhibit marked heterogeneity across and within organs [11]. Rudolf Virchow initially described these cells as "spindle-shaped cells of the connective tissue" in 1858. Subsequently, Ernst Ziegler coined the term "fibroblasts" in 1985. Fibroblasts exhibit reversible plasticity in phenotype and cell fate. In physiology, they produce a complex extracellular matrix and create signaling niches for stem/progenitor cells through biomechanical and microarchitectural cues in the extracellular matrix (ECM). They synthesize various components of the ECM, including collagens, proteoglycans, hyaluronan, elastin, fibronectin, and laminins [12].

Additionally, fibroblasts play a central role in remodeling the ECM microstructure through the secretion of multiple metalloproteinases (MMPs) and MMP inhibitors. Recent studies have shown that stromal biglycan, an unfavorable indicator for survival and immunotherapy response in cancer, may be derived from fibroblasts in the tumor microenvironment (TME) [13]. Moreover, fibroblasts serve as the progenitors of specialized mesenchymal cells, such as adipocytes, chondrocytes, and osteoblasts [14].

When observed under a microscope, fibroblasts appear as large cells with numerous cytoplasmic processes, basophilic cytoplasm rich in rough endoplasmic reticulum, and light-stained vesicular oval nuclei with a prominent nucleolus **(**Fig. 1**).** They should be differentiated from fibrocytes, smaller spindle cells with dark nuclei and acidophilic cytoplasm. Moreover, fibroblasts have been shown to form a network of cells connected by philopodia [15].

Analyses of mesenchymal stromal cell populations, including fibroblasts, in different organs revealed specific properties and lineage capabilities that vary from one organ to the next. When tissue damage occurs, fibroblasts can be activated and may temporarily adopt a contractile phenotype, becoming myofibroblasts [16]. Myofibroblasts originate from various cellular sources in different organs, including specialized fibroblast progenitors, alveolar fibroblasts, lipofibroblasts, pericytes, myoblasts, adipocytes, and adipocyte precursors. These cell types may undergo reversible conversion toward a myofibroblastic state [10]. Histologically, myofibroblasts appear as loosely arranged cells with a spindle or stellate morphology, vesicular nuclei, and small nucleoli characterized by a prominent eosinophilic cytoplasm **(**Fig. 2**).** Similar to fibroblasts, myofibroblasts are characterized by high plasticity and heterogeneity, as evidenced by their variable immunophenotype. At least five phenotypes have been reported in myofibroblasts, according to their different immunohistochemical profile: i) V-type (expressing only vimentin); ii) VD-type (expressing both vimentin and desmin); iii) VAD-type (expressing vimentin, alpha-SMA and desmin); iiii) VA-type (expressing vimentin and alpha-SMA); iiiii) VM-type (expressing vimentin and myosin) [17]. In clinical practice, Alpha-SMA is a valuable tool for identifying myofibroblasts during wound healing [18] and in the peritumoral stroma [19].

Fibroblasts are involved in various physiological processes, going beyond their traditional role in forming and remodeling the extracellular matrix. They secrete cytokines and growth factors, produce metabolites affecting glycolysis, regulate innate immunity by influencing macrophage polarization and antigen presentation to T lymphocytes, act as signaling centers for stem cell niches, and capsulate foreign bodies and parasites. Additionally, fibroblasts serve as progenitor cells for their renewal and the maintenance of mesenchymal lineage. Moreover, activated fibroblasts may also secrete platelet-derived growth factor (PDGF)

and the stem cell factor (SCF), promoting the differentiation of embryonic stem cells and actively participating in organogenesis [20].

In pathological conditions, fibroblasts play a relevant role in tissue repair. They can temporarily adopt a contractile myofibroblastic phenotype in response to tissue damage. Fibroblasts promote alternative macrophage activation during wound healing, thus improving the healing process [21]. Aberrant activation of fibroblasts can contribute to fibrotic disorders, such as pulmonary fibrosis and liver cirrhosis. Emerging evidence in the last few years also suggests that fibroblasts play a significant role in organizing the TME [3].

Fibroblasts' proliferation and function are influenced by various molecular pathways, including platelet-derived growth factor-D (PDGF-D), Transforming growth factor-β (TGF-β), and WNT signaling pathway [22]. The pro-fibrogenic role of PDGF-D is mediated by activating of the TGF-β1 pathway, which is predominantly involved in cardiac fibrosis [23]. TGF-β signaling can induce fibroblast proliferation and lineage transition by other cell types toward a fibroblastic state, including the induction of epithelial-to-mesenchymal transition (EMT) [24]. WNT/β-catenin signaling regulates fibroblast proliferation and migration, as well as the activation of the myofibroblast state and ECM deposition [8]. In a recent study, cancer-associated fibroblasts have been indicated as the user of the "Wnt language" in the tumor microenvironment to communicate messages among themselves and other TME components, including tumor cells [22].

2.1. Markers of human fibroblasts

Fibroblasts can be identified in the tumor microenvironment using a specific panel of antibodies. This panel includes alpha-smooth muscle actin (alpha-SMA), Desmin, Vimentin, Fibroblast activation protein-alpha (FAP-alpha), and Fibroblast-specific protein-1 (FSP-1) [25]. FSP-1 is particularly useful for identifying an inflammatory fibroblast subgroup [26]. It has been suggested that FAP and FSP are markers of a subset of fibroblasts derived from epithelial cells through the process of EMT [27]. A recent study analyzing gene expression through The Cancer Genome Atlas (TCGA) database proposed a new panel with 12 markers for CAFs in hepatocellular carcinoma [28]. The panel includes markers such as fibroblast growth factors (FGF4, FGF5, FGF8, FGF17, FGF19, FGF23), C-X-C motif chemokine 5 (CXCL5), insulin-like growth factors (IGFL1, IGFL2), matrix metalloproteinase 1 (MMP1), A disintegrin and metalloproteinases 18 (ADAM18), and 32 (ADAM32) [28]. More recently, a CAF signature has been proposed using the following ten markers: alpha-SMA, Desmin, Vascular endothelial growth factor (VEGF), MMP2, MMP9, TGF- β, Tenascin, Fibroblast activation protein (FAP), Beta-fibroblast growth factor (β-FGF), basic fibroblast growth factor (bFGF), Stromal cell-derived factor 1 (SDF1) [29]. Additionally, GFAP, a marker of innate immune cells previously identified in fibroblasts has been confirmed in a subpopulation of CAFs [30,31]. Furthermore, recently findings have reported CD36 expression in CAFs [32].

2.2. Fibroblasts and cancer: cancer-associated fibroblasts

The TME includes fibroblasts, which are crucial stroma cells involved in the growth, development, and progression of tumor cells [33]. They play a key role in modifying the TME, promoting the epithelial-mesenchymal transition of tumor cells, and favoring tumor cell migration and metastasis [34]. Regarding their origin, tumor-associated fibroblasts are believed to originate mainly from different local mesenchymal cells, including fibrocytes, peritumoral fibroblasts, mesothelial cells, smooth muscle cells, and pericytes rather than from circulating precursors [35]. Endothelial cells represent another possible source for CAFs. Through the process of endothelial-to-mesenchymal transition (EndMT), endothelial cells of the peritumoral vessels detach from neighboring cells, change their shape, lose their specific markers, and acquire a migratory phenotype, eventually originating CAFs [36]. The origin of CAFs is changeable, being also related to the type of tumor: for example, in hepatocellular carcinoma, hepatic stellate cells (HSCs) have been identified as the predominant origin of CAFs [37]. Studies suggest that CAFs can also originate from circulating precursors, such as bone marrow-derived mesenchymal stromal cells, differentiating into a distinct subpopulation of CAFs in primary breast tumors. Unlike resident CAFs, bone marrow-derived CAFs do not express platelet-derived growth factor receptor alpha (PDGFRα) and are associated with a worse prognosis. Therefore, PDGFRα expression has been suggested as a valuable tool for

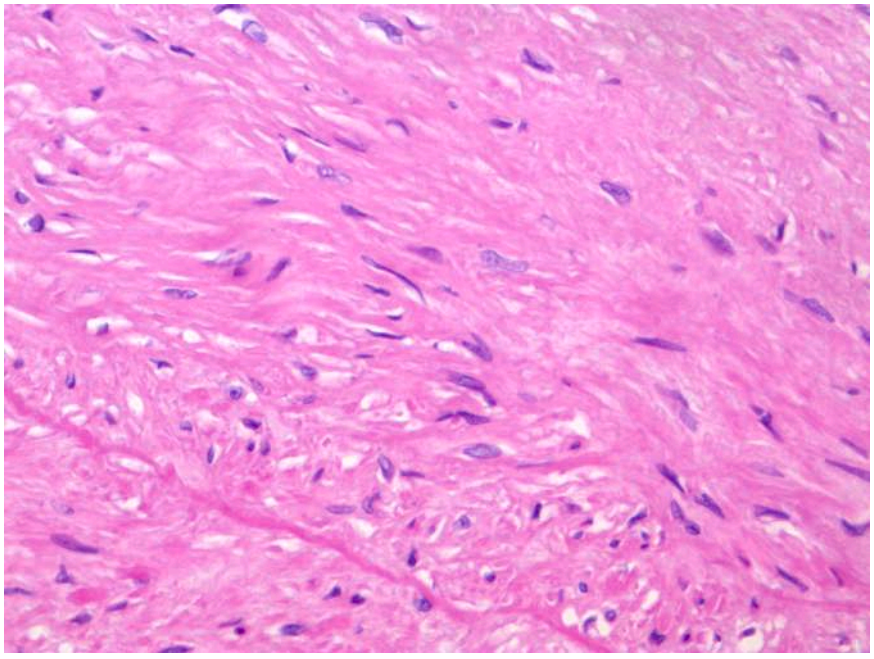

Fig. 1. Pathological intimal tickening of the coronary artery. Plaque-associated fibroblasts appear as large cells, with elongated irregular nuclei and vesicular chromatin. On the left side, the internal elastic lamina separates the atherosclerotic lesion from the underlying tunica media. H&E ooriginal magnification X 400.

distinguishing two functionally distinct CAF populations in breast cancer [38].

Another source of CAFs is circulating fibrocytes, a specific subpopulation of leukocytes with a distinct immunohistochemical marcature [39]. Fibrocytes, derived from hematopoietic stem cells, primarily respond to inflammation and exhibit stromal behavior [40]. These cells express fibroblastic markers such as collagen type I, vimentin, and fibronectin, along with leukocyte markers like CD45. Moreover, circulating fibrocytes may also express CD34, CD80 and CD86 [29].

Recent evidence suggests that CAFs might influence cancer cells by releasing exosomes that increase miR-92–3p levels, thereby enhancing the metastatic potential of colorectal cancer cells [41]. CAFs play a crucial role in synthesizing and remodeling the ECM surrounding tumor cells. The ECM has various biochemical, physical and biomechanical properties that allow it to either facilitate or hinder cell migration, depending on different physiological and pathological situations. Specific ECM components, such as heparan sulfate and CD44, may selectively bind to different growth factors and act as signal "presenters", influencing the direction of cell–cell communications within the TME, involving multiple cell types [42]. Additionally, exosome-derived microRNAs released by CAFs play an essential role in regulating TME, influencing tumor metabolism, immunity, tumor vessel permeability, angiogenesis and drug resistance [43]. Recent studies have also linked the downregulation of specific microRNAs secreted by CAFs to high TGF-β-R1 expression and poor clinical outcomes in patients with hepatocellular carcinoma [44].

These findings emphasize the plasticity of fibroblasts acting in the TME, where CAFs may exert contrasting effects on tumor growth and progression. On one hand, they may promote cancer progression and metastasis. On the other hand, CAFs may produce factors that inhibit tumor growth and hinder cancer progression, potentially leading to a positive outcome. For instance, a study using a mouse model of pancreatic cancer found that CAFs depletion accelerated cancer progression and reduced survival [45]. Furthermore, CAFs expressing meflin were found to inhibit pancreatic cancer insurgence and progression [46], revealing previously unknown heterogeneity and plasticity of CAFs [47].

CAFs are heterogeneous cells, and distinct fibroblast subpopulations produce different factors, sometimes with conflicting effects on tumor cells. The balance between Gremlin1 (GREM1) and the immunoglobulin super family containing leucine-rich repeat (ISLR), two CAF-specific genes involved in the bone morphogenic protein (BMP) signaling pathway in the TME, may play a crucial role in driving tumor progression [48]. High levels of GREM1 expression are associated with poor survival, whereas high levels of ISLR expression correlate with favorable outcomes in colorectal cancer [49].

The plasticity of CAFs' function in cancer is mainly related to their interactions with the multiple cell types detectable in the TME, including immune cells and endothelial cells, as well as with cytokines, chemokines, and multiple non-coding RNAs [50]. CAFs have been found to influence the metabolic reprogramming of immune cells in the TME and communicate with immune cells, either promoting or suppressing immune responses against tumor cells [51]. Additionally, CAFs may also serve as antigen-presenting cells within the TME [52].

Recently, multiple subpopulations of CAFs have been identified, including Inflammatory (iCAFs), myofibroblastic (myCAFs), antigen-presenting (apCAFs), CAFs with a highly activated metabolic state (meCAFs), and complement-secreting (csCAFs) [6]. These findings support the hypothesis that CAFs consist of multiple plastic and heterogeneous populations participating in bidirectional signaling pathways between the multiple cell types that give rise to the TME [53]. The complexity of CAFs' role in cancer development and progression has been further highlighted by the report, indicating that CAFs may express high levels of the L1 cell adhesion molecule (L1CAM), a molecule with pro-tumorigenic abilities [54]. Additionally, the heterogeneity of CAFs has been recently confirmed by the discovery of a subpopulation of CAFs producing prolargin, a powerful tumor-suppressor in hepatocellular carcinoma, which inhibits several pro-angiogenic proteins, leading to tumor suppression and improved outcomes [55].

Recent studies have emphasized the crucial role of the Wnt signaling in the crosstalk between tumor cells and cancer-associated stromal cells. This suggests that all cells within the tumor microenvironment may use this signaling pathway to communicate. In addition to its direct impact on cancer cells, Wnt signaling might significantly facilitate cross-communication between tumor cells and the TME. It has been discovered that not only cancer cells, but also various cell types within the

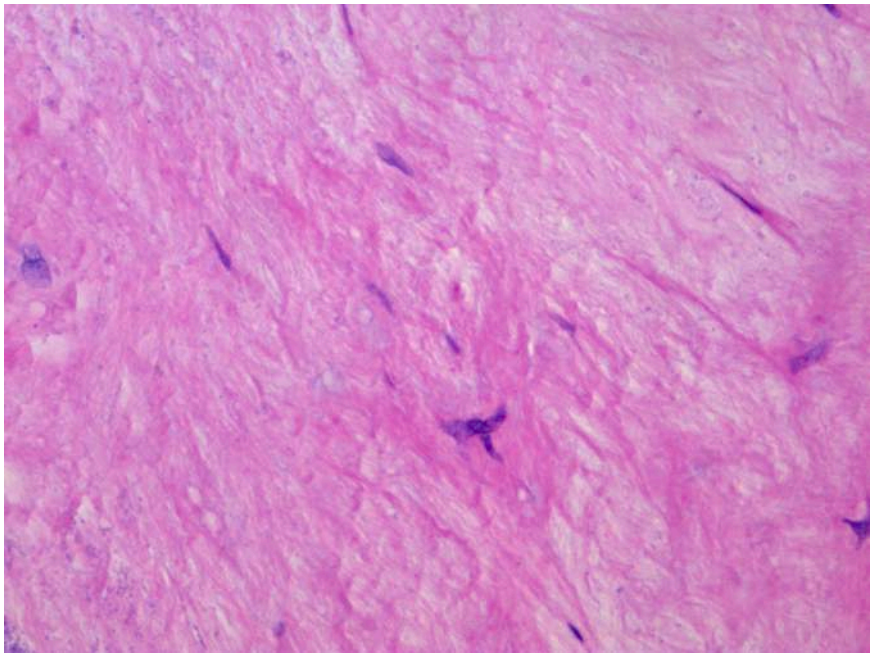

Fig. 2. Fibroatheroma of the aorta. Plaque-associated fibroblasts (PAFs) show a myofibroblastic-like appearance, with stellate morphology and prominent eosinophilic cytoplasm. PAFs appear embedded in a abundant myxoid matrix. H&E original magnification X 630.

TME, such as CAFs, macrophages, endothelial cells, monocytes, and lymphocytes, utilize the Wnt signaling pathway to communicate with each other and with cancer cells. Understanding and interpreting this signaling pathway is a critical challenge in the field of oncology, as highlighted by Katanaev VL [22].

2.3. Origins of fibroblasts in the atherosclerotic plaque

The classical theory of atherosclerosis suggests that plaque formation starts when low-density lipoproteins (LDLs) penetrate the arterial through the endothelial layer, a process driven by endothelial dysfunction [56]. Over time, the formation of atherosclerotic plaques in the walls of the coronary arteries is generally thought to occur as a result of smooth muscle cells migrating from the tunica media to the intima and into the newly formed plaque. This process produces ECM components for fibrous cap formation [57]. However, recent evidence challenges this classical theory, suggesting that the origin of fibroblasts and fibroblast-like cells within the atherosclerotic plaque is more complex and cannot be solely attributed to the migration of smooth muscle cells from the tunica media [58].

Vascular smooth muscle cells (VSMCs) exhibit phenotypic and functional plasticity, allowing them to respond to vascular injury by transitioning from a quiescent, contractile state to an activated, motile, and pro-inflammatory phenotype [59]. These cells can move from the tunica media of the arterial wall to the intima and undergo a phenotypic modulation, transforming into fibroblast-like cells known as "fibromyocytes." Fibromyocytes play various roles in the development and progression of the atherosclerotic plaque [60]. Traditionally, the role of VSMCs in atherosclerosis has been associated with their abnormal proliferation and migration into the intima could contribute to pathological intimal thickening and plaque formation. However, recent studies have revealed a more complex picture: while the phenotypic switching of VSMCs can directly promote atherosclerosis [61], VSMC proliferation may also be beneficial during atherogenesis by strengthening the fibrous cap and stabilizing the plaque. Additionally, VSMC apoptosis may promote inflammation, leading to plaque instability [62]. Recent research confirms the complexity of VSMCs, demonstrating that these cells can exhibit various phenotypes, including macrophage-like, myofibroblast-like, foamy cell-like, osteogenic-like, chondrogenic, and mesenchymal stem cell-like phenotypes [63].

PAFs may originate from endothelial cells through EndMT [64]. The vasa vasorum contains endothelial progenitor cells that can transform into myofibroblasts [65]. EndMT is a specific type of endothelial dysfunction responsible for vascular remodeling, a key factor in the development of atherosclerosis [66]. Endothelial cells lining the arterial lumen have the potential to change into mesenchymal cells, also known as "hybrid cells" [67], which can give rise to a subset of fibroblasts migrating into the atherosclerotic plaque [68]. The process of EndMT involves the reorganization of actin filaments, leading to a mobile phenotype, followed by migration of the newly formed "hybrid cells" into the plaque [69]. EndMT may be induced by various factors, including hypoxia, oxidative stress, and TGF-β signaling [70]. EndMT-derived fibroblasts have been implicated in plaque progression due to increased secretion of matrix components and matrix metalloproteinases, ultimately destabilizing plaque [69]. EndMT-derived fibroblasts have also been associated with plaque calcification [71]. Recent findings suggest that EndMT in the atherosclerotic plaque is more common than previously thought [70]. However, the differences in structure and function between EndMT-derived fibroblasts and VSMC-derived fibroblasts, as well as their respective roles in the early and late stages of atherosclerosis, are still not fully understood.Inizio modulo

While much of the current understanding of PAFs derives from in vitro studies, several in vivo models have demonstrated their role in atherosclerosis progression and plaque stability. VSMCs have been shown to transition into fibroblast-like cells (fibromyocytes) in murine models, contributing to both extracellular matrix remodeling and fibrous cap formation [58,62,72]. EndMT has also been identified as a key mechanism generating fibroblast-like cells within atherosclerotic plaques, as evidenced by experimental models demonstrating increased EndMT activity in unstable plaques [64,66,70]. Additionally, adventitial fibroblast progenitors and circulating fibrocytes have been implicated in plaque remodeling and fibrosis, highlighting their potential contribution to fibroblast heterogeneity in vivo [73,74]. Furthermore, critical signaling pathways such as TGF-β, Wnt/β-catenin, and PDGF-D have been shown to regulate fibroblast activation and ECM remodeling in atherosclerosis, providing potential therapeutic targets [22,23,75]. These findings underscore the need for further in vivo investigations to fully elucidate the role of PAFs in atherosclerotic disease.

Another possible source of PAFs is the adventitial stem/progenitor cells, which include adventitial fibroblast progenitors like Sca1 (stem cell antigen-1)-positive cells [73]. In mice, four subtypes of fibroblast precursors have been identified within the adventitial layers [76]. The adventitia is the most complex layer of blood vessels, characterized by a complex cell composition, including fibroblasts, dendritic cells, pericytes, vascular smooth muscle cells, endothelial cells, stem/progenitor cells, and adrenergic nerve cells [77]. This dynamic adventitial microenvironment regulates the structural and functional properties of the three layers of arteries and serves as a crucial source of cells that migrate towards the neointima during atherogenesis. Another interesting aspect of PAFs is their potential origin from circulating cells that might migrate into the plaque by crossing through the tight junctions of endothelial cells. Among these circulating cells, monocytes play a significant role in differentiating into fibroblasts. In healing wounds, instead of becoming macrophages, they can differentiate into fibroblast-like cells [78]. Circulating fibrocytes, hematopoietic-derived cells, are another cell type that might contribute to the generation of PAFs. After an injury, these cells contribute to wound healing with tissue fibrosis, by producing collagen fibers [79]. The recent identification of the circulating fibrocyte as a possible precursor cell of tissue fibroblasts [74] opens new possibilities for understanding the role of fibrocytes in the development of the atherosclerotic plaque, representing a potential source of PAFs. Additionly, monocytes and macrophages may also differentiate into fibroblasts and myofibroblasts inside the plaque [65] through a process defined as macrophage-to-myofibroblast transition (MMT) [80].

In histology, PAFs can be found in all types of atherosclerotic lesions, including early lesions such as adaptive intimal thickening (AIT) and pathological intimal thickening (PIT) (see Fig. 3). In fibroatheromas, PAFs are more commonly observed within the fibrous cap (see Fig. 4). However, they may also appear near the internal elastic lamina in the basal regions of the plaque. Proliferating fibroblasts may also be detected in the adventitia and in the fat surrounding coronary vessels (see Fig. 5). This suggests that the adventitial layer could be a source for fibroblasts in the arterial wall and the newly formed plaque [81]. An accurate examination of the boundaries between the tunica media and the intimal plaque may show the fragmentation of the elastic lamina and the presence of hybrid cells with intermediate features between VSMCs and fibroblasts, migrating from the tunica media into the atherosclerotic plaque [82].

2.4. PAFs and cardiovascular risk factors

PAFs actively interact with key cardiovascular risk factors such as hyperlipidemia, hypertension, and chronic inflammation, further contributing to atherosclerosis progression. Hyperlipidemia promotes oxidative stress and foam cell formation, activating PAFs via the TGF-β and Wnt/β-catenin pathways. This activation leads to extracellular matrix remodeling and fibrosis [22,23,75]. Hypertension induces mechanical stress and endothelial dysfunction, which enhance PAF proliferation and their differentiation into a contractile phenotype, thereby reinforcing the fibrotic component of the plaque [24,57]. Additionally, chronic inflammation, driven by cytokines such as IL-6 and TNF-α,

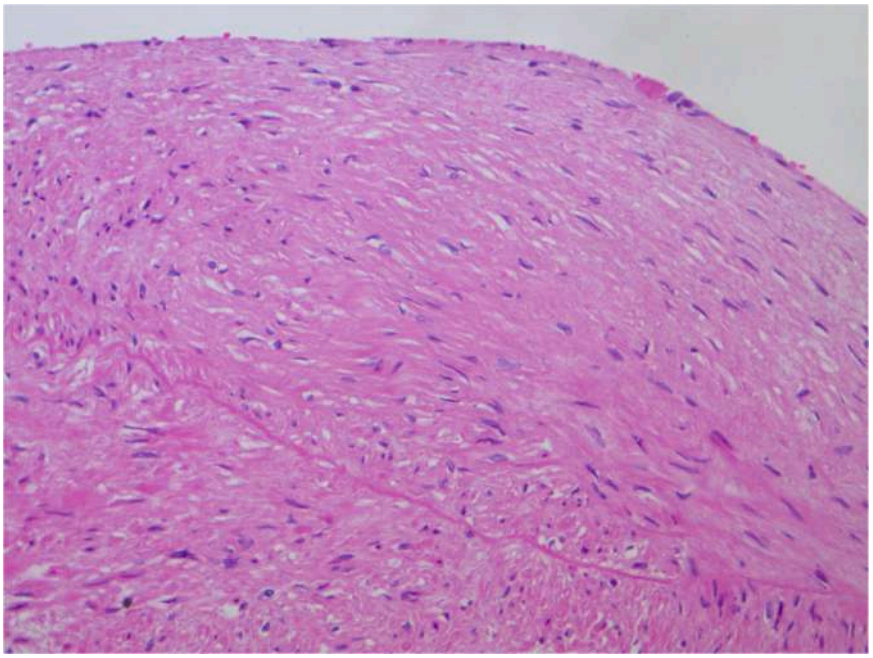

Fig. 3. Pathological intimal thickening of a coronary artery. Plaque-associated fibroblasts are admixed with scattered inflammatory cells. The endothelium is focally missing. H&E original magnification X 250.

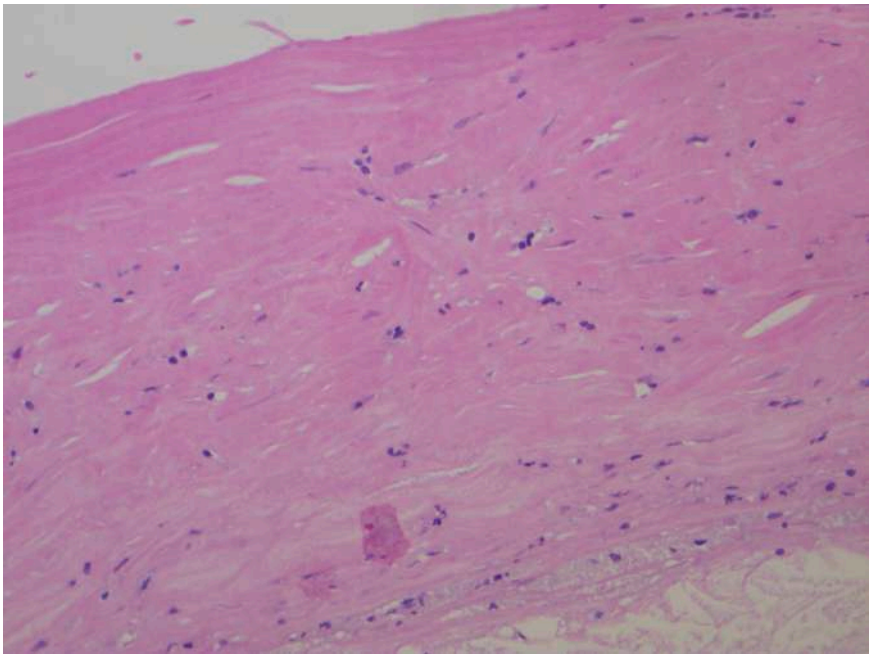

Fig. 4. Fibroatheroma of a coronary artery. Plaque-associated fibroblasts appear embedded in a dense fibrotic collagen-rich fibrous cap. Lymphocytes and monocytes are also found. H&E original magnification X 250.

modulates PAF activity by promoting immune cell recruitment and influencing macrophage polarization within the plaque microenvironment, potentially affecting its stability [83,84].

These interactions suggest that PAFs act as mediators linking traditional cardiovascular risk factors with the structural and functional evolution of atherosclerotic lesions.

By integrating these findings, a more comprehensive understanding of PAFs emerges, positioning them not only as structural components of atherosclerotic plaques but also as dynamic players influenced by systemic risk factors. This highlights the need for further investigation into targeted therapeutic strategies aimed at modulating PAF activity to mitigate plaque progression and instability.

2.5. Interactions of PAFs with other cells inside the plaque

In atherosclerosis, PAFs and myofibroblasts actively remodel the ECM under the influence of immune cell-derived signals. Pro-inflammatory cytokines, such as IL-1 and IL-6, drive immune cell recruitment into the plaque, shaping its inflammatory status [65]. The crosstalk between fibroblasts, macrophages, and VSMCs is crucial in determining plaque stability. Macrophages influence myofibroblast differentiation by producing matrix MMPs and releasing TGF-β, a key

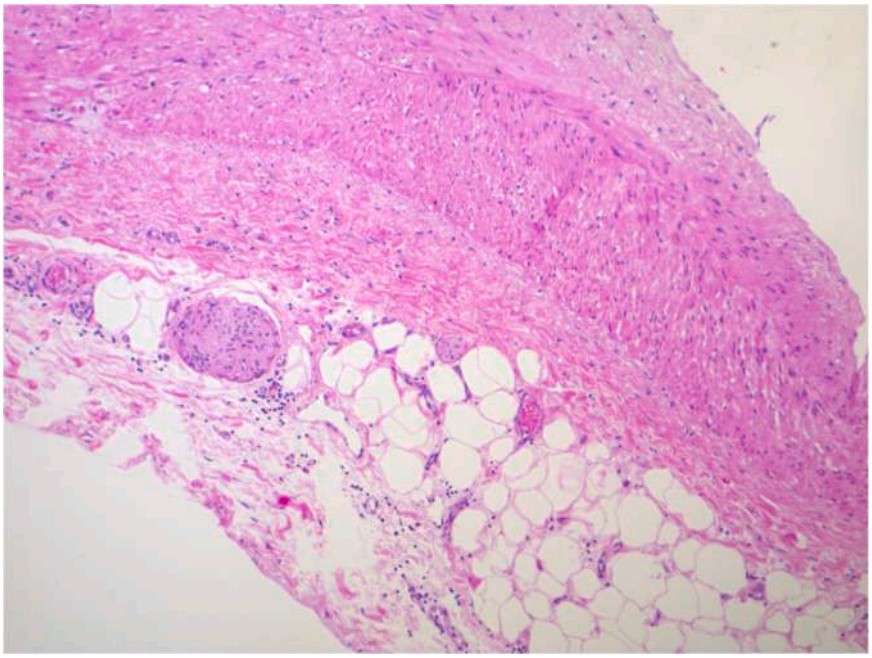

Fig. 5. Pathological intimal tichkening of a coronary artery. On the left side, proliferating plaque-associated fibroblasts infiltrate the perivascular fat, intermingled with lymphocytes. H&E, original magnification X 100.

pro-fibrotic factor [83].

PAFs closely interact with endothelial cells and VSMCs, contributing to plaque composition and progression. Through EndMT, endothelial cells acquire a fibroblast-like phenotype, enhancing ECM production and migration [64,66,70]. This process is regulated by various signaling pathways such as TGF-β [24,64,66], Wnt/β-catenin [22,75], and Notch [69], which modulate both fibroblast activation and inflammation. Similarly, PAFs regulate VSMC behavior via paracrine signaling, promoting their transition into fibroblast-like cells through TGF-β and PDGF-D [23,24], contributing to fibrous cap stabilization, while excessive activation may result in pathological intimal thickening and increased vascular stiffness [57,62].

Beyond ECM remodeling, PAFs actively modulate immune responses within the plaque. By secreting TGF-β, IL-6, and CCL2, they influence macrophage polarization, driving either pro-inflammatory M1-like macrophages, which promote plaque instability, or M2-like macrophages, which support tissue remodeling [85,86]. Additionally, PAFs interact with myeloid-derived suppressor cells (MDSCs), fostering an immunosuppressive environment that sustains chronic inflammation.

ECM remodeling is a key function of PAFs that strongly influences plaque stability. On one hand, PAFs support fibrous cap integrity by synthesizing ECM components such as collagen types I and III, fibronectin, and proteoglycans, largely under the control of TGF-β and PDGF-D signaling [22,23,75]. This contributes to mechanical stability and reduces the likelihood of rupture.

On the other hand, pro-inflammatory PAFs can secrete matrix metalloproteinases (MMPs), especially MMP2 and MMP9, which degrade structural ECM proteins and promote fibrous cap weakening [84,87]. The phenotypic plasticity of PAFs allows them to switch between matrix-producing and matrix-degrading states, depending on inflammatory signals and biomechanical stress. Recent spatial and transcriptomic studies show that collagen-producing fibroblasts are enriched in stable plaque areas, while MMP-expressing subsets are concentrated in rupture-prone regions [87,88]. This duality highlights the dynamic role of PAFs in ECM remodeling and their potential as targets to modulate plaque composition and prevent acute events.

Additionally, recent findings suggest that lipid metabolism may indirectly influence PAF function within the atherosclerotic plaque. Oxidized low-density lipoproteins (oxLDL) and cholesterol crystals, which accumulate in lipid-rich regions, activate TGF-β and NF-κB signaling pathways, leading to enhanced fibroblast proliferation and cytokine production [34]. In macrophages, activation of PPARγ and LXRα induces transcription of ABCA1 and ApoE, which are critical for cholesterol efflux and lipid homeostasis [89,90]. While these pathways have been extensively studied in macrophages, similar signaling circuits may operate in fibroblasts exposed to lipid-rich environments. This could contribute to paracrine modulation of lipid handling and inflammation. Furthermore, fibroblast-derived cytokines such as IL-6 and CCL2 can influence foam cell formation by modulating macrophage phenotype and lipid uptake [91,92]. These interactions suggest that, while PAFs are not primary lipid-storing cells, they may still play a role in to lipid metabolism and plaque progression through indirect mechanisms.

The interplay between cytokines, chemokines, and signaling pathways is crucial for the PAF function. Pro-inflammatory mediators such as IL-6, TNF-α, and IL-1β enhance fibroblast activation and immune cell recruitment [83,84]. Meanwhile TGF-β drives fibroblast differentiation into a myofibroblast-like state, promoting fibrous cap formation [24,64,66]. Chemoattractants like CCL2 and CXCL12 recruit monocytes, macrophages, and MDSCs, influencing plaque stability based on immune signaling balance [85,86]. Notably, PAF-derived cytokines regulate macrophage polarization, reinforcing the inflammatory or reparative response depending on the microenvironmental context [93].

Recent co-culture studies have demonstrated that direct interactions between fibroblasts and macrophages can shape macrophage polarization and cytokine production.This supports a bidirectional regulatory loop that influences both inflammation and ECM remodeling [94]. Additionally, lineage tracing experiments in murine models have shown that fibroblast–endothelial cell crosstalk via Notch and TGF-β signaling contributes to EndMT, fibroblast differentiation, and spatial organization within the plaque [64,95]. These lineage-tracing approaches have helped confirm endothelial and VSMC origins for fibroblast-like cells in vivo.

Spatial transcriptomics has further revealed discrete niches within atherosclerotic plaques where PAFs colocalize with VSMCs, macrophages, and immune cell clusters, facilitating localized cytokine

gradients and matrix deposition [96,97]. These niches often correspond to regions of active remodeling or fibrous cap formation, indicating a role for PAFs in spatially coordinated plaque stabilization. These advanced methodologies provide strong evidence of dynamic, spatially organized cell-cell interactions involving PAFs, which actively contribute to plaque evolution and disease progression.

The Wnt/β-catenin and TGF-β pathways further integrate inflammatory and fibroblast-driven responses, highlighting their dual role in fibrosis and immune modulation [22,24,75].

PAFs play a dual role in atherosclerosis, influencing plaque stability and contributing to clinical events such as myocardial infarction and stroke. Some PAF subsets drive plaque destabilization by secreting pro-inflammatory cytokines like IL-6 and TNF-α, and matrix MMPs, which degrade the extracellular matrix and weaken the fibrous cap, increasing the risk of rupture [83,84]. Conversely, other PAF subpopulations contribute to plaque stabilization by producing extracellular matrix components and reinforcing the fibrous cap, thus limiting lesion vulnerability [62,98]. The balance between these phenotypes is tightly regulated by key signaling pathways, including Wnt/β-catenin, TGF-β, and PDGF-D, which modulate fibroblast activation, immune interactions, and extracellular matrix remodeling [22,23,75].

Recent studies have uncovered that lipid metabolism strongly influences fibroblast activation through multiple mechanisms. For example, oxidized LDL (oxLDL) and cholesterol crystals stimulate TGF-β and NF-κB signaling, leading to fibroblast proliferation and cytokine secretion [99]. Moreover, lipid-laden macrophages in the plaque secrete IL-1β and TNF-α, which enhance fibroblast activation, linking lipid-driven inflammation with fibrotic remodeling [100].

Notably, the Notch signaling pathway, along with TGF-β and Wnt/β-catenin, has emerged as a key regulator of fibroblast-endothelial interactions and fibroblast activation in vascular injury and atherosclerosis [101].

Understanding these mechanisms is crucial for developing therapeutic strategies to mitigate plaque instability and reduce cardiovascular risk.

PAF-derived TGF-β and CCL2 facilitate the recruitment and expansion of MDSCs, mirroring mechanisms observed in tumor progression, where fibroblasts support an immunosuppressive environment [102]. This highlights fibroblasts' dual role in sustaining inflammation or promoting immune evasion.

Recent studies highlight that PAFs exhibit functional heterogeneity, adopting either pro-inflammatory or pro-repair phenotypes depending on microenvironmental signals [65,103].

Pro-inflammatory PAFs contribute to plaque instability by secreting cytokines such as IL-6 and TNF-α, promoting chronic inflammation and matrix degradation through MMPs, which increases the risk of rupture [83,84]. In contrast, pro-repair PAFs support plaque stabilization by enhancing extracellular matrix deposition and fibrous cap formation, expressing markers such as alpha-SMA [104]. The balance between these subtypes is modulated by TGF-β and Wnt/β-catenin signaling, which serve dual roles in fibrosis and inflammation [22,24,75].

One unresolved challenge in atherosclerosis is identifying the molecular pathways activated within the atherosclerotic plaque that enable communication among the different cell types characterizing the plaque microenvironment (PME). In a rat model of atherosclerosis, the Wnt signaling pathway was activated, with significantly higher expression of the Wnt protein compared to control animals [75]. The activation of the Wnt signaling in the plaque was associated with increased levels of VEGF, Beta-catenin, and Dickkopf-related protein 1 (DKK1), an inhibitor of the Wnt signaling. This study demonstrated that Wnt signaling activation in the aorta of rats with atherosclerosis may lead to increased expression of inflammatory cytokines, promoting atherosclerosis progression and accelerating neoangiogenesis, which is the primary cause of intra-plaque hemorrhage (IPH) [105]. The basic helix-loop-helix ARNT-like protein 1 (BMAL1) has been identified as responsible for transforming smooth muscle cells into cells with a fibroblast-like phenotype, contributing to atherosclerotic plaque stabilization [106].

Recent histological and molecular studies in human atherosclerotic plaques have clarified that PAFs contribute to plaque stabilization and features of vulnerability. For example, collagen-producing fibroblasts are frequently observed in thick fibrous caps and are associated with stable lesions. In contrast, pro-inflammatory, MMP-expressing fibroblasts are enriched in rupture-prone regions characterized by thinning caps and necrotic cores [107–109]. Spatial transcriptomics has confirmed that these fibroblast subtypes are compartmentalized within distinct anatomical zones of the plaque, suggesting that fibroblast density and phenotype may serve as potential histopathological markers of vulnerability [110]. This duality reinforces the relevance of PAFs in clinical outcomes such as myocardial infarction and stroke, where plaque morphology is a critical determinant.

2.6. Molecular pathways driving atherosclerosis: the role of plaque-associated fibroblasts

The activation and differentiation of PAFs are influenced by multiple molecular pathways that regulate extracellular matrix remodeling, inflammatory signaling, and cellular plasticity. Among these, the TGF-β, Wnt/β-catenin, and PDGF-D pathways are critical in fibroblast activation and function within the atherosclerotic plaque [22,23,75]. The TGF-β signaling pathway induces fibroblast proliferation and lineage transition, promoting EMT and EndMT [24,64,66]. The Wnt/β-catenin pathway, while well characterized in tumor fibroblast activation [22], is also involved in atherosclerosis by promoting inflammation and neoangiogenesis, contributing to intraplaque hemorrhage [75]. Similarly, PDGF-D signaling has been identified as a key profibrotic mediator that enhances fibroblast activation and extracellular matrix remodeling in vascular pathologies [23].

Through these signaling pathways, PAFs regulate the balance between collagen synthesis and matrix degradation, a central process in determining plaque stability versus rupture [22,23,75].

In addition to these pathways, MMT represents another critical process by which macrophages acquire a fibroblast-like phenotype, increasing the myofibroblast population within the plaque [78]. Significantly, while specific fibroblast populations promote plaque instability, others contribute to fibrous cap stabilization, highlighting the heterogeneity of PAFs [62].

Advanced molecular technologies have significantly revolutionized the study of fibroblast heterogeneity in various pathological contexts, including atherosclerosis. Techniques like single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and proteomics provide powerful tools to dissect the complexity of PAF subpopulations, offering unprecedented insights into their functional roles in atherosclerosis and potential as therapeutic targets.

Recent advances in scRNA-seq have uncovered multiple transcriptionally distinct PAF subpopulations, including pro-inflammatory PAFs (characterized by high expression of IL6, TNF, and MMP9), pro-fibrotic PAFs (enriched in ACTA2, COL1A1, and TGFBI), pro-reparative PAFs (marked by genes such as DCN, TIMP1, and IGF1). These subsets reflect the diverse activation states of fibroblasts within the plaque and are modulated by signaling pathways such as TGF-β, Wnt/β-catenin, and PDGF-D [22,23,75,96,111,112]. Transcription factors such as KLF4, SNAIL1, and TWIST1 are selectively upregulated across these states and govern fibroblast plasticity in the plaque microenvironment. Integrating scRNA-seq with spatial transcriptomics allows researchers to localize these PAFs subtypes within distinct plaque regions, enhancing our understanding of their role in atherosclerosis progression and therapeutic targeting [96,111,112].

ScRNA-seq enables the identification of distinct PAF subsets by resolving transcriptomic profiles at the single-cell level. This approach has been instrumental in uncovering fibroblast diversity in various fibrotic and inflammatory diseases, allowing researchers to map differentiation states, activation pathways, and potential disease-driving

subsets in atherosclerosis [96].

Complementing scRNA-seq, spatial transcriptomics preserves the spatial organization of fibroblast populations within the plaque microenvironment. This technology allowss for the identification of localized cellular niches and interaction networks between PAFs, immune cells, and vascular components, shedding light on the spatial regulation of plaque progression and stability [97].

Additionally, proteomics, including single-cell proteomics and secretome analysis, provides a further layer of functional insight by characterizing post-transcriptional modifications, extracellular matrix remodeling dynamics, and fibroblast-derived signaling molecules. This approach has revealed key protein mediators that drive fibroblast plasticity and influence immune responses in atherosclerosis [113].

The integration of these technologies into atherosclerosis research holds great promise for identifying novel biomarkers, therapeutic targets, and disease-modifying pathways, ultimately leading to more precise and effective treatment strategies.

2.7. Markers of plaque-associated fibroblasts

The current markers used to identify fibroblasts include vimentin, FSP1 (fibroblast-specific protein 1), PDGFR-alpha, Prolyl-4-hydroxylase, Discoidin-Domain Receptor, Fibronectin, COL1A1 (Collagen Type 1 Alpha 1 Chain), Decorin (DCN) [77]. However, these markers are also expressed in other cell types and may be absent in some fibroblast populations, which limits their clinical utility. In atherosclerotic plaque, typical myofibroblastic markers are alpha-SMA and PDGF-beta. Furthermore, smooth muscle cells in these plaques may transform into a fibroblast and myofibroblast phenotype. Compared to smooth muscle cells, plaque-associated myofibroblasts express lower levels of PDGF-beta and Myocardin (MYOCD) and higher levels of ACTA-2 (smooth muscle actin alpha-2), MyH11 (Myosin Heavy Chain-11), KLF4 (Krüppel-like Factor 4), and CNN1 (Calponin 1) [72]. In short, plaque myofibroblasts represent a transitional cell state, exhibiting an intermediate phenotype between smooth muscle cells and fibroblasts.

According to this concept, different subpopulations of myofibroblasts may be identified in atherosclerotic plaques based on their cell of origin and the stage of transdifferentiation towards the myofibroblastic phenotype [111]. A recent study identified specific phenotype markers for PAFs in myofibroblast-like smooth muscle cells within atherosclerotic plaque: Vimentin+ , CD90 + , FSP 1 + , PDGFR-alpha+ , FAP + [114].

Emerging evidence suggests that specific PAF markers, such as alpha-SMA, Desmin, VEGF, and TGF-β, could be integrated into clinical practice as potential biomarkers for plaque stability assessment. Their expression profiles, combined with advanced molecular techniques such as ScRNA-seq, may facilitate early detection and risk stratification in atherosclerosis, opening new avenues for targeted therapeutic interventions [72,77,114–116].

2.8. PAF plasticity and phenotypic transitions

As previousy discussed, PAFs exhibit remarkable plasticity, allowing them to transition between distinct phenotypic states in response to microenvironmental changes. Under inflammatory conditions, PAFs can adopt a pro-inflammatory phenotype characterized by the secretion of cytokines such as IL-6 and TNF-α, contributing to plaque instability [83,84].

Conversely, in fibrotic regions of the plaque, PAFs can differentiate into contractile myofibroblast-like cells expressing alpha-SMA and collagen-producing markers, reinforcing the fibrous cap and potentially stabilizing the lesion [104].

This phenotypic switching is driven by key molecular pathways, including TGF-β, Wnt/β-catenin, and MMT [22,24,75]. Recent studies also suggest that macrophages within the plaque microenvironment can transition into fibroblast-like cells via MMT, further contributing to fibroblast heterogeneity [80]. Additionally, mechanical stress induced by hypertension and extracellular matrix remodeling influences fibroblast activation, highlighting the adaptability of PAFs to vascular pathology [57,62].

The ability of PAFs to undergo these transitions suggests that targeting fibroblast plasticity could be a promising therapeutic approach for modulating plaque composition and stability. Future studies using ScRNA-seq and lineage-tracing models may further elucidate the mechanisms governing fibroblast heterogeneity in atherosclerosis, providing novel insights for therapeutic interventions [72,77,114].

PAFs demonstrate a high degree of plasticity, enabling them to switch between functional phenotypes depending on microenvironmental cues. Under inflammatory conditions, PAFs may adopt a pro-inflammatory profile, secreting IL-6, TNF-α, and CCL2, which promotes chronic inflammation and ECM degradation [83,84]. In contrast, in fibrotic or reparative environments, PAFs transition into matrix-producing myofibroblasts, characterized by alpha-SMA expression and collagen synthesis, thereby contributing to fibrous cap stabilization [104].

As already mentioned, recent scRNA-seq data support the existence of at least three functionally distinct fibroblast states in atherosclerotic plaques: inflammatory fibroblasts (involved in cytokine production and immune recruitment), matrix-producing fibroblasts (contributing to fibrosis and structural integrity), regulatory fibroblasts (supporting tissue repair and resolution of inflammation). These phenotypes are influenced by lipid accumulation, cytokine gradients, and mechanical stress [96,112,117]. Transcription factors such as KLF4, SNAIL1, and TWIST1 are key regulators of these transitions, while epigenetic mechanisms, including histone acetylation and DNA methylation, further modulate fibroblast responses [117].

This dynamic behavior underscores the therapeutic potential of modulating fibroblast phenotypes to control plaque progression and stability.

Beyond the pro-inflammatory and myofibroblastic states, emerging evidence indicates that PAFs may also undergo osteogenic differentiation, contributing to vascular calcification—a key feature of advanced atherosclerotic plaques. Lineage-tracing studies in murine models and scRNA-seq analyses have identified fibroblast-like cells expressing osteoblast-related genes such as RUNX2, BMP2, and SPP1 within calcified plaques [118]. These osteoblast-like transitions appear to be driven by chronic inflammation, oxidative stress, and mechanical strain, which activate signaling pathways including BMP, Wnt/β-catenin, and TGF-β [119]. This plasticity reinforces the multifaceted role of PAFs in fibrosis, inflammation, and in plaque mineralization. Understanding these phenotypic transitions may aid in developing targeted therapies to limit vascular calcification and improve plaque stability.

3. CAFs and PAFs: similarities and differences between two distinct populations originating from different cells

Numerous authors have highlighted parallels between atherosclerosis and cancer (Table 1; Fig. 6). Both conditions involve the dysregulation of cell proliferation, changes in the synthesis of various transcription factors, altered control of neoangiogenesis, and the emergence of cell transdifferentiation towards different phenotypes [120]. Striking cellular plasticity and clonal expansion of cellular subtypes have been observed in both carcinogenesis and the formation of atherosclerotic plaques [121]. Atherosclerosis and cancer share a common pathophysiological substrate, with chronic inflammation playing a critical role in both diseases [122]. Research on the molecular mechanisms involved in atherosclerosis and cancer indicates a connection between lipid metabolism and glucose homeostasis in both conditions [114]. Furthermore, multiple common features have been identified between the microenvironments of atherosclerotic plaques and tumors, including the significant role played by activated fibroblasts in both diseases [103]. The dual role, either inhibiting or promoting cancer

Table 1
Comparison of Cancer-Associated Fibroblasts (CAFs) and Plaque-Associated Fibroblasts (PAFs). This table synthesizes the immunohistochemical and functional similarities and differences between CAFs and PAFs, highlighting their unique and shared roles in disease. TME: Tumor Microenvironment; PME: Plaque Microenvironment; EndMT: endothelial-mesenchimal transitions; VSMCs: Vascular Smooth Muscle Cells; ECM: Extracellular Matrix; MMP: Matrix Metalloproteinases; α-SMA: Alpha-Smooth Muscle Actin; FAP: Fibroblast Activation Protein; VEGF: Vascular Endothelial Growth Factor; FSP-1: Fibroblast-Specific Protein-1; PDGFR: Platelet-Derived Growth Factor Receptor; TGF-β: Transforming Growth Factor Beta; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor Alpha; Tregs: Regulatory T Cells; MDSCs: Myeloid-Derived Suppressor Cells.

Feature	Cancer-Associated Fibroblasts (CAFs)	Plaque-Associated Fibroblasts (PAFs)	Reference
Role in Disease Progression	Promote tumor progression, metastasis, and drug resistance	Contribute to atherosclerosis progression and plaque stability (fibrous cap formation)	[34,124]
Microenvironment	Reside in the TME	Reside in the PME, interacting with endothelial cells, smooth muscle cells, and immune cells	[125,126]
Cellular Origin	Derive from local mesenchymal cells, EndMT, EMT, fibrocytes	Derive fromVSMCs, EndMT, adventitial fibroblast progenitors, circulating fibrocyte	[34–36,59, 60–64,73,74]
Plasticity and Heterogeneity	Display high plasticity, differentiating into pro-tumorigenic or tumor-suppressive fibroblasts	Exhibit dual functional roles, with subsets promoting either plaque stability (fibrous cap formation) or plaque destabilization (inflammation, ECM degradation)	[131,132]
Phenotypic Plasticity & Transdifferentiation	Exhibit reversible switching between iCAFs, myCAFs, apCAFs, etc., influenced by microenvironmental cues	Capable of transitioning into myofibroblasts or osteoblast-like cells, contributing to fibrosis or vascular calcification	[22,24,75,104, 118,119]
Extracellular Matrix (ECM) Remodeling	Actively degrade and remodel ECM to promote tumor invasion and metastasis	Can stabilize plaques via ECM deposition, but some subsets promote instability by degrading ECM and increasing MMP activity	[34,132,133]
Immunophenotype	Express markers such as alpha-SMA, FAP, Desmin, VEGF, FSP−1, PDGFR-α/β, TGF- β	Express markers like alpha-SMA, Desmin, VEGF. TGF- β. Typically, no or low FAP expression, less expression of PDGFR.	[127–130]
Cytokine Production	Secretes pro-inflammatory and immunosuppressive cytokines (e.g., TGF-β, IL−6), recruits Tregs and MDSCs to promote immune evasion	Secretes pro-inflammatory cytokines like IL−6, TNF-α and MMPs, promoting chronic inflammation and ECM remodelling	[129,130]
Immune Cell Recruitment and Modulation	Recruit Tregs and MDSCs to suppress immune responses	Modulate macrophages (M1/M2 polarization) and recruit Tregs, influencing plaque inflammation and fibrosis	[84,135,136]
Lipid Interaction & Foam Cell Crosstalk	Interact with adipocytes; modulate metabolism via PPARγ and lipid-associated pathways	Influence macrophage lipid uptake via IL−6, CCL2; respond to oxLDL/cholesterol crystals via TGF-β/NF-κB; may indirectly affect cholesterol efflux	[34,83–86,89, 90,93]
Therapeutic Targeting	Potential target in cancer therapy by inhibiting FAP, TGF-β, or ECM enzymes	Targeting fibroblast activation (e.g., Wnt/β-catenin, PDGF-D, TGF-β inhibitors) could stabilize plaques in cardiovascular diseases	[84,115,116, 135,141–143]

progression, or stabilizing versus destabilizing atherosclerotic plaque, underscores a compelling parallel between these two pathologies [123]. The considerable plasticity and heterogeneity exhibited by CAFs and PAFs significantly impact their respective disease microenvironments, as expounded by Kalluri R in 2016. [34].

In the context of atherosclerosis, PAFs predominantly emerge from VSMCs that migrate from the tunica muscularis, as well as from endothelial cells that migrate into the neointima, from the vasa vasorum or the arterial lumen's endothelium [62]. These cells undergo phenotypic alterations, assume fibroblast-like traits, and contribute to the formation of fibrous caps within atherosclerotic plaques [124].

In contrast, in the TME, CAFs have a more complex origin, reflecting the specific organ they come from. For example, in liver tumors, some CAFs originate from hepatic stellate cells, while in pancreatic cancer, CAFs may arise from pancreatic stellate cells [125]. CAFs can also derive from bone marrow-derived mesenchymal stem cells, local tissue-resident fibroblasts, and even epithelial-to-mesenchymal transition (EMT) of cancer cells [126].

While PAFs and CAFs share common features, PAFs exhibit distinct characteristics specific to atherosclerosis. Unlike CAFs, which primarily derive from resident fibroblasts and mesenchymal cells, PAFs originate from VSMCs [62], endothelial cells undergoing EndMT [62,64], adventitial fibroblast progenitors [73], and circulating fibrocytes [74].

Functionally, PAFs play a dual role in atherosclerosis. Some subpopulations promote plaque destabilization by secreting inflammatory cytokines (IL-6, TNF-α) and MMPs, thus enhancing extracellular matrix degradation [83,84]. Others contribute to plaque stabilization by reinforcing the fibrous cap and promoting extracellular matrix remodeling [104]. These processes are influenced by atherosclerosis-specific pathways, including Wnt/β-catenin and PDGF-D signaling [22,23,75]. While TGF-β signaling is shared between CAFs and PAFs, its role in atherosclerosis is more context-dependent, balancing fibrosis and tissue remodeling [24,64,66].

PAFs also engage in distinct immune interactions, modulating macrophage polarization (M1/M2 balance), recruiting regulatory T cells, and influencing endothelial function, processes that contraste with the immune evasion mechanisms seen in tumors [83,84]. Understanding these atherosclerosis-specific fibroblast functions may reveal new therapeutic targets for cardiovascular disease.

These differences in origin lead to complex differences in immunophenotype between CAFs and PAFs. In atherosclerosis, a major characteristic of PAFs is the expression of alpha-SMA, a marker of myofibroblasts and VSMCs [127]. This marker, however, is also expressed in some CAFs, highlighting the shared characteristics between these fibroblasts in different disease contexts [128]. Moreover, CAFs express multiple other factors depending on their origins and activation states, including FAP, PDGFR, and various cytokines and chemokines that modulate the TME [129]. For instance, CAFs secrete TGF-β, which promotes tumor growth and immune evasion [130].

The plasticity and heterogeneity of fibroblasts in atherosclerosis and various cancer types underscores the complexity of fibroblasts in both normal physiology and human pathology [131]. Both PAFs and CAFs contribute to the remodeling of the ECM, which is critical for the structural integrity and pathological progression of tissues in atherosclerosis and cancer [132]. In the context of atherosclerosis, PAFs aid in ECM deposition and plaque stability [104], while in cancer, CAFs facilitate tumor growth, invasion, and metastasis through ECM remodeling [133]. Moreover, CAFs can create a physical barrier to immune cell infiltration, contributing to immune evasion in cancer [134].

Furthermore, the interaction of fibroblasts with immune cells is another area of similarity. In both atherosclerosis and cancer, fibroblasts can modulate immune responses by secreting pro-inflammatory and immunosuppressive factors, thereby influencing disease progression [135]. For instance, in cancer, CAFs can recruit regulatory T cells (Tregs) and MDSCs to the TME, enhancing immunosuppression and tumor growth [115,136]. Similarly, in atherosclerosis, PAFs can secrete cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), contributing to chronic inflammation and plaque instability [84].

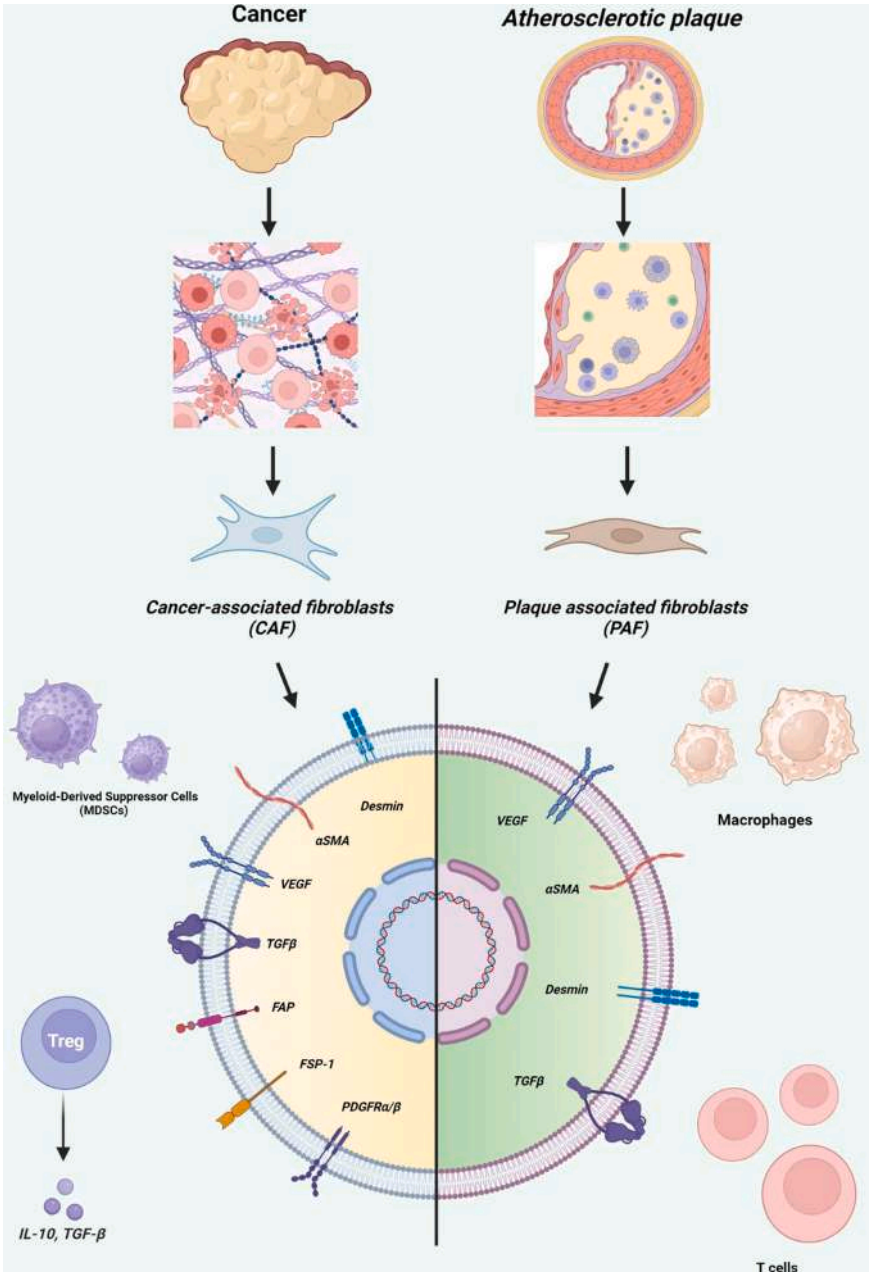

Fig. 6. CAFs and PAFs: similarities and differences between two distinct populations originating from different cells.

Understanding these interactions and the dual role of fibroblasts can provide insights into potential therapeutic targets for both atherosclerosis and cancer.

PAFs play a key role in atherosclerosis and may serve as both biomarkers and therapeutic targets. Their involvement in extracellular matrix remodeling, immune modulation, and plaque stability suggests they could indicate disease progression. Markers such as alpha-SMA, Desmin, VEGF, and TGF-β help distinguish PAF subsets linked to either plaque stabilization or vulnerability [72,77,114,116]. Advanced techniques like single-cell RNA sequencing and spatial transcriptomics have identified distinct PAF subpopulations with potential prognostic value [96,97].

Therapeutically, targeting PAFs could help modulate plaque composition and reduce cardiovascular risk. Key pathways such as Wnt/β-catenin, TGF-β, and PDGF-D regulate fibroblast activation and extracellular matrix remodeling, making them promising intervention points [22,23,75]. Inhibitors of TGF-β—already explored in oncology for CAFs—could limit fibroblast-driven plaque instability [137,138]. Similarly, targeting FAP may mitigate fibroblast-mediated pathology [139]. Emerging strategies, including nanomedicine and targeted drug delivery, offer promising approaches for selective PAF modulation [140].

Further research is needed to integrate PAF-targeted therapies into cardiovascular treatments. Given the similarities between CAFs and PAFs, insights from cancer research could aid in developing innovative fibroblast-modulating interventions for atherosclerosis.

We recognize that previous studies have explored the comparisons between CAFs and PAFs. However, we believe our manuscript introduces several novel contributions to this topic. While past research has compared CAFs and PAFs, our work systematically examines the functional, molecular, and immunophenotypic characteristics of both types of fibroblasts [34,131]. We emphasize the importance of PAFs in the context of atherosclerosis, shifting the focus away from the traditional lipid- and immune-centered perspectives [62,124]. Moreover, we investigate the interactions between PAFs and other components of the

microenvironment, drawing novel parallels to the tumor microenvironment, an area that has not been thoroughly explored before [103,123]. Finally, we discuss potential therapeutic implications, suggesting that targeting PAFs may provide new strategies for the treatment of atherosclerosis. We believe these insights significantly enhance the understanding of the field.

3.1. Functional convergence between CAFs and PAFs: translational insights

Both CAFs and PAFs contribute to disease progression by reshaping the extracellular matrix, modulating immune responses, and driving chronic inflammation through similar signaling axes. In both contexts, TGF-β signaling promotes the differentiation of fibroblasts into myofibroblasts, enhancing fibrosis and altering tissue architecture [22,24,64,66]. Similarly, Wnt/β-catenin signaling, widely studied in CAFs, is also active in atherosclerotic plaques and contributes to fibroblast-driven inflammation and vascular remodeling [22,75]. PDGF-D, a potent activator of fibroblasts in cardiac and cancer contexts, has been shown to stimulate fibroblast proliferation and matrix deposition in atherosclerosis [23].

Functionally, both CAFs and PAFs exhibit immunosuppressive functions. CAFs facilitate immune evasion by recruiting regulatory T cells (Tregs) and MDSCs, while PAFs support an immunosuppressive plaque microenvironment through the secretion of CCL2 and TGF-β, influencing macrophage polarization and MDSC recruitment [85,86,93,102]. This immune modulation underscores a shared mechanism of chronic inflammation, which promotes tumor growth in cancer and plaque destabilization in atherosclerosis.

These parallels support the hypothesis that therapies targeting fibroblast activation, differentiation, or immune interactions,such as TGF-β inhibitors, FAP-targeted drugs, or Wnt modulators, may have therapeutic relevance cross both cancer and cardiovascular disease [137,138].

3.2. Controversies and knowledge gaps in PAF and CAF research

While significant parallels have been drawn between CAFs and PAFs, important controversies and unresolved questions remain in both fields. A major challenge lies in the dual role of fibroblast subsets: some CAFs and PAFs are associated with disease progression and inflammation, while others appear to have protective roles, promoting tissue repair and structural integrity [45,46,104]. This functional dichotomy complicates therapeutic targeting and reflects an incomplete understanding of fibroblast heterogeneity.

Additionally, although markers such as alpha-SMA, FAP, and PDGFRα are used to identify fibroblast subtypes, these markers lack specificity and often overlap with those expressed by other stromal cell types, leading to ambiguous identification and lineage tracing [77,114]. This issue is especially pronounced in atherosclerosis, where the contribution of VSMC-derived fibroblasts versus adventitial or endothelial-derived populations remains under debate [62,64,73].

Another controversial area involves the plasticity and origin of fibroblasts. While CAFs may arise from local mesenchymal sources or epithelial cells via EMT [36,37], PAFs have been reported to originate from VSMCs, endothelial cells (via EndMT), and circulating fibrocytes [62,64,74,80]. However, lineage-tracing studies confirming these transitions in vivo are still limited.

Furthermore, while scRNA-seq and spatial transcriptomics have revealed significant fibroblast heterogeneity, these techniques often lack functional validation, and multi-omic datasets' integration remains both technically and interpretatively challenging [96,97].

From a therapeutic standpoint, fibroblast-targeting strategies, such as FAP or TGF-β inhibitors, have shown promise in cancer [136,137], but their applicability to atherosclerosis remains hypothetical. Clinical studies on fibroblast modulation in cardiovascular disease are currently lacking, representing a critical gap in translational research.

Future studies should aim to resolve these controversies by combining lineage tracing, functional assays, and spatial multi-omics to dissect fibroblast dynamics in both tumor and plaque microenvironments.

Although recent histological and transcriptomic data suggest a correlation between fibroblast subtypes and plaque vulnerability [110], further studies are needed to determine whether specific PAF populations causally contribute to plaque rupture or stability in humans. Establishing these links is essential to translate fibroblast-targeting strategies into clinically effective interventions for myocardial infarction or stroke.

Despite the progress made using single-cell technologies, important challenges remain in the classification and interpretation of PAF subpopulations. While inflammatory, fibrotic, and regulatory fibroblast subsets have been identified [96,112], their precise ontogeny, spatial dynamics within plaques, and functional interplay with immune and vascular cells are not fully understood. Moreover, it remains unclear whether these transcriptionally defined states represent stable phenotypes or transient activation states in response to local stimuli. Further studies are needed to integrate transcriptional, epigenetic, and spatial data with functional assays to determine the causative roles of distinct PAF subtypes in plaque rupture, remodeling, or stabilization. Understanding these dynamics is essential to selectively target pathogenic fibroblast populations while preserving or enhancing reparative functions.

4. Conclusions and future perspectives

In recent years, growing evidence has highlighted the importance of fibroblast heterogeneity and plasticity in various pathological contexts. Our study reinforces this concept by drawing a detailed comparison between PAFs and CAFs, emphasizing their shared molecular mechanisms, microenvironmental interactions, and functional roles.

Recent research has shown that fibroblasts, including CAFs and PAFs, are capable of undergoing phenotypic changes in response to various stimuli or environmental cues. This adaptability extends to acquiring stem cell properties, suggesting a potential similarity between fibroblasts and mesenchymal stem cells [141]. The discovery of previously unrecognized heterogeneity and multiple functions of tissue fibroblasts within the atherosclerotic plaque has unveiled their plasticity. This plasticity enables fibroblast lineages to re-enter the cell cycle, generating new extracellular matrix-producing cells and contractile myofibroblasts. While understanding these complexities poses a significant challenge for researchers, it also holds promising therapeutic potential for advancing the treatment of atherosclerosis. Recognizing the potential of PAFs is vital for advancing atherosclerosis treatment. These cells can have the same clinical and therapeutic significance in the modern approach to atherosclerosis as CAFs in the field of oncology [115,142]. CAFs are considered one of contemporary oncology's most crucial and promising therapeutic targets [143].

Understanding the similarities and differences between CAFs and PAFs can provide valuable insights into potential therapeutic targets. This enhanced knowledge of fibroblast biology in different pathological contexts is not just academic; it has the potential to significantly advance therapeutic interventions and improve patient outcomes. Emerging research suggests that targeting the shared pathways between atherosclerosis and cancer, such as those involving inflammation, cellular metabolism, and immune regulation, could offer novel therapeutic approaches. For example, anti-inflammatory agents and metabolic modulators that have been explored in cancer treatment could potentially be repurposed for atherosclerosis management, and vice versa. Understanding the molecular crosstalk between these diseases could lead to innovative strategies for prevention and therapy.

Both PAFs and CAFs exhibit the ability to undergo phenotypic transitions, remodel the extracellular matrix, and influence immune

responses. These similarities are not only of theoretical relevance but also have significant therapeutic implications [131]. The PME and the TME share key signaling pathways, such as TGF-β, Wnt/β-catenin, and PDGF-D, which regulate fibroblast activation in both conditions [22,135]. Moreover, PAFs and CAFs contribute to immune modulation by secreting cytokines like IL-6 and TGF-β, which sustain chronic inflammation and disease progression [84,115].

By understanding these parallels, we propose that therapeutic strategies targeting CAFs, such as TGF-β inhibitors or FAP inhibitors, could be effectively repurposed for atherosclerosis treatment. This perspective opens new avenues for translational research, suggesting that lessons learned from oncology may be applied to cardiovascular disease [137].

Targeting the ECM remodeling capabilities of fibroblasts or their interactions with immune cells offers promising avenues for therapy. For example, inhibitors of FAP or TGF-β signaling are being explored for their potential to disrupt the pro-tumorigenic activities of CAFs [137,138]. In atherosclerosis, strategies aimed at modulating PAF activity and reducing inflammation could enhance plaque stability reduce the risk of acute cardiovascular events [139]. Acknowledging the analogous importance of PAFs based on the presented data could potentially revolutionize the management and treatment of atherosclerosis [116].

Recent research suggests that understanding PAF heterogeneity could enable the development of targeted therapies, similar to approaches explored for CAFs in cancer [115,116]. Several key molecular pathways, including TGF-β, Wnt/β-catenin, and PDGF-D, regulate PAF activation and differentiation, making them attractive therapeutic targets [22,23].

Additionally, targeting ECM remodeling and immune interactions mediated by PAFs could help stabilize plaques and slow down atherosclerosis progression [139]. Inhibitors of FAP or TGF-β signaling, which are currently being investigated for CAF modulation in oncology, may also have potential applications in atherosclerosis [137].

Furthermore, emerging strategies targeting inflammation have been proposed for atherosclerosis treatment. Recent studies indicate that modulating the immune system to reduce chronic inflammation may be an effective therapeutic approach [144]. Selective inhibition of key inflammatory pathways has also been suggested as a promising direction for cardiovascular disease management [145,146]. Moreover, advancements in nanomedicine offer novel diagnostic and therapeutic possibilities for atherosclerosis by leveraging nanomaterials for targeted drug delivery and imaging [140].

Therefore, by exploring the similarities and differences between CAFs and PAFs, researchers can develop more targeted strategies for treating these complex diseases. Recognizing the analogous role of fibroblasts in these two diseases could provide novel therapeutic opportunities and redefine current treatment approaches for atherosclerosis.

CRediT authorship contribution statement

Saba Giorgio: Writing – review & editing, Writing – original draft. **D'Agata Alessandra Pia:** Writing – review & editing, Writing – original draft. **Castagnola Massimo:** Writing – review & editing, Writing – original draft. **Spanu Dario:** Writing – review & editing, Writing – original draft. **Pretta Andrea:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology. **Cau Flaviana:** Writing – review & editing, Writing – original draft. **Faa Gavino:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Saba Luca:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Ziranu Pina:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology. **Suri Jasjit:** Writing – review & editing, Writing – original draft. **Scartozzi Mario:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Tiwari Ekta:** Writing – review & editing, Writing – original draft.

Consent for publication

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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