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FGF-TGFβ dialogues, endothelial cell to mesenchymal transition, and atherosclerosis

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Introduction

Atherosclerosis is a chronic disease characterized by accumulation of fat and cholesterol in the arterial wall leading to restriction of blood flow[1–3]. Atherosclerotic plaques contain a number of cell types including smooth muscle cells (SMCs), macrophages, endothelial cells (ECs), B cells, T cells, and fibroblasts, among others[4–8]. Recent lineage tracing studies provide strong evidence that a substantial proportion of cells in the plaque are derived from the endothelium. This process, referred to as endothelial-to-mesenchymal transition (EndMT) is characterized by the loss of normal endothelial and gain of mesenchymal fate markers. Functional consequences include deposition of pro-inflammatory extracellular matrix, facilitation of recruitment of leukocytes and growth of unstable plaque. Here, we review the current understanding of molecular controls of EndMT and its contribution to the development of atherosclerosis.

Atherosclerosis

Atherosclerosis is best viewed as a chronic, progressive inflammatory disease. The slow evolution of atherosclerotic lesions combines endothelial dysfunction with recruitment of leukocytes, extensive lipid deposition, proliferation of medial SMCs, and remodeling of the extracellular matrix. Endothelial cells play a critical role in the development of atherosclerosis. The normal endothelium is involved in multiple aspects of vascular physiology including regulation of vascular barrier function, leukocyte trafficking, thrombosis prevention, and regulation of vascular tone. Endothelial dysfunction is an important step in the development and progression of atherosclerotic lesions and its occurrence has been considered a predictor of subsequent development of atherosclerosis. Most atherosclerosis triggers, including both mechanical and local inflammatory factors, can activate the endothelium, resulting in expression of chemokines and cytokines (e.g. IL-1, IL-6, IL-8, MCP-1) and adhesion receptors (e.g. ICAM-1, VCAM-1, E-selectin) that attract and facilitate immune cell extravasation[9].

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Endothelial to mesenchymal transition (EndMT)

Recent studies have demonstrated that endothelial cells exhibit a high degree of organ heterogeneity and plasticity both in physiologic and pathologic settings. Endothelial plasticity can range from a subtle shift from quiescent to activated state to a full-blown fate change characterized by a nearly complete loss of endothelial and acquisition of mesenchymal, fate markers. The latter process, termed EndMT, is not necessarily pathologic. Indeed, EndMT is critical to normal embryogenesis, most notably in developing cardiac valves. Here, EndMT results in conversion of endocardial cells of the atrio-ventricular canal into mesenchymal cells that populate A-V cushions and subsequently give rise to the mitral and tricuspid valves[10]. EndMT is also involved in generation of cardiac fibroblasts and formation of intracardiac septa[11]. While some degree of EndMT in adult tissues may be a normal component of wound healing/injury recovery response, prolonged and/or extensive EndMT is clearly pathologic[12]. Various studies demonstrated its occurrence in a number of disease settings including organ fibrosis[13–15], restenosis[16], transplant arteriopathy[17], vein graft remodeling[18], pulmonary hypertension[19], and cancer[20].

More recently, EndMT has been shown to be an important contributes to atherosclerosis, both in mouse models and in patients[21–23]. Of note, there is a strong correlation between the anatomically determined severity of human coronary artery disease and the extent of EndMT in luminal coronary endothelial cells[22, 23]. Indeed, this correlation may be causative: macrophage-derived foam cells impair endothelial barrier function by inducing EndMT[24] while EndMT promotes deposition of fibronectin and expression of endothelial adhesion molecules ICAM-1 and VCAM-1, thereby promoting recruitment of circulating monocytes and leukocytes and accumulation of monocyte-derived macrophages[22]. One may hypothesize that this leads to establishment of a feed-forward loop that further aggravates endothelial cell dysfunction and drives progression of atherosclerosis[12].

Abnormal shear stress occurring in certain segments of the arterial vasculature has long been known to be responsible for the preponderance of atherosclerotic lesions in these locations via its effect on luminal endothelial cells[25]. Low shear stress promotes, while high shear stress suppresses, vascular inflammation and thrombosis. More recently, this has also been linked to EndMT with uniform laminar shear stress inhibiting EndMT development via activation of ERK5 signaling, whereas disturbed flow promoted it[21]. Low shear stress-dependent stimulation of may involve upregulation of expression of TWIST and Snail transcription factors[26,27].

The high-density (HDL) cholesterol fraction that has been associated with anti-atherosclerotic effects, reduces TGFβ1-induced EndMT via upregulation of the inhibitor Smad (Smad7) and decreases expression of EndMT transcription factor Slug and ZEB1[28]. Furthermore, the lipoprotein ApoA-I/ABCA1 inhibits TGFβ1-induced EndMT through repression of the TGFβ1/Smad2/Smad3/Snail/Slug pathway in human coronary artery endothelial cells[29].-Overall, all these data point to a potentially critical role played by EndMT in atherosclerosis.

Signaling pathways regulating EndMT

Fibroblast growth factor (FGF) signaling pathway

The twenty-two fibroblast growth factors family members signal via four plasma membrane tyrosine kinase receptors (FGFR1–4). In the vasculature, FGF signaling is involved in numerous biological processes including modulation of angiogenesis, maintenance of vascular integrity, and regulation of endothelial cell identity[30, 31]. Binding of an FGF ligand to an FGFR induces the latter to dimerize and trans-phosphorylate specific tyrosine residues in its cytoplasmic kinase domains thereby leading to its activation[32]. Subsequent phosphorylation events in receptors' cytoplasmic domains and a constitutively docked adaptor protein fibroblast growth factor receptor substrate 2 alpha (FRS2α), generate docking sites for numerous cytoplasmic proteins. This, in turn, results in activation of downstream signaling cascades including Ras/mitogen-activating protein (MAP) kinase, phosphoinositide-3-kinase (PI3K)/Akt pathway, and phospholipase C gamma (PLCγ) pathways[33].

All FGF receptors (FGFR1–4), the adaptor protein FRS2α, and their co-receptor Klotho and Syndecan-4 have been genetically knockout in mice[34–41]. However, these global knockout phenotypes are not very informative with regard to vascular development either due to very early embryonic lethality occurring prior to critical stages of blood vessel development (i.e. *Fgfr1*$^{-/-}$) or the absence of a phenotype due to compensation by other FGFRs. More detailed insights in the role of FGF signaling in the endothelium emerged from cell-type specific knockouts of FGF receptors. A conditional endothelial-specific knockout of *Fgfr1* and *Fgfr2* showed that mice are viable with no vascular developmental defects[42]. However, there was a significant impairment of angiogenic response after eye injury and delayed skin wound healing in adult mice. At the same time, an endothelial-specific knockout of *Fgfr1* in combination with a global *Fgfr*3 knockout resulted in impaired development of blood and lymphatic vessels[43]. Interestingly, an endothelial-specific knockout of either *Fgfr1* or *Frs2α* increased neointima formation in transplant arteriopathy and atherosclerosis models due to induction of EndMT[17, 22]. Finally, FGF signaling also plays an important role in the maintenance of VEGFR2 expression and is required for the maintenance of both blood and lymphatic endothelial cells identity through FGF-Ras-MAPK signaling[31, 44–46].

Transforming growth factor β (TGFβ) signaling pathway

TGFβ, a member of the TGF superfamily of growth factors, has been reported to be involved in a wide range of diverse and often contradictory functions. It plays important roles both in physiological (embryonic development, differentiation, cell growth, cell death, tissue homeostasis) and pathological processes (auto-immune, inflammation, fibrosis, angiogenesis, oncogenesis, and cardiovascular disease)[47]. The three TGFβ isoforms (TGFβ1, TGFβ2, and TGFβ3) signal through two types of serine/threonine kinase receptors, called types I and II TGFβ receptors[48]. Once dimerized by ligand binding. these protein complexes trigger signal transduction by phosphorylation of their specific receptor-regulated Smads (R-Smads2 and 3). Activated R-Smads interact with the common partner Smad, Smad4, and accumulate in the nucleus, where the Smad complex directly binds to defined elements on the DNA and regulates target gene expression together with other factors[49, 50].

In addition to activating the canonical Smad signaling pathway, TGFβ signaling can also activate non-canonical cascades including PI3K/AKT, MAPK and Rho-like GTPase signaling pathways[51, 52]. However, the relationship between TGFβ signaling and non-Smad activation has been poorly understood. The type III TGFβ receptors, betaglycan and endoglin, function as ligand reservoirs, holding ligands close to the cell surface in a manner analogous to the role played by heparan sulfate proteoglycans in FGF signaling[53].

In vitro, TGFβ has been shown to inhibit endothelial cell proliferation and migration and to stimulate smooth muscle and mesenchymal cell differentiation and extracellular matrix accumulation[54–56]. TGFβ signaling in endothelial cells is essential for precise regulation of blood vessel assembly, normal embryonic development, postnatal angiogenesis, and homeostasis maintenance in the adult vasculature. When induced early, endothelial cell-specific knockouts of *Tgfbr1* or *Tgfbr2* result in embryonic lethality at ~E10.5 with extensive yolk sac vascular network defects[57]. Endothelial-specific excision activation of *Tgfbr2* at E11.5 leads to abnormal ventricular septation and cerebral hemorrhage[58]. Finally, endothelial *Tgfbr2* excision at the postnatal day 2 (P2) results in angiogenic defects in the retina[59]. Extensive studies also showed that TGFβ promotes SMC differentiation and stimulates SMC marker gene expression through Smad2/Smad3 activation[60–62]. Selective deletion of *Tgfbr1* or *Tgfbr2* in SMCs cause embryonic lethality due to vascular deformities[57]. Adult mice lacking *Tgfbr2* in VSMCs also show vascular defects including increased VSMC proliferation, decreased smooth muscle contractile markers, and exhibiting aortic thickening, dilatation, and dissection[52].

FGF-TGFβ cross-talk

As already outlined, FGF and TGFβ signaling pathways play important roles in regulating endothelial and smooth muscle cell behaviors. However, the two signaling systems often have diametrically opposite effects: for example, while FGFs induce SMC proliferation, TGFβ inhibits it[56, 63]. Even though the fact that these signaling cascades can influence, and counteract, each has been known for some time, until now little was known about molecular details of these interactions.

Early studies showed that in vitro FGF2 inhibits TGFβR1 expression[64]. It also antagonizes TGFβ-mediated induction of SMC markers expression in pericytes and smooth muscle cells[65] and can revert TGFβ-induced epithelial-to-mesenchymal transition (EMT)[66]. More recent studies showed that inhibition of FGF signaling in the endothelium induced by *Fgfr1* or *Frs2α* deletion results in increased TGFβ signaling leading to EndMT[17, 67]. The molecular basis of this cross-talk proved rather unusual. FGF signaling input is required for maintenance of *let-7* miRNA expression. Both TGFβR1 and Smad2 3'UTR contain multiple *let-7* binding sites: a decrease in FGF signaling input leads to a 20–120 decline in *let-7* levels. This, in turn, markedly prolongs TGFβR1 (and Smad 2) mRNA half-lives, thus increasing their protein expression and allowing activation of TGFβ signaling[17].

The effect of FGF signaling shutdown is not limited to TGFβR1: expression of all TGFβ receptors is increased as is expression of TGFβ ligands, with TGFβ2 demonstrating the biggest increase[17]. Whether all of these TGFβ family members' expression is also directly

regulated by *let-7* or is due to something else, has not been established. While initially described in endothelial cells, the FGF-*let-7*-TGFβ cross-talk appears quite universal, having also been observed in smooth muscle cells and fibroblasts[56].

FGF-TGFβ cross-talk in endothelial cells

While FGF regulation of TGFβ signaling appears pretty universal, functional consequences of this cross-talk are quite different for different cell types. It is particularly instructive to construct biological consequences of extinguishing FGF signaling and activating TGFβ signaling in endothelial vs. smooth muscle cells. In vitro, endothelial cells treated with TGFβ undergo EndMT as demonstrated by changes in cell shape, loss of endothelial cell markers and gain mesenchymal marker gene expression. A dominant-negative form of Smad4, the TGFβR1 kinase inhibitor SB431542, and the TGFβ antagonist BMP7, all block TGFβ-induced EndMT[13]. In agreement with these data, in vivo studies confirmed the central role played by activation of endothelial TGFβ signaling in EndMT induction including both in development[68] and disease settings[17, 22]. Like these in vitro observations, EndMT in blood vessels vivo results in endothelial cells losing their highly differentiated state, becoming proliferative, and acquiring mesenchymal characteristics. This, in turn, promotes disease processes such as atherosclerosis[22].

FGF-TGFβ cross-talk in smooth muscle cells

As in endothelial cells, there is strong evidence linking FGF signaling to suppression of TGFβ signaling and the loss of FGF signaling input to activation of TGFβ signaling output. Yet biological consequences are very different. FGF2 is a potent SMC mitogen and a powerful inducer of the SMC contractile-to-proliferative phenotype switch[63]. The induction of a proliferative phenotype is characterized by the loss of normal contractile protein expression, appearance of non-muscle isoforms of muscle proteins, secretion of extracellular matrix and increased proliferative and migratory behavior. In vivo, this is commonly observed in injury settings when local FGF release leads to contractile-to-proliferative phenotype transition. The end result is a marked increase in medial SMC proliferation and neointima formation, features of several common diseases including atherosclerosis and restenosis[69, 70].

In contrast to FGF, TGFβ promotes SMC differentiation and converts proliferative SMCs back to contractile state[63]. In vivo activation of SMC TGFβ signaling induced by the loss of FGF signaling input engineered by an SMC-specific *Frs2a* deletion, results in markedly reduced neointima lesion development in both atherosclerosis and carotid artery ligation models[56, 63]. Thus, the loss of FGF signaling in both the endothelium and smooth muscle cells activates TGFβ signaling. In the endothelium this leads to the loss of cell differentiation, transition to an undifferentiated state and leads to promotion of diseases such as atherosclerosis. In contrast, in SMCs, the same process shifts undifferentiated cells to the differentiated phenotype and suppresses atherosclerotic progression (Figure 1). In summary, FGF-TGFβ cross-talk is a common biological occurrence that plays multifactorial roles both in development and disease. Importantly, while a decline in FGF signaling invariably leads to an increase in TGFβ signaling, the functional consequences of this interplay are highly cell type-dependent.

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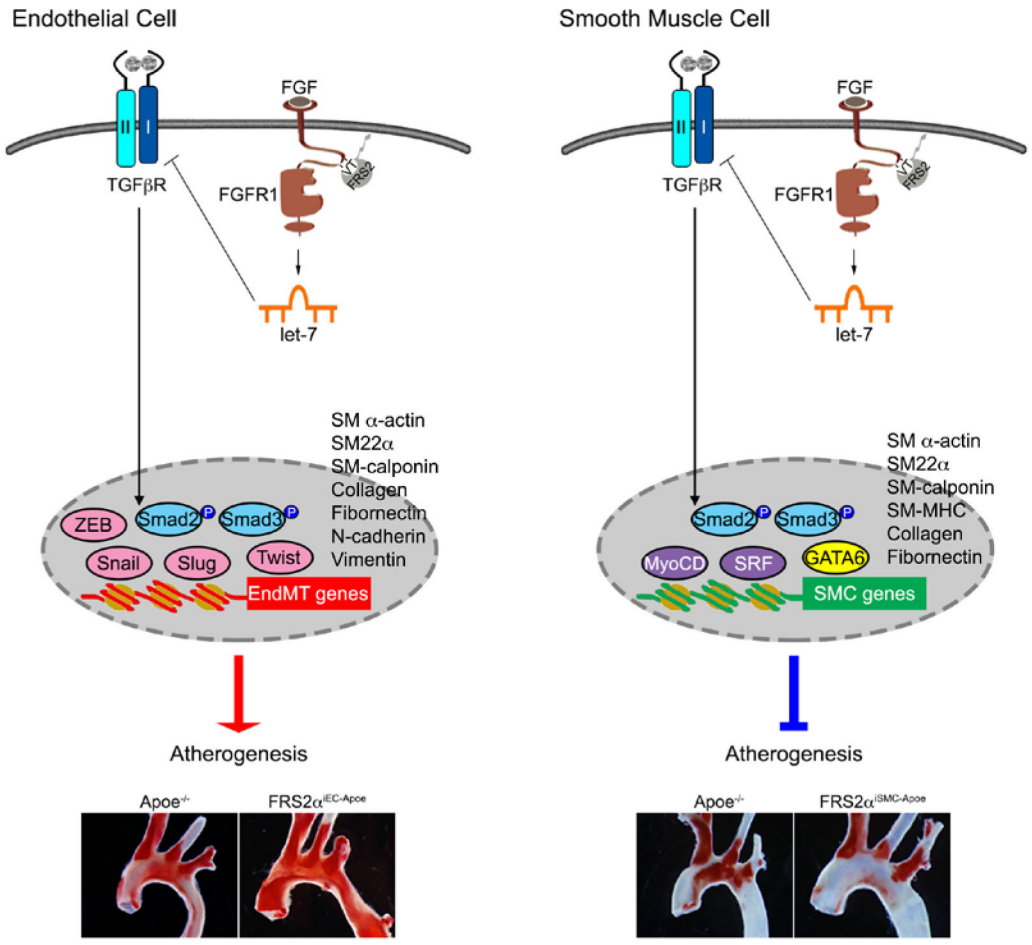

Figure 1: FGF-TGFβ signaling antagonizing in endothelial cells and smooth muscle cells.

In both endothelial cells and smooth muscle cells, inhibition of FGF signaling leads to upregulate TGFβ signaling activity, however, the biological outcome of this antagonizing effects is completely different. In endothelial cell (left panel), activation of TGFβ signaling cascade induces endothelial cell to mesenchymal transition (EndMT), increases inflammation, permeability, and extracellular matrix (ECM) deposition, and therefore, accelerates atherosclerosis. In smooth muscle cell (right panel), activation of TGFβ signaling cascade promotes differentiation/maturation, maintains vascular homeostasis, and increases extracellular matrix deposition, therefore inhibits the progression of atherosclerosis[22, 56].