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The Role of TGF- β and TGF- β Receptors in Atherosclerosis

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1. Introduction

Researchers discovered a new cytokine with the capability to transform fibroblasts in 1983 while studying epidermal and platelet derived growth factors in rat fibroblasts. Originally called sarcoma growth factor, TGF β was first isolated from neoplastic mouse tissue by Moloney sarcoma virus (Assoian et al., 1983). After more than three decades TGF- β family comprise several members including - nodals, activins, bone morphogenic proteins (BMPs), myostatin, anti-Muellerian hormone (AMH) and others - control cell division, differentiation, migration, adhesion, organization and programmed cell death (Massague, 1998). There are three TGF- β isoforms currently described in humans, including TGF- β 1, TGF- β 2, and TGF- β 3. Alignment of the amino acid sequences of the three mammalian TGF- β isoforms reveals that the different isoforms share a high level of similarity between the active domains; TGF- β 3 is 86% similar to that of TGF- β 1 while it shares 91% similarity with that of TGF- β 2. However, despite TGF- β 2 and - β 3 sharing the highest level of sequence similarity of the three isoforms, TGF- β 2 binds to the TGF- β receptor II (T β R β II) in a different way from TGF β 1 and - β 3. Furthermore, while TGF- β 1 and - β 3 are both capable of binding directly to the type II receptor, presentation of TGF- β 2 to the receptor requires the presence of a co-receptor (beta glycan or endoglin), which may explain the differences in activities of TGF- β 2 and - β 1 (Lavery et al., 2009). The importance of TGF- β isoforms in mammalian biology is highlighted by the lack of viability in TGF- β ^{-/-} mice. Targeted disruption of the TGF- β 1 genes leads to hematopoietic and vasculogenic defects that result in death of about half of null embryos by 10 days gestation. Moreover, embryos that survive die within 3 weeks due to widespread inflammatory disease (Shull et al., 1992). TGF- β 2 null mice die in the perinatal period due to cyanotic heart disease, pulmonary insufficiency, and another abnormalities in urogenital, visual, auditory, neural and skeletal systems (Sanford et al., 1997). Additionally, mice lacking TGF- β 3 exhibit cleft palate with 100% penetration and die immediately after birth due to an inability to suckle effectively (Proetzel et al., 1995). In addition, other organs are not affected when compared with mice lacking TGF- β 1 and TGF- β 2.

Several other papers showed differences in postnatal effects of different TGF- β isoforms, including different role in neovascularization (Wu et al., 1997), collagen production and bone production (ten Dijke et al., 1990). Moreover, TGF-betas are released by immune cells

and detected in wound fluid, especially during inflammation and tissue repair. Although all three TGF- β isoforms participate in wound healing TGF- β 1 plays a dominant role in the wound repair process while TGF- β 2 and TGF- β 3 have been shown to play a key role in embryonic development and scarless wound healing (Tandon et al., 2010).

TGF- β 1 (the first member of the family to be discovered and the best-studied member to date) is present at high levels in the healthy blood vessel wall, whereas TGF- β 2 and TGF- β 3 isoforms are either absent (β 2) or present only at low levels (β 3) (Lebrin et al., 2005). Moreover, TGF- β 1 is a potent regulator of vascular development and vessel remodeling and plays key roles in atherosclerosis and restenosis, regulating endothelial, smooth muscle cell (SMC), macrophage, T-cell and probably vascular calcifying cell responses (Bobik, 2006).

Thus, in this review, we will focus on TGF- β 1 cytokine and its receptors and transducers related mostly to *in vivo* atherogenesis, both in animals and humans.

2. TGF- β 1 and atherogenesis

There are a number of studies which demonstrate the role of TGF- β 1 cytokine in atherosclerosis. TGF- β 1 is produced by both inflammatory and vascular cells and is expressed in human and mouse atherosclerotic plaques (Mallat et al., 2001).

There is some controversial information regarding the role of TGF- β 1 in atherogenesis. One group of papers show anti-atherogenic role of TGF- β 1 cytokine. Inhibition of TGF- β 1 activity by various approaches results in pro-atherogenic changes in the vessel wall in animal models of atherosclerosis (Singh and Ramji, 2006). Deletion of a single allele of the TGF- β 1 gene, which reduces the amount of TGF- β 1 protein in the vessel media by \sim 50%, results in reduced SMC differentiation, and increased susceptibility to endothelial cell activation and vascular lipid lesion formation in response to pro-atherogenic stimuli such as a lipid-rich diet (Grainger et al., 2000). Moreover treatment with neutralizing anti-TGF- β 1 antibodies led to increased vascular inflammation, accelerated lipid lesion formation and a shift in plaque morphology towards an unstable phenotype (Mallat et al., 2001). Inhibition of TGF- β 1 with a recombinant soluble TGF- β receptor fusion protein was associated not only with increased inflammation but also with intraplaque hemorrhage (Lutgens et al., 2002). Additionally, TGF- β 1 has been shown to increase bovine aortic endothelial cell (BAEC) and human umbilical vein endothelial cell (HUVEC) steady-state eNOS mRNA expression (Inoue et al., 1995), suggesting the protective role of this cytokine in the vessel endothelium. Moreover, smooth muscle cells in stable lesions express greater amounts of TGF- β 1 than unstable lesions (Cipollone et al., 2004). Furthermore, disruption of TGF- β 1 signaling specifically in T-cells also results in increased lesion size and development of an unstable phenotype (Li et al., 2006; Robertson et al., 2003). Additionally, TGF- β 1 attenuates macrophage foam cell formation, increases cholesterol efflux (Panousis et al., 2001) and inhibits lipoprotein lipase expression (Irvine et al., 2005). Furthermore, TGF- β 1 reduces cytokine-stimulated inducible nitric oxide synthase (iNOS) expression (Werner et al., 2000), promotes iNOS protein degradation (Mitani et al., 2005), and inhibits expression of cell adhesion molecules (DiChiara et al., 2000).

On the other hand, there have been some reports discussing a possible atherogenic activity of this cytokine. Elevated TGF- β 1 levels have been found in vessel wall lesions (Majesky et al., 1991; Nikol et al., 1992). Moreover, TGF- β is a potent stimulator of proteoglycan biosynthesis in human SMCs (Chen et al., 1987), its presence in fatty lesions is likely to contribute to the synthesis of lipoprotein-trapping proteoglycans, which can contribute to

accumulation of lipoproteins in the vessel wall (O'Brien et al., 1998) and their subsequent chemical modification (Grainger et al., 1995). Moreover TGF- β 1 stimulates leukocyte chemotaxis (Ashcroft, 1999), suggesting that TGF- β contributes to early macrophage migration and lipid accumulation. When infused into rats with preexisting vascular lesions, TGF- β 1 caused an 80% increase in lesion size due to extracellular matrix accumulation (Majesky et al., 1991). Localization of TGF- β 1 correlated with areas of neointimal formation, where increase in expression of fibronectin and collagen types I and III was observed (Bahadori et al., 1995; Majesky et al., 1991). Antibodies against TGF- β 1 suppressed intimal hyperplasia in a rat model (Wolf et al., 1994). Similarly, Schulick et al. demonstrated that overexpression of active TGF- β 1 in uninjured rat arteries results in the development of a matrix-rich neointima (Schulick et al., 1998). All these data generally suggest a strong participation of TGF- β 1 in the development of atherosclerosis.

In summary, TGF- β 1 seems to participate in the development of atherosclerosis, but maybe more interestingly promote a stable lesion phenotype, suggesting its role in the protection of acute ischemic situations like myocardial infarction.

TGF- β 1 is secreted in a latent form, where it is associated in a complex with latency-associated protein (LAP) and latent TGF- β 1 binding protein-1 (LTBP). Latent TGF- β 1 can be activated by a number of physical processes, including heat, acid, reactive oxygen species, and biological processes such as proteolysis or integrin - mediated activation. A number of proteases, including plasmin, thrombin, elastase, MMP-2 (matrix metalloproteinase-2) and MMP-9, have been shown to be capable of directly activating latent TGF- β 1 *in vitro* (Jenkins, 2008). TGF- β 1 can bind a heteromeric complex of type I and type II transmembrane serine/threonine kinase receptors. This complex is usually formed by ligand, one TGF- β type II receptor (T β R-II) and two TGF- β type I receptors called activin receptor-like kinase (ALK) (ten Dijke and Hill, 2004). This process can be affected by type III receptor known as endoglin (CD105) (Grainger, 2007). In the ligand-bound complex, the type II receptor phosphorylates serine and threonine residues in the GS region of the type I receptor. After that, conformational changes in the type I receptor appear and subsequently, phosphorylation of signaling molecules named Smads propagate the signal to the nucleus, where they finally regulate transcription of several genes, including those with importance in atherogenesis (Lebrin et al., 2005). Human genome encodes seven type I receptors (ALKs 1-7) and five type II receptors (ActR-IIA, ActR-IIB, BMPRII, AMHR-II and T β R-II) that are paired in different combinations as receptor complexes for various members of TGF- β family (Massague and Gomis, 2006). Moreover, there are also three distinct types of Smad proteins (Feinberg and Jain, 2005).

In the following part of this review we will discuss the role of TGF- β receptors in atherogenesis.

2.1 TGF- β receptors I and their role in atherogenesis

As mentioned above there are seven type I receptors, designated activin receptor-like kinases (ALK-1 to ALK-7) (de Caestecker, 2004; Miyazono et al., 2000). The decision which type I receptor is activated is determined by receptor expression and/or ligand concentration (Goumans et al., 2002). The most important and the most studied type I receptors with respect to atherogenesis are ALK-1 and ALK-5.

Many previously published *in vitro* studies demonstrated a large interplay and mostly opposite effects of ALK-1 and ALK-5 (Goumans et al., 2003). In endothelial cells, TGF- β type

II receptor can activate endothelial cell-restricted ALK-1 and/or broadly expressed ALK-5, which have opposite effects on endothelial cell behavior (Lebrin et al., 2005). Both ALK-1 and ALK-5 can activate various Smad proteins, which will be discussed later. ALK-5 was found to be important for recruitment of ALK-1 into a TGF- β receptor complex, and additionally, the kinase activity of ALK-5 is essential for efficient ALK-1 activation (Massague and Gomis, 2006).

Both ALK-1 and ALK-5 are important for endothelial cell regulation. The TGF- β /ALK-1 pathway stimulates endothelial cell proliferation and migration, whereas the TGF- β /ALK-5 pathway inhibits these processes. ALK-1 stimulates the expression of Id-1, an inhibitor of basic helix-loop-helix proteins, and promotes endothelial cell proliferation, migration and tube formation (Valdimarsdottir et al., 2002), whereas ALK-5 induces expression of fibronectin, an extracellular matrix protein (Lebrin et al., 2005), and plasminogen activator inhibitor-1, a negative regulator of endothelial cell migration and angiogenesis (Watabe et al., 2003).

Very little is known about changes in expression patterns of type I receptors during atherogenesis.

The study of Yao et al. showed that ALK-1 is minimally expressed in atherosclerosis-free segments of human coronary arteries. On the other hand, ALK-1 expression was strongly upregulated in atherosclerotic lesions. The expression was detected in neointima, coronary endothelium and in areas of the shoulder region that appeared to be a site of neoangiogenesis. In addition, the expression was detected in the core of the lesions and in areas that appeared to undergo cellular organization (Yao et al., 2007). Authors also suggested that ALK-1 signaling in the endothelium may be important in the initiation of the atherosclerotic lesion. Moreover, ALK-1 expression in atherosclerotic lesions may contribute to regulation of proliferation and promotion of SMC differentiation, both during development and progression of atherosclerosis (Yao et al., 2007). Another study showed that ALK-1 may stimulate expression of vascular endothelial growth factor (VEGF) in endothelial cells (Yao et al., 2008), which might represent a protective effect on vessel endothelium with respect to the development of endothelial dysfunction (Walshe et al., 2009). In line with these results, ALK-1 expression was related to decreased plaque size after both atorvastatin treatment (Rathouska et al., 2011) and reduction of cholesterol in apoE/LDLr-deficient mice (Strasky et al., 2011).

In many studies, ALK-5, usually named simply TGF- β receptors I, is weakly expressed in intimal cells in human non-atherosclerotic aortas. On the other hand, strong ALK-5 expression was detected in fatty streaks/fibrofatty lesions. Additionally, its expression was strongly decreased in fibrous plaques (Bobik et al., 1999), suggesting that ALK-5 might support TGF- β 1 activity in the promotion of lipoprotein retention, activation of proteolytic systems of macrophages, and also limitation of SMC proliferation in fatty lesions (Bobik et al., 1999). On the other hand, ALK-5-mediated signaling plays an important role in keeping the endothelium quiescent by inhibiting EC proliferation, tube formation and migration, thus angiogenesis (Goumans et al., 2002). Additionally, most of the effects of TGF- β on SMC function appear to be mediated via ALK-5 (Bobik, 2006). All effects of ALK-5 are mediated by Smad2/3 proteins which will be discussed later.

2.2 TGF- β receptor II and its role in atherogenesis

As mentioned above, T β R-II interacts with various T β R-I, including ALK-1 and ALK-5. However, there are some studies focusing on the role T β R-II in atherosclerosis alone.

In general, it was shown that T β R-II expression is strong in non-atherosclerotic human vessels in the majority of cells in media and intima and also in fatty streaks, predominantly in smooth muscle cells and macrophages. On the other hand, the expression of T β R-II was reduced in fibrous plaque and associated media (Bobik et al., 1999). These data assume strong activity of TGF- β 1/T β R-II system in fatty streaks/fibrofatty lesions. Moreover, Piao and Tokunaga observed in human aortic atherosclerotic lesions increased levels of T β R-II, mainly in intima, SMCs, and macrophages, as well as in endothelial cells, when compared with non-atherosclerotic vessels, proposing its participation in atherosclerosis (Piao and Tokunaga, 2006). On the other hand, papers showed that there are some differences in TGF- β receptor expression patterns in vascular SMCs derived from normal versus diseased arteries. It was demonstrated that the type II receptor is decreased in SMCs derived from atherosclerotic lesions, with little change in the type I or III receptors. Subsequent analysis of human lesion versus normal tissues confirmed that the type I receptor is consistently present in the lesion, while the type II receptor was much more variable and commonly absent in both coronary artery and carotid artery lesions (McCaffrey, 2000). Additionally, others suggested an important role of T β R-II expression with respect to plaque stability. In mouse, suppression of TGF- β signaling through expression of a dominant negative type II TGF- β receptor, either systemically (Lutgens et al., 2002) or selectively in T-cells (Gojova et al., 2003); (Robertson et al., 2003), results in accelerated lipid lesion formation, increased vascular inflammation and a shift to an unstable lesion phenotype, thus more macrophage and lymphocyte and less collagen content. In addition, Lutgens et al. showed that inhibition of TGF- β activity following systemic administration of a recombinant soluble TGF- β type II receptor leads to change of plaque morphology into inflammatory phenotype that is low in fibrosis (Lutgens et al., 2002).

In summary, these data suggest a protective role of T β R-II expression in atherosclerosis.

3. Endoglin, the accessory type III receptor

Endoglin (or CD105) is a homodimeric transmembrane glycoprotein, that interacts with TGF- β 1 and TGF- β 3, but only when it is associated with T β RII (Lastres et al., 1996). Endoglin is not the true receptor but it strongly modulates activities of TGF- β RII (Guerrero-Esteo et al., 2002), ALK-1 (Guerrero-Esteo et al., 2002; Lebrin et al., 2004) and ALK-5 (Guerrero-Esteo et al., 2002). Endoglin physically interacts with TGF- β RI and TGF- β RII, and this interaction is not modified by the presence of exogenous ligand or by the activation state of the signaling kinases (Wrana et al., 1994). Additionally, endoglin inhibits phosphorylation levels of TGF- β RII *in vivo* and *in vitro*. On the other hand, endoglin was found to affect not only the phosphorylation status of TGF- β RII but also that of TGF- β RI. The presence of endoglin also appears to affect signaling downstream of TGF- β RI-TGF- β RII complex (Lopez-Novoa and Bernabeu, 2010). In general, endoglin is highly expressed by vascular endothelial cells (Li et al., 2000), SMCs (Adam et al., 1998), macrophages (Lastres et al., 1992) and T-cells (Bobik, 2006), which are cells strongly participating in the atherogenesis.

There are some studies showing the expression of endoglin in atherosclerotic lesions, both in humans and experimental animals. Low levels of endoglin expression in endothelial cells, medial smooth muscle cells and adventitial fibroblasts were detected in normal porcine coronary arteries. However, balloon injury in these vessels significantly increased its expression in both endothelial cells and smooth muscle cells (Ma et al., 2000). Moreover, in atherosclerotic human coronary artery tissue, endoglin was overexpressed in SMCs, in

smooth muscle alpha-actin (SM a-actin) positive cells of atherosclerotic plaques, but it was not expressed in normal vascular smooth muscle, suggesting that endoglin may play a role in the response of the vessel wall to injury, including the development of atherosclerosis (Conley et al., 2000). Also other studies showed higher expression of endoglin in atherosclerotic vessels when compared with non-diseased vessels, suggesting that endoglin participates in atherogenesis (Piao and Tokunaga, 2006; Tashiro et al., 2002). Additionally, endoglin expression was linked to neo-angiogenesis within atherosclerotic aortic and carotid plaques, supporting its role in this process (Krupinski et al., 2008). Moreover, endoglin serum levels were found to be elevated in patients with atherosclerosis and correlated with total cholesterol levels (Blann et al., 1996).

On the other hand, several papers suggested an important role of endoglin in regulation of expression and activity of endothelial NO synthase (eNOS). The levels of eNOS are strongly related to the amount of endoglin, both *in vivo* and *in vitro* (Jerkic et al., 2004; Toporsian et al., 2005). Toporsian et al. found that partial or total loss of endoglin in murine endothelial cells is associated with a 50% decrease in eNOS levels (Toporsian et al., 2005). In addition, eNOS - derived NO seems to play a major role in endoglin-dependent angiogenesis (Jerkic et al., 2006). Santibanez et al. demonstrated that endoglin-dependent induction of eNOS occurs at the transcriptional level and moreover that endoglin is able to regulate eNOS expression independently of TGF- β (Santibanez et al., 2007). Endoglin colocalization with eNOS in aortic endothelial cells in mice atherosclerosis was also demonstrated (Nachtigal et al., 2009b). More recently, it was demonstrated that endoglin serum levels are decreased by extracorporeal LDL-cholesterol elimination in patients with familial hypercholesterolemia, suggesting that endoglin can serve as a marker for evaluation of the treatment efficacy of these procedure (Blaha et al., 2008).

In the light of above mentioned data, it is suggested that endoglin plays a role in atherogenesis, however its role with respect to atherogenic and/or atheroprotective effects remains to be elucidated.

4. Smad proteins in atherogenesis

As mentioned above, TGF- β 1 and its receptors activate intracellular signal transducers called Smad proteins (Derynck et al., 1996). Eight Smad proteins are encoded in the human and mouse genomes but only five of them are substrates for TGF- β receptors, which are commonly referred to as receptor-regulated Smads, or RSmads (Smad1, Smad2, Smad3, Smad5, and Smad8) (Massague, 1998). Smad4, named Co-Smad, serves as a common partner for all RSmads. Moreover, there are inhibitory Smad6 and Smad7 (Miyazono et al., 2000).

In general, no expression of Smad2 and Smad3 was detected in healthy human non-atherosclerotic aorta. On the other hand, strong Smad2 and Smad3 expression was detected in macrophages after differentiation from monocytes in fatty streaks/fibrofatty lesions (Kalinina et al., 2004). Smads were not detected in smooth muscle cells in these lesions. On the contrary, strong SMAD2 and SMAD3 expression was detected in SMC in aortic fibrous plaques, suggesting their participation in collagen production in these lesions, which seems to be important for lesion stability (Kalinina et al., 2004). Several other, mostly *in vitro*, studies revealed the effects of various Smads on the cellular components of atherosclerotic lesions. Smad3 was shown to be important for suppressing the inflammatory response in macrophages, including inhibition of

inducible nitric oxide synthase (iNOS), monocyte chemoattractant protein-1 (MCP-1), and MMP-9 (Feinberg et al., 2004a; Werner et al., 2000). These inhibitory effects of Smad3 were attributed to inhibition of transcription factors, including AP-1, and to competition with NF- κ B for limiting quantities of the co-activator p300/CBP (Feinberg and Jain, 2005).

Moreover, Smad3 seems to be important also in the modification of T-cell activity related to atherosclerosis. CD4⁺ and CD8⁺ T-cells from Smad3-deficient mice had increased IL-2 production (McKarns and Schwartz, 2005). Moreover, it was demonstrated that Smad3 stimulates production of Th2 cytokine shown to have anti-inflammatory effects in various experimental atherosclerotic models (Blokzijl et al., 2002). Smad3 potentiated by Smad4 is also able to reduce expression of SMC activation markers IL-6 and iNOS (Feinberg et al., 2004b), which are also linked to the progression of atherosclerosis.

Smad2 was shown to be important in endothelial cells. Saura et al demonstrated that the overexpression of Smad2 induces expression of eNOS, a critical regulator of vascular function and response to inflammation (Saura et al., 2002). Potential role of Smad2 in regulation of vascular inflammation can be related to its inhibition of NF- κ B via competition with NF- κ B for limiting amounts of p300/CBP (DiChiara et al., 2000).

These data nicely demonstrate anti-inflammatory and endothelial-protective effects of Smad2 and Smad3 in atherogenesis.

Smad1 effects on atherogenesis are not well documented so far. In general, Smad1 can be activated by BMP ligands, as well as by TGF- β 1/ALK-1 activation mostly in endothelial cells (Goumans et al., 2002). This activation is related to activation of cell proliferation and angiogenesis (Oh et al., 2000). Since the specific role of angiogenesis in atherosclerosis with respect to pro- or anti-atherogenic effects is still not clear, the role of Smad1 in atherosclerosis remains to be elucidated in the future (Khurana et al., 2005).

Smad4 can form a complex with other Smads, including Smad2 and/or Smad3, and participates in augmenting of several effects of these Smads in a variety of cell types important in vascular inflammation (Feinberg and Jain, 2005). Smad4 was expressed together with Smad2 and Smad3 in fibrous plaques participating in collagen production, suggesting its effects on stable plaque phenotype (Kalinina et al., 2004).

Smad6 and Smad7 are inhibitors of both Smad2 and Smad3 phosphorylation (Shi and Massague, 2003). However, their effects in different tissues are not the same. For example, Smad7 blocked the TGF- β 1-induced growth inhibition in VSMCs, Smad6 did not possess this ability (Ikeda et al., 2003). NF- κ B and IFN- γ signaling rapidly induce Smad7 expression. This results in an increased expression of pro-inflammatory cytokines (IL-1 β or TNF- α) in macrophages and vascular SMCs, suggesting that Smad7 blocks anti-inflammatory effects of TGF- β 1 at least *in vitro* (Kato et al., 2001).

Recently, a splice variant of Smad6 (Smad6s) expressed in endothelial cells has been shown to affect TGF- β signaling. Both isoforms were detected in both normal vessels and atherosclerotic lesions localized in endothelial cells of the intima and in vasa vasorum as well as in smooth muscle cells of media (Krishnan et al., 2001). However, functional roles of these two isoforms in the context of atherogenesis have not been determined.

It can be concluded that Smad proteins are expressed in atherosclerotic lesions, where Smad2 and Smad3 play potential anti-atherogenic roles. The role of other Smads in relation to *in vivo* atherogenesis remains to be elucidated.

5. TGF- β 1 related signaling pathways and atherogenesis

In previous chapters, we described studies that focused on the role of one or two members of TGF- β pathway. In this part, we are going to focus on studies, in which at least 3 members were part of the study.

As mentioned previously, TGF- β 1 activates TGF- β receptor II which is followed by activation of different TGF- β receptor I, e.g. ALK-1 and ALK-5, with subsequent phosphorylation of various Smad proteins (Goumans et al., 2009). All these pathways can be modified by accessory TGF- β III receptors, mainly by endoglin (Lopez-Novoa and Bernabeu, 2010).

In general, TGF- β /ALK-5 signaling induces Smad2/3 phosphorylation and blocks angiogenesis by inhibiting EC proliferation, tube formation and migration. TGF- β /ALK-5/Smad2/3 signaling plays an important role in keeping the endothelium quiescent (Goumans et al., 2009; Goumans et al., 2002).

In contrast to TGF- β /ALK-5, TGF- β /ALK-1 signaling induces Smad1/5 activation and has been shown to stimulate EC migration, proliferation and tube formation (Goumans et al., 2003). Strong interplay between both cascades has been demonstrated *in vitro*. ALK-5-deficient ECs are not only defective in TGF- β /ALK-5 signaling but also exhibit impaired TGF- β /ALK-1 responses. Furthermore, ALK-1 can directly antagonize ALK-5/Smad2/3 signaling at the level of Smads (Goumans et al., 2002; Oh et al., 2000).

Piao et al studied the expression of TGF- β 1, endoglin and TGF- β receptor II in human aortic atherosclerotic lesions and non-atherosclerotic aortas. Immunohistochemical analysis revealed a weak expression of all studied markers in the vessel wall. On the other hand, they described simultaneous expression of TGF- β 1, endoglin and T β R-II in most atherosclerotic aortas in endothelium, macrophages and smooth muscle cells, suggesting the participation of these proteins in atherosclerosis (Piao and Tokunaga, 2006).

In another *in vitro* study Santibanez et al revealed a mechanism in which endoglin regulates the expression of eNOS. They showed that endoglin strongly supports TGF- β /Smad2 signaling by increasing the levels of Smad2 protein as a consequence of enhancing Smad2 stability. Secondary to the increase in Smad2 protein levels, they observed increased association of Smad2 with the receptor complex, higher levels of Smad2 phosphorylation, and an increase in Smad2/Smad4 heteromeric complex formation which was followed by increased expression of eNOS (Santibanez et al., 2007). These data suggest an important role of TGF- β 1/endoglin/Smad2/eNOS pathway in the function of endothelium and atherosclerosis.

Moreover, Chen et al also demonstrated an important role of TGF- β receptors and Smad2 with respect to cholesterol levels. They demonstrated that cholesterol inhibits TGF- β 1/T β R-II/T β R-I/Smad2 signaling by lowering of T β R-II/T β R-I binding ratio in plasma membrane and decrease in Smad2 phosphorylation, which was related to progression of atherosclerosis (Chen et al., 2008; Chen et al., 2007). These data were supported recently by Strasky et al, who demonstrated that hypercholesterolemia decreases endoglin, phosphorylated Smad2 and endothelial protective VEGF expression simultaneously with increased atherosclerosis in mice aorta (Strasky et al., 2011). In addition, Bot et al, described endoglin/TGF- β 1/Smad2/3 expression and signaling in human atherosclerotic lesions. These authors demonstrated that endoglin/TGF- β 1/Smad2/3 expression and activity correlates with a fibrous plaque phenotype, increased collagen levels, less matrix degradation, more SMC proliferation, reduction in inflammatory cell number and decreased amount of intraplaque

thrombi. This suggests that these markers are associated with more stable plaque phenotype in human atherosclerosis (Bot et al., 2009).

In summary, activation of TGF- β 1 signaling pathway, which includes endoglin and Smad2, seems to play a protective role in atherogenesis via protection of vascular endothelium and atherosclerotic plaque stabilization.

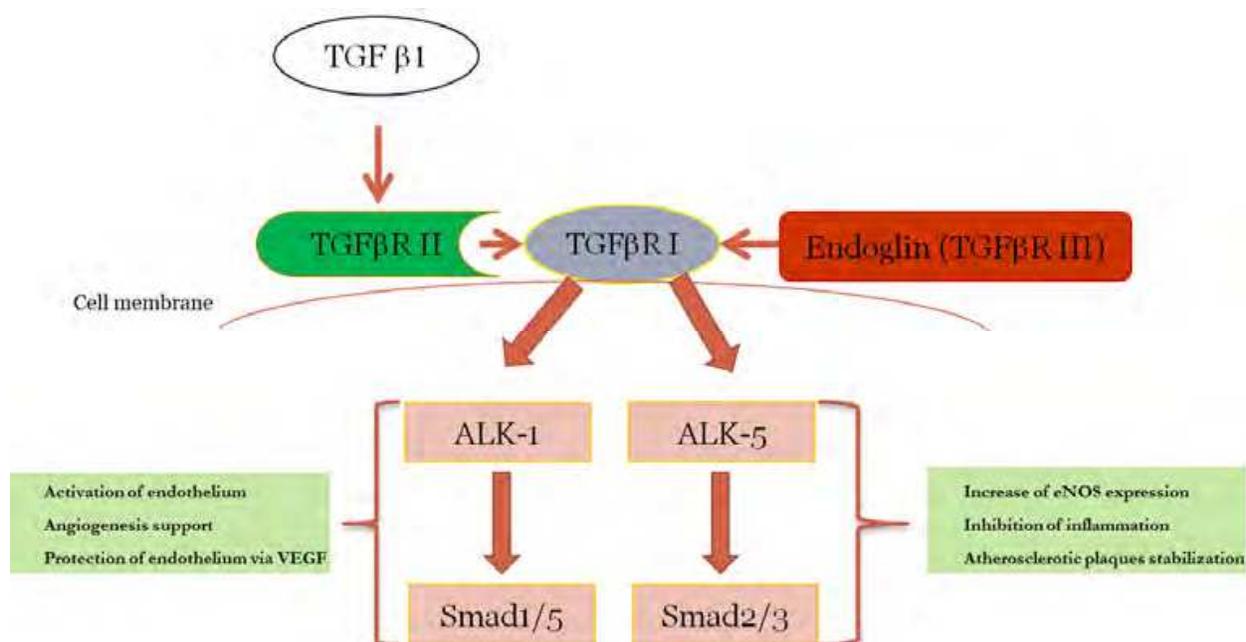


Fig. 1. TGF- β 1 signaling pathway. TGF- β 1 activates T β R-II, and the complex TGF- β 1/TGF-R-II is presented to TGF-R-I, which can represent several subtypes called activin-like kinases or ALKs. In atherogenesis, the activation of ALK-1 or ALK-5 under the control of endoglin is the most common. Activation of TGF- β 1/T β R-II/endoglin/ALK-5/Smad2/3 signaling is related to several anti-atherogenic effects, including increased eNOS expression, increased collagen production (plaque stabilization), inhibition of inflammatory activities of macrophages, T-cells and inhibition of NF- κ B signaling. On the other hand activation of TGF- β 1/T β R-II/endoglin/ALK-1/Smad1 was related to increased VEGF production which was demonstrated to be important in angiogenesis and/or vascular endothelium protection.

5.1 TGF- β 1 related pathways and statins

In this part we would like to discuss TGF- β 1 pathway and possible effects of the most used hypolipidemic drugs in clinical practice. 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) inhibitors, commonly known as statins, inhibit the rate-limiting step of the cholesterol biosynthesis pathway. This hypolipidemic effect is very important, regarding the benefit of statin treatment in humans. However, statins also have non-lipid effects that were demonstrated in both humans and experimental models of atherosclerosis (Zhou and Liao, 2010). Statins regulate many of cellular responses, via the blockade of isoprenoid production and inhibition of intracellular signaling systems, including transcription factors, such as NF- κ B, and kinases, like mitogen-activated protein kinases (MAPK) cascade and RhoA/ROCK pathway (Zhou and Liao, 2010).

Baccante et al showed that pravastatin induces TGF- β 1 expression and down-regulates the expression of type A scavenger receptor in THP-1 cells (human macrophage cell line) by a TGF- β 1-dependent mechanism, suggesting the protection against formation of foam cells (Baccante et al., 2004). Additionally, pravastatin treatment up-regulated TGF- β 1 serum levels in hypercholesterolemic patients, and also TGF- β 1 production *in vitro* in human monocytes (Porreca et al., 2002). Chen et al. showed that fluvastatin and lovastatin increase accumulation of T β R-II in non-lipid raft microdomains, and attenuate degradation of T β R-II which results in enhanced TGF- β 1 signaling (Chen et al., 2008; Chen et al., 2007) in endothelial cells. Moreover, simvastatin and atorvastatin significantly increased TGF- β 1 secretion, T β R-II expression and induced Smad2 and Smad3 phosphorylation in a dose-dependent manner in vascular smooth muscle cells (Rodriguez-Vita et al., 2008). Additionally, atorvastatin increased phosphorylation of Smad3 and expression of T β R-II in atherosclerotic lesions in apoE-deficient mice (Rodriguez-Vita et al., 2008). This increase was related to decreased plaque size and increased production of collagen in vascular smooth muscle cells. Further studies also confirmed atheroprotective effects of statin administration via TGF- β 1 dependent pathway. Atorvastatin treatment significantly induced expression of endoglin, SMAD2, phosphorylated SMAD2/3 and eNOS in mice aortic atherosclerotic lesions (Nachtigal et al., 2009a). Moreover, in another study atorvastatin treatment increased expression of endoglin/ALK-1/p-Smad1/VEGF pathway simultaneously with decreased atherosclerosis in aorta of ApoE/LDLR double knockout mice (Rathouska et al., 2011). In addition, colocalization of all these proteins was demonstrated in endothelial cells, suggesting that activation of these pathways might contribute to TGF- β related protection of endothelial cells (Nachtigal et al., 2009b). In summary, statin treatment activates TGF- β 1 signaling cascades involving T β R-II, endoglin, Smad2/3 which results in reduced plaque size, increased collagen content and increased production of NO in endothelium.

6. Conclusion

In conclusion, the data presented in this chapter show the importance of TGF- β 1 signaling in atherosclerosis in both animals and humans. Despite a few papers showing participation of TGF- β 1 in early atherosclerosis, most of the papers demonstrate atheroprotective effects of TGF- β 1 signaling. Activation of TGF- β 1 signaling pathway results in anti-inflammatory effects, including decreased expression of cell adhesion molecules (with participation of Smad2 and endoglin), inhibition of inflammation in macrophages, T-cells (with participation of Smad3), increased expression of nitric oxide synthase (with participation of endoglin and Smad2), smooth muscle cells production of collagen and plaques stabilization (with participation of endoglin and Smad2/3). Moreover, reduction of cholesterol levels and/or statin treatment significantly enhances atheroprotective effects of TGF- β 1 signaling.

7. Acknowledgments

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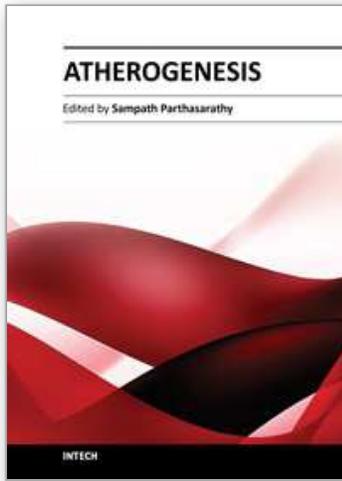
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