Immune Network
http://dx.doi.org/10.4110/in.2014.14.5.237
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

Contrasting Roles of Different Endoglin Forms in Atherosclerosis

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Endoglin (also known as CD105 or TGF-β type III receptor) is a co-receptor involved in TGF-β signaling. In atherosclerosis, TGF-β signaling is crucial in regulating disease progression owing to its anti-inflammatory effects as well as its inhibitory effects on smooth muscle cell proliferation and migration. Endoglin is a regulator of TGF-β signaling, but its role in atherosclerosis has yet to be defined. This review focuses on the roles of the various forms of endoglin in atherosclerosis. The expression of the two isoforms of endoglin (long-form and short-form) is increased in atherosclerotic lesions, and the expression of the soluble forms of endoglin is upregulated in sera of patients with hypercholesterolemia and atherosclerosis. Interestingly, long-form endoglin shows an atheroprotective effect via the induction of eNOS expression, while short-form and soluble endoglin enhance atherogenesis by inhibiting eNOS expression and TGF-β signaling. This review summarizes evidence suggesting that the different forms of endoglin have distinct roles in atherosclerosis.

[Immune Network 2014;14(5):237-240]

Keywords: Endoglin, Atherosclerosis, TGF-β, Smad

INTRODUCTION

TGF-β is a multi-functional cytokine and its signaling pathway contributes to a wide range of immunological and biological effects on various cell types and several diseases. TGF-β has regulatory functions in cell proliferation, differentiation, migration, and survival that affect multiple biological processes such as cell development, carcinogenesis, fibrosis, and wound healing, as well as immune responses (1). There is some controversy in the literature as to the precise functions of TGF-β; for example, in atherosclerosis, it is not clear whether TGF-β is pro-atherogenic or anti-atherogenic. The inhibition of TGF-β1 activity induces pro-atherogenic changes in the vessel wall of atherosclerotic animal models (2). Furthermore, the neutralization of TGF-β1 leads to an inflammatory response of the vessel wall and provokes plaque instability (3). After the engagement of TGF-β type I & II receptors, the Smad-dependent pathways are activated. The biological effects that result depend on the types of Smad complex involved in this signaling response (4). This process is modulated by other accessory receptors such as TGF-β type III receptor (5). The major type III receptor expressed in atherosclerotic lesions is endoglin. Although the expression of endoglin is increased in atherosclerotic lesions, the functional roles of endoglin in atherosclerosis have not been fully clarified. This review aims to suggest a hypothetical role for endoglin in atherosclerosis on the basis of previous reports.

STRUCTURE AND EXPRESSION

Endoglin (CD105) is a homodimer composed of two identical 95 kDa disulfide-linked subunits, and it is known as a hypoxia-inducible transmembrane glycoprotein (6). It consists of three domains: a large extracellular domain, a transmembrane domain, and a short intracellular domain. The extracellular domain contains an Arg-Gly-Asp (RGD) tri-peptide,

Received on September 5, 2014. Revised on October 4, 2014. Accepted on October 10, 2014.

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Abbreviations: TGF-βR, TGF-β receptor; MMP-14, membrane-type metalloprotease-14; Sp1, stimulating protein 1; HIF-1, hypoxia-inducible factor-1; ALK, activin receptor-like kinase; eNOS, endogenous nitric oxide synthase

four N-linked glycosylation sites, and one O-linked glycosylation site (7). The intracellular domain includes several serine and threonine residues, some of which are phosphorylation sites (8). The human endoglin gene, which is located on chromosome 9, is composed of 15 exons. The extracellular domain of endoglin is coded by exons 1∼13 (9). Endoglin homologues have been identified in mice and pigs; the amino acid sequences of these homologues each have more than 70% identity with human endoglin and more than 69% homology with β-glycan, another type III TGF-β receptor (TGF-βR) (10). Two isoforms of endoglin were reported, long-form endoglin and short-form endoglin, which differ in the length of their intracellular domains and the degree of phosphorylation. Long-form endoglin has 47 amino acids in its cytoplasmic tail, has a high degree of phosphorylation and is expressed predominantly in endothelial cells, whereas short-form endoglin has only 14 amino acids in its intracellular domain and has a low level of phosphorylation (6,11). A soluble form of endoglin has also been identified in the sera of both cancer patients and healthy persons. Soluble forms are generated by the cleavage of the extracellular domain of endoglin by membrane-type metalloprotease-14 (MMP-14), which may serve as a naturally occurring antagonist for TGF-β signaling (12). MMP-14 cleaves endoglin at position 586 to release a soluble fragment representing almost the entire endoglin extracellular domain (13). MMP-14 is highly expressed in malignant epithelial cells and endothelial cells.

Endoglin is expressed by various cells found in the blood vessel wall, including endothelial cells, monocytes/macrophages, fibroblasts and vascular smooth muscle cells (14). Endoglin is upregulated during wound healing and tumor vascularization and in inflammatory tissues and developing embryos. Endoglin expression in blood vessels is increased during hypoxia or following vascular injury. In hypoxic conditions, endoglin transcription is induced by the formation of a multiprotein complex with Smad3/Smad4, stimulating protein 1 (Sp1), and hypoxia-inducible factor-1 (HIF-1) (15). Smad-dependent TGF-β signaling also enhances endoglin expression whereas TNF-β was reported to inhibit the expression of endoglin by endothelial cells (16,17). In contrast to these results, expression of the soluble form of endoglin was increased following treatment with TNF-β and hydrogen peroxide, which are known as pro-atherogenic mediators (18).

FUNCTION

Endoglin was originally identified as a non-signaling co-receptor for TGF-β since it does not contain intrinsic kinase activity. The main function of endoglin is thought to be the regulation of TGF-β signaling via interactions with several proteins within the TGF-β signaling pathway. Endoglin binds to both of the TGF-β1 and TGF-β3 isoforms, following which the cytosolic domain of endoglin can be targeted by serine and threonine kinases, leading to the formation of a functional receptor complex (19). Indeed, endoglin is not a true receptor for TGF-β, but it strongly modulates the phosphorylation levels of TGF-βRII, activin receptor-like kinase (ALK)-1, and ALK-5 (20). The presence of endoglin can also modulate the downstream signaling by TGF-βRI/TGF-βRII complexes. Recent studies have demonstrated that endoglin functions in an interplay between two signaling pathways involving ALK-1 and ALK-5, respectively, that have differential effects on target cells. Endoglin/ALK-1/Smad1/5 signaling stimulates the migration, proliferation, and tube formation of endothelial cells, resulting in angiogenesis (21). In contrast, the endoglin/ALK-5/Smad2 pathway inhibits the activity of endothelial cells and angiogenesis by inhibiting the proliferation, tube formation, and migration of endothelial cells (22). In addition, endoglin has inhibitory effects on Smad3-dependent TGF-β signaling, resulting in effects on endothelial cells opposite to those that result from Smad2-dependent signaling (23). Mutations in endoglin have been reported in hereditary hemorrhagic telangiectasia, a disease characterized by malformations of vascular structure (24). The long-form and short-form endoglin isoforms are both able to bind to their ligands and interact with ALK-1 and ALK-5; however, the two membrane-bound endoglin isoforms differ in their affinity for each receptor, level of phosphorylation, and capacity to regulate TGF-β-dependent responses (25). Long-form endoglin has pro-angiogenic effects through induction of endogenous nitric oxide synthase (eNOS) expression, whereas short-form endoglin has anti-angiogenic effects. Thus, short-form endoglin contributes to the cardiovascular pathology associated with senescence. In addition, soluble endoglin, which inhibits TGF-β signaling, is thought to be cleaved from the cell membrane and enter the systemic circulation, and may represent a useful candidate marker of endothelial injury, activation, inflammation, and senescence (12).

ENDOGLIN AND ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disease of the arteries. Endothelial dysfunction plays an important role in the development of atherosclerosis by inducing infiltration of inflammatory cells and a prothrombogenic state. In addition, the migration and proliferation of smooth muscle cells, which are processes that affect the plaque stability, are crucial in the progression of advanced atherosclerotic lesions. TGF-β signaling results in inhibition of the proliferation and migration of smooth muscle cells, as well as endothelial cell regeneration (26). It was also reported that inhibition of TGF-β signaling reduced collagen content and plaque stability in a mouse model of atherosclerosis (3). In this model, TGF-β showed a protective effect against atherogenesis. Therefore, as an accessory receptor for TGF-β, endoglin expressed by endothelial cells and smooth muscle cells may play an important role in modifying the development of atherosclerosis via the regulation of TGF-β-induced atheroprotective effects. Although the expression of endoglin was very low in non-atherosclerotic aortas, the expression of endoglin by macrophages, smooth muscle cells and endothelial cells was increased in early atherosclerotic lesions (14). In advanced atherosclerotic plaques, smooth muscle cells expressed high levels of endoglin, a parameter that was independent of smooth muscle cell morphology and leukocyte infiltration. Moreover, endoglin modulates the expression of genes that are known to be related to pro-angiogenic effects (VEGF, angiopoietin-1, and angiopoeitin-2) or anti-angiogenic effects (Notch signaling, Notch-3, and DLL4), respectively (27,28). Several studies have also reported that the concentration of soluble endoglin increased in the blood of patients with hypercholesterolemia and atherosclerosis (29). Increased soluble endoglin levels could be related to endothelial damage or dysfunction; furthermore, soluble endoglin is an indicator of cardiovascular damage in hypertension and diabetes-associated vascular pathologies (30). The circulating concentration of soluble endoglin was reported to increase at early stages of atherosclerosis due to damage of endothelial cells and then decrease in later stages of atherosclerosis, which suggests a potential role of soluble endoglin in acute heart failure (31). As a decoy receptor, soluble endoglin may inhibit the anti-atherogenic effects induced by TGF-β.

CONCLUSION

The expression levels of endoglin and soluble endoglin were higher in atherogenic lesions than in healthy arteries. Two isoforms of endoglin differentially transduce TGF-β signaling by activation of different Smad components, and thereby modulate the biological effects of TGF-β signaling. Long-form endoglin shows atheroprotective effect by induction of eNOS expression, while short-form endoglin and soluble endoglin forms enhance atherogenesis via down-regulation of eNOS expression and inhibition of TGF-β signaling.

ACKNOWLEDGEMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (NO. 2012R1A4A1029061).

CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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