Atherosclerosis 243 (2015) 383–388

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Soluble endoglin, hypercholesterolemia and endothelial dysfunction

Jana Rathouska, Katerina Jezkova, Ivana Nemeckova, Petr Nachtigal*

Charles University in Prague, Faculty of Pharmacy in Hradec Kralove, Department of Biological and Medical Sciences, Heyrovskeho 1203, Hradec Kralove 500 05, Czech Republic

ARTICLE INFO

Article history:
Received 25 July 2015
Received in revised form
1 October 2015
Accepted 2 October 2015
Available online 8 October 2015

Keywords:
Soluble endoglin
Hypercholesterolemia
Endothelial dysfunction

ABSTRACT

A soluble form of endoglin (sEng) is known to be an extracellular domain of the full-length membrane endoglin, which is elevated during various pathological conditions related to vascular endothelium.

In the current review, we tried to summarize a possible role of soluble endoglin in cardiovascular pathologies, focusing on its relation to endothelial dysfunction and cholesterol levels. We discussed sEng as a proposed biomarker of cardiovascular disease progression, cardiovascular disease treatment and endothelial dysfunction. We also addressed a potential interaction of sEng with TGF-β/eNOS or BMP-9 signaling.

We suggest soluble endoglin levels to be monitored, because they reflect the progression/treatment efficacy of cardiovascular diseases related to endothelial dysfunction and hypercholesterolemia. A possible role of soluble endoglin as an inducer of endothelial dysfunction however remains to be elucidated.

1. Introduction

Endoglin is a homodimeric transmembrane glycoprotein, also called TGF-β receptor III or CD105. There are two forms of endoglin currently studied with respect to many physiological and pathological states. Specifically, a membrane form expressed in various tissues and a soluble form (sEng) found in plasma of healthy people as well as in patients suffering from a variety of diseases. Several review papers discussed the role of the membrane endoglin in many cardiovascular pathologies, including hereditary hemorrhagic telangiectasia [1], preeclampsia [2], atherosclerosis [3], and cancer [4]. In addition, circulating levels of the soluble endoglin have been also reviewed in the context of preeclampsia and cancer diseases [5,6]. However, a possible role of sEng with respect to endothelial function/dysfunction, hypercholesterolemia and atherogenesis has not been summarized so far. The aim of the present review was then to resume the current knowledge about the changes of sEng during hypercholesterolemia, development of endothelial dysfunction and atherogenesis, and with respect to a possible role of sEng as an inducer of endothelial alteration.

2. Generation of soluble endoglin

A soluble form of endoglin (sEng) is known to be an extracellular domain of the full-length membrane endoglin entering the systemic circulation in various conditions related to endothelial injury, activation, inflammation and senescence of endothelium [7]. After testing several matrix metalloproteinases (MMPs) in HUVECs, sEng has been proposed as an N-terminal endoglin cleavage product chipped at position 586 predominantly by membrane-type metalloproteinase-14 (MMP-14) [8]. In addition, MMP-14 was demonstrated to be the most abundantly expressed metalloproteinase in endothelial cells. The authors proposed that MMP-14 might play an important role in endoglin shedding in patients with preeclampsia or cancer [8]. Moreover, the role of MMP-14 in endoglin shedding was demonstrated after oxysterol treatment that activated LXR transcription factor and MMP-14 expression in Jar cells and placental explants. In the same study, high levels of plasma sEng have been also detected in mice overexpressing MMP-14 [9]. On the contrary, Brownfoot et al. did not confirm these results and whilst there was a modest upregulation of sENG from HUVECs there was no change in sENG secretion from primary trophoblasts. Furthermore, MMP-14 was not upregulated in HUVECs suggesting that perhaps MMP-14 may not be the primary cleavage protease [10]. In addition, no data about the role of MMP-14 in endoglin cleavage during atherogenesis and/or hypercholesterolemia are available now.

* Corresponding author.
E-mail address: nachti@faf.cuni.cz (P. Nachtigal).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.10.003
0021-9150/

Apart from the awareness of the chipping enzyme, the real position of the membrane endoglin cleavage in various pathologies is also under investigation. An 80-kDa molecule of sEng cleaved from the surface of HUVECs at the cleavage site was shown to be at position 586, implying that the whole extracellular domain (Eng1-586) was released [8]. Thus, the Eng1-586 construct was used to generate a recombinant sEng. However, Gregory et al. purified sEng from the sera of preeclamptic women, showing a 65-kDa band, as opposed to the 80-kDa mass of recombinant Eng1-586, suggesting that the circulating sEng observed in preeclampsia is not cleaved at the position 586. Instead, the purified endoglin from sera of preeclamptic patients was identified of a lower molecular mass with C-terminal shortly after residue 406 [2]. It is of interest to mention that no similar study has been performed in the field of atherosclerosis, so there is currently no information about the structure of sEng cleaved from atherosclerosis-prone arteries (e.g. aorta). The chipping position of the tissue endoglin in various diseases is then a subject of relevant up-to-date studies, still being not fully clarified.

3. Soluble endoglin, hypercholesterolemia and endothelial dysfunction in various cardiovascular pathologies

Hypercholesterolemia is one of the most studied risk factors resulting in endothelial dysfunction and atherosclerosis. The first reference about the relation of cholesterolemia and sEng came from the work of Blann et al., demonstrating increased serum levels of sEng in patients with atherosclerosis. They found it associated with total cholesterol levels but not with other markers of endothelial damage or dysfunction e.g. E-selectin [11]. In the study of Li et al., they speculated that sEng levels increased in early stages of atherosclerosis due to the damage of endothelial cells and then decrease in later stages of atherosclerosis because of increased formation of CD105/TGF-β1 complexes [12]. sEng has been qualified as a marker increasing with high total cholesterol levels in patients with familial hypercholesterolemia [13].

In addition to hypercholesterolemia, other cardiovascular risk factors could affect soluble endoglin levels. From the point of pathophysiology of endothelial dysfunction and atherosclerosis, inflammation and oxidative stress play a crucial role. Soluble endoglin levels were increased after the treatment with inflammatory cytokine TNF-α and after the induction of oxidative stress by H_2O_2 [14]. On the other hand, it was demonstrated that a vessel-protective HO-1 inhibits sEng release from endothelial cells and placenta explants [15]. Other risk factors related to the development of endothelial dysfunction and atherosclerosis include arterial hypertension and type II diabetes mellitus. In line with this notion, serum sEng levels were proposed to be a possible indicator of hypertension and diabetes-associated vessel pathologies [16]. The study analyzed 288 patients with type II diabetes, hypertension and healthy controls showing significant correlations between endoglin and glycemia, glycated haemoglobin, systolic blood pressure, left ventricular hypertrophy and endothelial dysfunction. In addition, sEng levels were higher in patients with diabetes suffering from diabetic complications (retinopathy), and in patients with diabetes and hypertension when compared to healthy controls [16].

Coronary circulation and heart vessels were also studied with respect to soluble endoglin levels. Soluble endoglin has been proposed as an indicator of endothelial senescence, inflammation and oxidative stress in heart vessels showing that the membrane endoglin cleavage simply reflects the vascular damage (a direct proportion of damage and sEng levels), which corresponds to the adverse events in patients with coronary artery disease [14]. The elevation of sEng levels was also related to the atherosclerotic plaque morphology and correlated with unstable angina pectoris, acute myocardial infarction and post infarction heart remodeling [17].

A different point of view was presented in the study of Cruz-Gonzales et al. In the context of an acute myocardial infarction, they speculated that levels of sEng might reflect a membrane endoglin expression in the heart. They demonstrated that the decrease in sEng levels in patients with the poorest prognosis might be related to reduced expression of tissue/membrane endoglin regardless of MMPs expression, suggesting some kind of balanced ratio between the membrane and the soluble form [18]. Moreover, they also showed sEng levels to be lower in patients with acute myocardial infarction when compared with healthy subjects proposing that reduced sEng levels may reflect an impaired endothelial function. Finally, they suggested that early soluble endoglin decrease might be a novel prognostic marker of an early cardiovascular death [18].

Several papers also mentioned therapeutical interventions affecting soluble endoglin levels. Blaha et al. showed that LDL apheresis reduced levels of blood cholesterol particles followed by reduction of sEng and other biomarkers of endothelial dysfunction (hs-CRP and sCD40L) in patients with familial hypercholesterolemia. Thus, the observed drop of sEng levels was not attributed to LDL apheresis itself, but to decreased activity of endothelial cells and immune system following the removal of atherogenic elements [13]. In addition, Brownfoot et al. found that oxysterols increase sEng release from primary human tissues, however with no effect of pravastatin treatment on sEng levels [10].

In addition, it is of interest to point out that there is currently no evidence showing any correlation between changes of sEng levels in blood and the expression of its membrane form in aorta or any other specific organ. Thus, a direct link between therapeutical intervention and sEng levels still needs to be considered carefully.

In our previous studies with apoE/LDL receptor (apoE/LDLr) double knockout mice, blood soluble endoglin and cholesterol levels were increased and atherosclerotic plaques were naturally bigger after the administration of cholesterol-rich diet. Moreover, we detected a reduced expression of the membrane endoglin in aortas of these mice [19]. In addition, we revealed that atorvastatin treatment is able to reduce the levels of cholesterol and plaque size as well as the levels of soluble form of endoglin, and simultaneously increase expression of its membrane form in aorta [20].

After five-year continual studies on several mouse models of atherosclerosis [19–22], we summarized our results describing various stages of the atherosclerotic process and cholesterol levels facing the appropriate levels of sEng to reveal any possible relationship between these values. We tried to compare these parameters in various groups of mice, specifically in C57BL/6J mice on chow diet, in apoE-deficient mice on either chow diet or Western type diet containing 21% fat (11% saturated fat) and 0.15% of cholesterol, and in apoE/LDLr double knockout mice fed chow or cholesterol diet containing 1% of cholesterol. It is essential to mention that both apoE-deficient and apoE/LDLr deficient mice represent mouse models of atherosclerosis that develop spontaneous hypercholesterolemia, endothelial dysfunction and atherosclerosis [23]. These processes can be accelerated by administration of various types of cholesterol-rich diets [24]. Our data showed that sEng levels were significantly increased in apoE/LDLr deficient mice fed cholesterol diet when compared to C57BL/6J mice, apoE deficient mice and apoE/LDLr deficient mice fed chow diet (Fig. 1A). It must be stressed that apoE/LDLr deficient mice fed cholesterol diet also reached the highest cholesterol levels of all studied groups (Fig. 1B). In addition, a clear correlation between the mean group total cholesterol levels and their relevant mean group levels of sEng was found (Fig. 1C). Surprisingly, atherosclerotic plaque sizes in various groups of mice (Fig. 1D) did not correlate with either sEng or cholesterol levels. In accordance with the previous study of Blaha et al., we might speculate that hypercholesterolemia induced in blood vessels might be related to changes of