

EndMT

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Endothelial mesenchymal transition (EndMT) is a complex biological process in which endothelial cells lose their specific markers, such as vascular endothelial cadherin (VE-cadherin), and acquire a mesenchymal or myofibroblastic phenotype, expressing specific products, such as α -smooth muscle actin (α -SMA) and type I collagen.

endothelial mesenchymal transition

cardiovascular diseases

gasotransmitter

fibroblast phenotype

TGF- β

1. Introduction

Endothelial mesenchymal transition (EndMT) is a complex biological process in which endothelial cells lose their specific markers, such as vascular endothelial cadherin (VE-cadherin), and acquire a mesenchymal or myofibroblastic phenotype, expressing specific products, such as α -smooth muscle actin (α -SMA). From a histological point of view, during EndMT, the integrity of the endothelium is disrupted, manifesting a migratory, invasive and proliferative phenotype. Vascular endothelium can be viewed as a specialized form of epithelial tissue. Consistently, EndMT shares many molecular mechanisms with the best-known epithelial mesenchymal transition (EMT), a physiological reversible process, first described in the 1960s in chick embryos by Hay and today known to be required for normal embryonic patterning and organs' formation ^[1].

2. EndMT: Implications in Cardiovascular Fibrosis

Fibrosis is a complex process, in which tissue repair after damage becomes excessive and out of control, resulting in excessive formation of fibrous connective tissue. It can affect any tissue and cause organ dysfunction in different pathologies, such as heart disease, interstitial lung disease, liver cirrhosis, progressive systemic sclerosis and diabetic nephropathy ^[2].

Deposition of fibrotic scar tissue in the heart is typical after myocardial infarction in the post-ischemic stage, and in vessels of hypertensive subjects, it represents the way through which atherosclerosis develops. Other conditions can also induce and promote fibrotic processes in heart tissue, such as hypertensive cardiomyopathy, diabetic hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy and also physiological ageing ^{[3][4]}.

Vascular fibrosis is associated with many diseases and their pathological progression, including atherosclerosis, which is one of the primary causes of the development of cardiovascular diseases. Indeed, atherosclerosis is characterized by accumulation of ECM proteins, primarily collagen and fibronectin, in the vascular media, contributing to structural vascular remodeling, proliferation of vascular smooth muscle cells and inhibition of matrix degradation, and is responsible for the thickness of the wall of arteries and formation of plaques [5]. Endothelial dysfunction is a critical event in the development of atherosclerosis; indeed, in physiological conditions, the endothelium is a monolayer squamous epithelium located in the luminal surface of the blood vessels and is a major regulator of vascular homeostasis. Proinflammatory cytokines contribute to increase the atherosclerotic region, through arterial plaque formation and additional cell apoptosis, leading to lipids's expulsion into adjacent plaque areas [6].

Interestingly, plaque formation during atherosclerosis has been associated with the accumulation of mesenchymal cells in the arterial intima, deriving from transition of endothelial cells. It is noteworthy that, in plaques of murine atherogenic models and in humans, endothelial and mesenchymal markers have been found, demonstrating the presence of a transitioning state of EndMT. Recently, it has been suggested that mesenchymal cells advance the progression of atherosclerosis, since they secrete proinflammatory molecules and synthesize ECM proteins and metalloproteases (MMPs), which facilitate plaque build-up and regulate plaque stability [7]. Interestingly, in endothelial cells, TGF- β predominantly binds ALK-1, promoting smad1 and smad5, and contributes to regulation of vascular homeostasis, cell proliferation and angiogenesis; in contrast, when TGF- β binds ALK5, it induces the activation of smad2 and smad3, which inhibit cell proliferation and facilitate EndMT [8][9].

Angiogenesis is a vascular remodeling process, promoted by VEGF and other factors that stimulate proliferation and migration of vascular endothelial cells to form new blood vessels. As previously described, TGF- β , beyond its role in physiological [10] and degenerative processes, has been recognized as one of the key factors inducing the expression of VEGF in endothelial cells via the ALK-5 pathway, thus creating a pro-angiogenic milieu for the tumor or for the EndMT [11]. However, FGF signaling is involved in angiogenesis modulation and in the maintenance of vascular integrity and endothelial function. In this regard, recent studies show that FGF inhibition at the endothelial level is associated with TGF- β activation [10].

Very interestingly, EndMT of the specialized brain endothelial cells, forming the blood–brain barrier, has been described in different conditions of neuroinflammation and neurodegeneration, typical of central nervous system pathologies, such as multiple sclerosis [12].

Cardiac fibrosis is a hallmark of the heart's pathological remodeling response to mechanical or biochemical stress. Indeed, cardiac fibrosis is characterized by increased stiffness of the heart valves, due to excessive proliferation of cardiac fibroblasts, accumulation of myofibroblasts and to deposition of ECM in the cardiac muscle. Nevertheless, unlike cardiomyocytes, cardiac fibroblasts are unable to generate an action potential and are not excitable (although they are able to electrically couple with each other and with neighboring cardiomyocytes), causing impaired mechanical–electrical coupling and arrhythmias [13]. On the other hand, impaired tissue function, myocardial dysfunction and ultimately heart failure are also observed [14].

Myocardial infarction is the most common cause of cardiac fibrosis. However, various other conditions, such as hypertension, diabetic hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy and ageing, may be responsible for reparative mechanisms, addressed to the replacement of dead cardiomyocytes with a collagen-based scar.

Another pathological condition promoting myocardial fibrosis is diabetic cardiomyopathy (DCM); interestingly, about 75% of patients with unexplained idiopathic dilated cardiomyopathy are found to be diabetic [15]. Endoplasmic reticulum stress, mitochondrial dysfunction, sympathetic nervous system activation, excessive oxidative stress, increased inflammation and abnormal coronary microcirculation are characteristic symptoms. These pathophysiological changes result in fibrosis, hypertrophy, diastolic/systolic dysfunction and ultimately systolic heart failure. In particular, cardiac interstitial fibrosis is a major feature of DCM [16], which includes the overproduction and deposition of myocardial interstitial collagen, resulting in myocardial stiffness and cardiac dysfunction.

Another aspect that can greatly affect the cardiovascular system is ageing. Ageing causes a decreased production of NO and a process of generalized endothelial dysfunction at the vascular level. At the cardiac level, consequently, with the progress of ageing, compensatory mechanisms addressed at hypertrophy [17][18][19][20][21] cause an increase in the left ventricular wall, which in the long term worsens the overall cardiac performance, and also triggers fibrotic processes as a final manifestation. Along with the mechanical consequences, cardiac fibrosis can also slow down the propagation of the electrical impulse and affect heart rate, suggesting that ageing can also promote cardiac arrhythmias [6].

hypothesized that EndMT is a process at the basis of cardiac fibrosis. Indeed, they observed that under stimulation, adult human coronary endothelial cells trans-differentiated into fibroblasts, and bone marrow cells could contribute to the cardiac fibroblast population. In fact, the treatment with rhBMP-7, a TGF- β antagonist, was able to preserve the endothelial phenotype and ameliorate the progression of fibrosis in cells as well as in a murine model of heart disease [22], demonstrating that it was responsible for the total pool of cardiac fibroblasts. According to this evidence, Goumans' group confirmed the key role of the growth factor in EndMT in different in vitro and in vivo models [23].

More recently, Kong et al. [24] reported that accumulation and production of collagen and cardiac fibroblasts in human pathological patients were related to the process of EndMT.

Kovacic and colleagues also demonstrated that EndMT plays a main role in cardiac fibrosis that progresses to heart failure under hypertrophic cardiomyopathy, diabetes-induced cardiac fibrosis and genetic deficiency of PAI-1 in aged mice [25].

This is a relevant aspect, since a significant number of non-myocytes are present in the heart. In particular, it has been reported that about 64% of the non-myocyte cell population in the mouse and 54% in the human heart are endothelial cells [26].

3. Contribution of Hydrogen Sulfide in Cardiovascular Fibrosis Associated with EndMT

Hydrogen sulfide (H₂S) is an important endogenous mediator with a key role in the cardiovascular system. In this regard, it is noteworthy to underline that Mallat and co-workers have confirmed that inhibition of TGF- β signaling could promote the development of atherosclerosis with decreased collagen content in ApoE^{-/-} mice [27]. Lu and colleagues have demonstrated in a recent study that the use of NaHS, a hydrophilic fast H₂S release, could suppress the formation of atherosclerosis via the degradation of TGF- β , as well as the reduction of smad3 phosphorylation. Moreover, such effect is specific for H₂S, since CSE inhibitors, such as propargylglycine, can conversely accelerate the atherosclerosis development [28].

Interestingly, CSE-knockout mice fed an atherogenic diet exhibited severe atherosclerosis, suggesting that the CSE/H₂S pathway is somehow crucial to limit atherosclerosis development [29][30], which is also dependent on activation of inflammatory macrophages [31].

However, the mechanisms underlying the effects of H₂S in the suppression of fibrosis are different and involve diverse pathways, and thus have to be found in its pleiotropic actions [32]. Although vasorelaxation can induce beneficial action over fibrosis per se, the inhibitory activity of H₂S on ACE also abrogates vascular fibrosis associated with AngII proliferative pathways. Another alternative mechanism involving H₂S signaling in the control of vascular fibrosis is associated with its anti-inflammatory properties, since H₂S shows beneficial effects in cardiovascular remodeling through suppression of CD11b-positive leukocytes' migration [33]. Indeed, H₂S shows protective effects in hypertensive cardiovascular disease and this effect is mediated by the eNOS/NO axis [34][35].

In addition, the endogenous CSE/H₂S system has been shown to protect against the formation of UAAS via an alternative pathway involving the activation of protein kinase C β II (CPKC β II)/Akt signaling [36]. Thus, it should not be surprising that H₂S biosynthesis as well as CSE expression drop down in conditions of vascular calcification [37] or following the development of neointimal hyperplasia associated with induction of balloon injury. Again, this effect is reversed by H₂S treatment [38].

HHcy leads to vascular fibrosis, causing several disease conditions, including peripheral and cerebrovascular coronary occlusion as well as venous thromboembolism [39][40][41]. The interplay between Hcy and H₂S has been shown by Sen and colleagues as they demonstrated that activation of both MMP-2 and MMP-9 by HHcy was controlled following H₂S supplementation [42]. The accumulating evidence indicating H₂S as a crucial controller of vascular function leads to the straightforward conclusion that a lack of it results in pathological conditions affecting vascular tissues, including hypertension and fibrosis. Thus, it is not surprising that SG1002, a donor of H₂S, is able to normalize the histological and molecular scores for hypertrophy and fibrosis, leading to a decrease in collagen accumulation in HHcy mice and, consequently, preventing vascular fibrosis [43].

Indeed, Hcy induced the activation of MMP-9 together with the synthesis of collagen in endothelial cells, and this mechanism is driven by AT1-receptor activation by AngII [44]. Therefore, when an HHcy condition occurs, a

reduction in H₂S biosynthesis is observed, and this can undermine its ability to inhibit ACE, resulting in increased AngII-dependent profibrotic stimulation [45]. This aspect has also been investigated in pulmonary vasculature, where administration of NaHS is able to decrease the mean pulmonary arterial pressure and to inhibit smooth muscle cells' proliferation in the pulmonary artery wall [46]. In addition, administration of exogenous H₂S also decreases the expression of collagen I and III in the pulmonary arteries, again suggesting that H₂S plays an important role in the development of the fibrotic process and vascular structural remodeling, thus controlling homeostasis in pulmonary arterial pressure [46].

It is intuitive that the use of therapeutic tools aiming to rescue physiological H₂S levels could represent a possible way to tackle the fibrotic process as well as other vascular-based impairments such as hypertension at different levels (Figure 3). Indeed, H₂S could modulate activation of the EndMT process as well as interfere with intermediate steps towards fibrosis.

Necrosis of cardiomyocytes in ischemic hearts triggers a strong inflammatory response and promotes interstitial and perivascular fibrosis due to biochemical, geometric and biomechanical changes of the ventricular wall not affected by the lesion [47]. The high production of pro-inflammatory cytokines (TNF- α , IL-1 β and IL-6) accompanies myocardial damage and hypertrophic tissue remodeling, contributing to the deposition of fibrotic tissue.

Interestingly, a reduction of H₂S levels and of CSE expression has been found in post-ischemic hearts [48]. Furthermore, H₂S levels have been found to be inversely correlated with the severity of coronary heart disease [49].

Indeed, H₂S shows cardioprotective activity against I/R injury and it is considered an important modulator of the ischemic preconditioning process. The mechanisms of action responsible for the effects of H₂S are heterogeneous, for instance, protein sulfhydration of mitoKATP and mitochondrial voltage-gated potassium channels (mitoKv7). It is noteworthy that Kv7.4 channels have been recently described in cardiac mitochondria, where they seem to play a cardioprotective role, in inhibition of mast cell degranulation and inflammatory processes, as well as in antioxidant and pro-angiogenic action [50][51]. H₂S seems to also be involved in suppression of pro-fibrotic mechanisms associated with myocardial ischemia through the involvement of different signaling pathways, such as Nrf2 [52][53][54], signaling pathways involving miRNAs [48][55][56] and mitochondrial protection mechanisms [57][58][59][60][61].

Experimental evidence shows that NaHS and slow-release H₂S donors such as AP39, diallyl disulfide (DADS) and GYY4137 are able to reduce oxidative stress and apoptotic mechanisms [62][63][64], mitochondrial permeability transition pore (mPTP) opening [58][59][60], inflammatory responses and cardiomyocyte death [65] and iNOS expression in experimental models of myocardial infarction [66]. NaHS is also able to increase heme oxygenase-1 (HO-1) expression [66], to promote pathways of GSK-3 β / β -catenin [67], cGMP-dependent PKG/phospholamban [68] and to promote angiogenesis [69] and autophagy in elderly hearts [70][71].

GYY4137 preserves cardiac function, attenuates adverse remodeling and can exert post-ischemic cardioprotective effects. Indeed, hearts treated with GYY4137 had left ventricular fibrosis significantly lower than untreated hearts

after myocardial infarction. Greater blood vessel density was found in the left ventricular scar area of the GYY4137-treated animals compared to all other infarcted groups. Despite preserved left ventricular structure and function, treatment with GYY4137 increased the levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in association with increased cGMP levels, parallel to higher cGMP-type

Daily intraperitoneal administration of GYY4137 for 4 weeks to spontaneously hypertensive rats (SHR) decreased systolic blood pressure and inhibited myocardial fibrosis. This kind of treatment reduced the collagen deposition in the left ventricle, the ratio of perivascular collagen area vs. lumen area in perivascular regions and the concentration of hydroxyproline, collagen I and III mRNA expression and cross-linked collagen. GYY4137 also inhibited AngII-induced neonatal rat cardiac fibroblast proliferation, reduced the number of S-phase fibroblasts, decreased the expression and protein synthesis of collagen I and III mRNA, attenuated oxidative stress and suppressed α -SMA, by modulating the expression of TGF- β 1 and the phosphorylation of smad2. These results showed that GYY4137 improved myocardial fibrosis, possibly through a mechanism involving inhibition of oxidative stress, blockade of the TGF- β 1/sm2 signaling pathway and decreased expression of α -SMA in cardiac fibroblasts [64].

Even more innovative H₂S donors, such as ADT-OH (H₂S-aspirin hybrid molecule) or ZYZ-802 (a cysteine derivative), were able to positively intervene in the ischemic lesion by activating the AMPK signaling pathway [60] and reducing the miRNA-30 family [48].

Polhemus and co-workers demonstrated that administration of diallyl trisulfide (DATS), a long-acting H₂S-donor organic polysulfide compound present in garlic, could attenuate left ventricular dilatation and dysfunction in a model of pressure-overload heart failure, attenuating the development of perivascular and intermuscular fibrosis and then cardiac hypertrophy [72].

Finally, it is interesting that SG-1002, an orally active H₂S donor, is able to positively act in the fibrotic damage following a heart failure condition and in general of myocardial dysfunction, favoring the adiponectin-AMPK signaling pathway [73] and increasing the bioavailability of NO [74].

The metabolic dysregulation characteristic of diabetes, including hyperglycemia, hyperlipidemia and oxidative stress, causes the death of cardiomyocytic cells. The early stages of cardiac remodeling following diabetes are generally asymptomatic, with myocardial changes and damage almost exclusively at the molecular level. In the middle phase of remodeling, progressive hypertrophy of cardiomyocytes and myocardial fibrosis result in a reduced ejection fraction [75].

In patients with diabetes, as well as in rats treated with STZ, downregulation of the gene expression of the enzymes involved in the endogenous biosynthesis of H₂S, with consequent reduction of circulating levels of H₂S, was frequently found [76][77][78]. Growing evidence suggests that H₂S exogenous administration could exert cardioprotective effects in these pathological conditions. There is evidence that the JAK/STAT signaling pathway participates in the protective effects of exogenous H₂S against myocardial fibrosis in diabetes mellitus, though

other studies point to an involvement of the H₂S-forkhead box protein O1 (FoxO1) pathway in the pathogenesis of diabetic cardiomyopathy. This evidence suggests that H₂S could attenuate diabetes-induced cardiac fibrosis through the modulation of MMP/TIMP expression, the regulation of TGF- β 1 and other possible intracellular pathways, including the regulation of the PKC-ERK1/2/MAPK signaling pathway and the inhibition of inflammatory reactions [79][80][81].

Subsequent studies confirmed the protective effect of H₂S against diabetes-induced myocardial fibrosis and demonstrated that it was also associated with the attenuation of autophagy through upregulation of the PI3K/Akt1 signaling pathway [82].

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