Trends in Cardiovascular Medicine 27 (2017) 394–396

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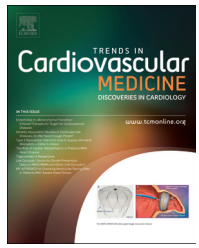

Editorial commentary: Endothelial-to-mesenchymal transition: When the good one goes bad

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The inner lumen of the blood vessels is covered by a thin layer of cells, known as endothelial cells. The integrity of endothelial cells is important for the development of the cardiovascular system and for the protection against cardiovascular diseases. Endothelial cells have been reported to possess the ability to transdifferentiate into mesenchymal cells (endothelial-to-mesenchymal transition, EndMT) [1–3]. During the process of EndMT, endothelial cells lose their specific cell surface markers of ve-Cadherin and CD31, and instead express markers for mesenchymal or myofibroblastic cells, such as α-SMA, type I collagen, and vimentin. In this current issue of *Trends in Cardiovascular Medicine*, Jackson et al. [4] reviewed the signaling mechanisms and the roles of EndMT in cardiovascular development and cardiovascular pathogenesis. Here, we emphasize and further discuss the main pathways that have been implicated in both physiological and pathological EndMT.

Accumulating evidence has demonstrated an intermediate role of EndMT in the embryonic development of the cardiovascular system, as discussed by Jackson et al. [4]. The authors described individual signaling pathways that have been shown to induce EndMT. Among the relevant pathways, the TGF-β/BMP and PI3K/Akt axis are particularly important, and discussed here in more detail. Endocardial suppression of TGF-β/BMP signaling by deletion of BMP receptors and Smad4, or attenuation of active Samd2/3/4 complex, resulted in a decreased number of mesenchymal cells in the endocardial cushion, and defective cushion formation in embryonic mouse hearts [5–7]. Additionally, inhibition of PI3K or PDK1 (mediating PI3K-induced Akt activation), or knockout of Akt, has been shown to induce impaired EndMT, defective formation of atrioventricular cushion, and subsequent septation defects and valves thickening in mice [8–10]. These results strongly suggest that TGF-β/BMP and PI3K/Akt mediated-EndMT is indispensable to cardiovascular development at the embryonic stage.

The review by Jackson et al. [4] primarily focuses on the signaling mechanisms of EndMT. Nonetheless, the evolution of the research field of EndMT is reflective of the intriguing identification of a “good ones turn bad” role of EndMT. The studies of EndMT were confined within embryonic development until the first report by Arciniegas et al. [11] documenting that EndMT could be induced in adult bovine aortic endothelial cells by TGF-β in vitro. As early as 5 days after TGF-β treatment, up to 60% of the cells were positively stained with α-SMA. Moreover, double-positive cells (both with endothelial and mesenchymal markers, FVIII, and α-SMA) were also identified, indicating the occurrence of EndMT in mature endothelial cells [11]. Another study by Frid et al. [12] provided rigorous evidence that bovine aortic and main pulmonary arterial endothelial cells have the potential to undergo endothelial to smooth muscle

The authors have indicated there are no conflicts of interest.

This study was supported by National Institute of Health National Heart, Lung and Blood Institute (NHLBI) Grants HL077440 (HC), HL088975 (HC), HL108701 (HC, DGH), HL119968 (HC), an American Heart Association Established Investigator Award (EIA) 12EIA8990025 (HC) and an AHA Postdoctoral Fellowship Award 14POST20380996 (YXZ).

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http://dx.doi.org/10.1016/j.tcm.2017.03.008

transdifferentiation in response to TGF-β. It was clearly shown that mature endothelial cells possess the ability to transit into smooth muscle cells that express smooth muscle myosin heavy chains (SM-MHC) [12]. SM-MHC is the most discriminating marker for contractile smooth muscle cells, while α-SMA can also be detected in mesenchymal, myofibroblastic, or smooth muscle cells at early stage of differentiation [13,14]. Until very recently, EndMT has emerged as a mechanism involved in the pathological progression of multiple cardiovascular diseases including cardiac fibrosis, pulmonary arterial hypertension (PAH), atherosclerosis, heart failure, diabetic retinopathy and cerebral cavernous malformations [15–17]. We will focus on the role of EndMT representatively in cardiac fibrosis and PAH.

In a classical study by Zeisberg et al. [15] using an aortic banding model, it was shown that increased TGF-β1 and its downstream signaling-mediated EndMT contribute to the progression of cardiac fibrosis. The attenuated cardiac fibrosis in Smad3$^{+/-}$ mice (downstream of TGF-β1) was accompanied by repressed EndMT [15]. It is worth noting that TGF-β signaling also mediates EndMT during embryonic development of the heart as discussed above, which is perhaps silent during adulthood unless triggered by a disease state. Of note, the expression level of TGF-β is very low in normal heart [18]. The mechanism of TGF-β signaling activation to induce cardiac fibrosis is not yet discussed in this review. The mechanism has remained incompletely understood, although it may involve increased expression of thrombospondin-1, a TGF-β activator that could be induced by angiotensin II in cardiac endothelial cells [19]. Another mechanism of elevating TGF-β levels may be through Krüppel-like factors 6 (KLF6), knockout of which decreased TGF-β expression and cardiac fibrosis through thrombospondin-4 [20]. There is more evidence supporting a role of PI3K/Akt signaling in cardiac fibrosis beyond what has already been presented in the review by Jackson et al. [4]. In an As_2O_3-induced cardiac fibrosis model, inhibition of PI3K with LY294002 repressed As_2O_3-induced EndMT and fibrosis [21]. Application of LY294002 also attenuated high-glucose-induced EndMT, which promotes fibrosis in diabetic hearts [22]. These results demonstrate that TGF-β and PI3K/Akt signaling pathways play important roles in EndMT-mediated cardiac fibrosis. Inhibition of these pathways might be beneficial in the prevention and/or treatment of EndMT-mediated cardiac fibrosis.

As stated in the review by Jackson et al. [4], PAH is associated with EndMT. EndMT-mediated endothelial dysfunction in PAH was initially observed by two independent groups in 2015 [16,17]. It was reported that both endothelial and mesenchymal cell markers can be detected in human PAH intimal and plexiform lesions [17]. Using electron microscopy, Ranchoux et al. [17] reported mixed ultrastructural phenotype of pulmonary endothelial cells isolated from PAH patients. These cells possess not only endothelial-specific organelle Weibel–Palade body, but also smooth muscle cell featured myofilaments. These results provided direct evidence of ongoing dynamic process of EndMT in endothelial cells in PAH. The other study by Good et al. [16] demonstrated that mesenchymal-transited endothelial cells failed to form an integral endothelial barrier and exhibited increased permeability, which contributes to leukocyte infiltration, a key feature of PAH. Interestingly, TGF-β, again, has been delineated as a major inducer of EndMT in PAH [16]. A deficiency in BMP receptor type 2 (BMPR2), a molecule that counteracts TGF-β signaling, is known to induce EndMT and subsequent vascular remodeling [17,23]. On the other hand, PI3K/Akt-mediated EndMT also participates in the progression of PAH. It has been shown that global knockout of Akt1, not Akt2, protected against hypoxia-induced pulmonary vascular remodeling and PAH [24]. Transgene of PTEN, a repressor of Akt activity, attenuated PAH in mice [24]. Of interest, rapamycin, an inhibitor for mTOR (downstream of Akt), also partially reversed EndMT process and reduced mean pulmonary artery pressure [17]. While further investigations of detailed mechanistic roles of EndMT in PAH are necessary, these data suggest that TGF-β and PI3K/Akt signaling are likely essential mediators of EndMT in PAH, and of related features of vascular remodeling.

Though indispensable to physiological embryonic development, emerging evidence appears to demonstrate a recognizable pathological role of EndMT in the pathogenesis of various cardiovascular diseases such as cardiac fibrosis and PAH. Similar pathways of TGF-β and PI3K/Akt are involved in both physiological and pathological EndMT. Given further investigations, these pathways, as well as those discussed by Jackson et al. [4], may prove to be novel targets to attenuate EndMT to prevent and/or treat EndMT-dependent cardiovascular disorders. Initially characterized as a physiological mediator of cardiovascular development, EndMT has "gone bad" during adulthood to mediate disease pathogenesis. Continued efforts in delineating full details of signaling mechanisms of EndMT and EndMT-dependent pathophysiological consequences are important endeavors to reveal novel therapeutic targets and options.

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