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The role of GPCR signaling in cardiac Epithelial to Mesenchymal Transformation (EMT)☆,☆☆

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ABSTRACT

Congenital heart disease is the most common birth defect, affecting 1.35 million newborns every year. Heart failure is a primary cause of late morbidity and mortality after myocardial infarction. Heart development is involved in several rounds of epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET). Errors in these processes contribute to congenital heart disease, and exert deleterious effects on the heart and circulation after myocardial infarction. The identification of factors that are involved in heart development and disease, and the development of new approaches for the treatment of these disorders are of great interest. G protein coupled receptors (GPCRs) comprise 40% of clinically used drug targets, and their signaling are vital components of the heart during development, cardiac repair and in cardiac disease pathogenesis. This review focuses on the importance of EMT program in the heart, and outlines the newly identified GPCRs as potential therapeutic targets of reprogramming EMT to support cardiac cell fate during heart development and after myocardial infarction. More specifically we discuss prokineticin, serotonin, sphingosine-1-phosphate and apelin receptors in heart development and diseases. Further understanding of the regulation of EMT/MET by GPCRs during development and in the adult hearts can provide the following clinical exploitation of these pathways.

EMT during heart development and diseases

Epicardial-to-mesenchymal transition (EMT) plays a critical role in cardiac development [1]. The down-regulation of intercellular adhesion junctions and the expression of EMT-inducing transcription factors are the two key events in the EMT process (Fig. 1). All cells in the heart arise from one or more rounds of endocardial-EMT and epicardial-EMT. Endocardial-EMT plays a key role for formation of the cardiac valves and for complete cardiac septation. The early developing heart consists of an endocardial layer surrounded by a myocardial layer. These layers are separated by extracellular matrix, also known as cardiac jelly. The endocardial cushions become visible in the midgestation embryos. These cushions later develop into the atrioventricular (AV) and outflow tract (OFT) valves [2,3]. Endocardial cells that line the AV cushions undergo EMT in the midgestation embryos to populate them with mesenchymal cells, thus contributing to precursors of the future valve interstitial cells. OFT cushion development also involves endocardial EMT in a similar manner as that of AV but occurs later in development [2,3] (Fig. 2).

Epicardial-EMT is a physiological process in developing heart, such as myocardial differentiation, development of coronary vascular network, fibrous annulus and valves. Epicardium originates as proepicardium, a cluster of coelomic cells at the caudal end of the developing heart (E9.0–E9.5 in the mouse). The formation of most nonmyocardial cells starts with the development of the proepicardium [4]. Proepicardial cells are transferred to the myocardial surface, where they attach and spread, forming a continuous monolayered patch of epithelial cells, called epicardium [5]. Epicardial cells are important for both myocardium and coronary development (Fig. 2). During formation of the epicardial epithelium, EMT is initiated, allowing epicardial-epithelial cells to transform into a population of highly invasive, mesothelial epicardium-derived cells (EPDCs) [6]. The EPDCs formed via EMT invade the sub-epicardial matrix and migrate into the myocardium, where they differentiate into several cardiac lineages, including coronary smooth muscle cells [7], and perivascular and cardiac interstitial fibroblasts [8], coronary endothelial cells [9], possibly cardiomyocytes [10,11] and adipocytes [12]. Importantly, reactivated epicardial cells after heart injury proliferate and undergo EMT or mesenchymal-to-epithelial transition (MET), and subsequently

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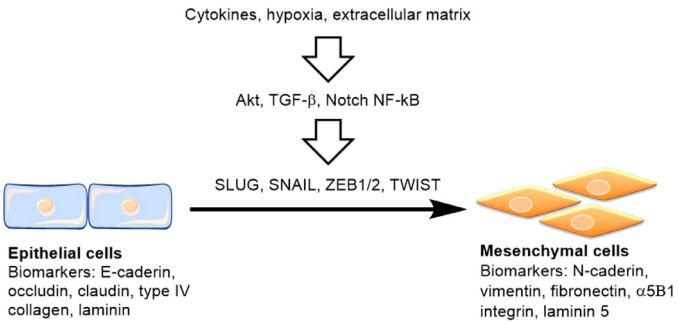

Fig 1. EMT activating signals and gene expression define epithelial and mesenchymal phenotypes.

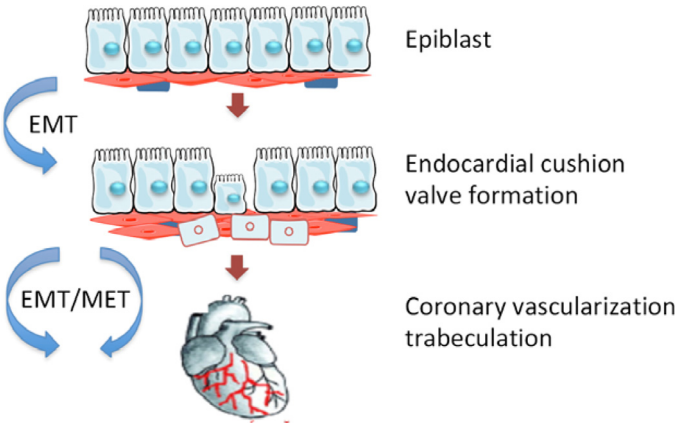

Fig 2. EMT-mediated events during heart development. Endocardial-EMT leads to development of endocardial cushion and valves. Several epicardial-EMT and MET is involved in coronary arteriogenesis and primary cardiomyocyte proliferation (trabeculation).

differentiate into cardiac cells to contribute to cardiac repair, or protect cardiomyocytes via paracrine interaction [13,14].

The impact of errors in EMT on the heart

Several studies have suggested that EMT is essential for proper embryogenesis, without which developmental defects or embryonic lethality can occur [1]. In the adult heart, disease-mediated activation of EMT may contribute to degenerative valve disease, cardiac fibrosis, and the myocardial injury response [3]. Valve diseases lead to significant morbidity and mortality. Valve diseases are described by expression of mesenchymal markers, such as vimentin (VIM) and smooth muscle actin in the valvular interstitial cells [15]. During development, progenitor cells derived from endocardial-EMT also express these markers indicating that potential reactivation of endocardial-EMT occurs in valve disease. In accord with these findings, enhanced valve endocardial-EMT has been shown to contribute to pathological changes in diseased leaflets in animal models and patients [16]. Endocardial-EMT forms valve progenitor cells that can be differentiated towards osteogenic or chondrogenic phenotypes, therefore contributing to valve calcification a hallmark of adult valve disease [3].

The disturbance in epicardial-EMT not only causes non-compaction cardiomyopathies, but also early coronary vascular diseases [17]. Defective epicardial outgrowth leads to lack of annulus fibrosis formation with electrophysiological evidence of the Wolff-Parkinson-White (WPW) syndrome [18]. An Ebstein-like valve phenotype could be related to impaired homing of EPDCs to valves [17]. Myocardial infarction reactivates endogenous epicardium which re-expresses embryonic markers, such as WT1, raldh2, Tbx18, tcf21 [10,19]. Injection of human EPDCs (hEPDCs) into the infarcted myocardium preserves cardiac function and reduces remodeling after the onset of infarction [20].

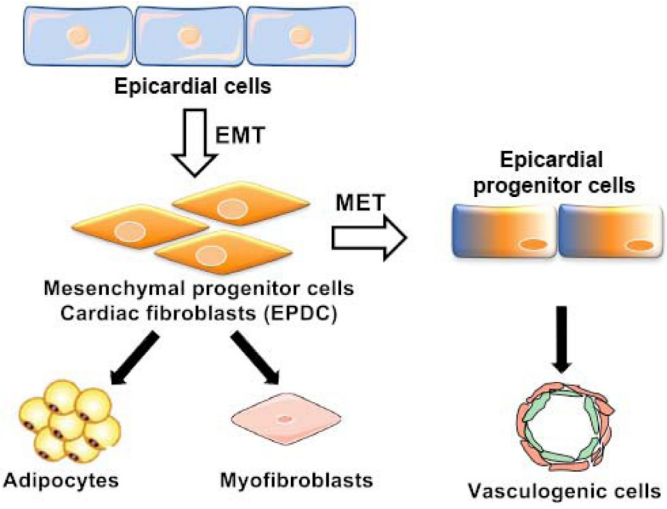

Fig 3. EMT and MET-mediated biological events in adult hearts. Epicardium undergoes EMT to form mesoepithelial EPDCs that can be differentiated into adipocytes or myofibroblasts, thereby inducing arrhythmia and scars. EPDCs can undergo MET leading to the formation of epithelial progenitor cells and vascular and epithelial/endothelial precursors that can further differentiate into vasculogenic cells, thereby contributing to regeneration of heart.

Cardiac fibrosis is also defined as an abnormal thickening of the heart valves due to an inappropriate number of fibroblasts. Fibroblast plasticity occurs either by replication of the resident myocardial fibroblasts, migration and transformation of circulating bone marrow cell-derived fibroblast precursor cells (fibrocytes), or transformation of resident non-fibroblast cells such as endothelial and perivascular cells into fibroblasts and myofibroblasts [21,22]. However, the epicardium is the major source of cardiac fibroblasts, and reactivated by epicardial-EMT during pathologic fibrogenesis after myocardial infarction [23]. Indeed, cardiac adaptive fibrosis is necessary to maintain the cardiac structural integrity and pressure-generating capacity of the heart. However, transforming into myofibroblasts by pathological stress, cardiac fibrosis leads to the progression to heart failure [3]. Fibrogenesis also contribute to arrhythmogenesis by increasing ventricular stiffness.

After the myocardial infarction, epicardial-EMT increases number of fibroblast that can be differentiated into adipocytes to generate epicardial adipose tissue (EAT) [12]. Formation of EAT, myofibroblasts and vasculogenic cells are regulated by EMT and MET in epicardial cells (Fig. 3). EAT plays a key role in the association between obesity and coronary artery disease (CAD). Although anatomically EAT may provide mechanical support for the coronary arteries, adipokines produced by EAT play key roles in the development of atherosclerotic plaque [24]. Since adipogenesis is a mesenchymal developmental process, the suppression of spontaneous EMT and retention of mesothelial cells at the epithelial stage reduces EAT formation in response to adipogenic stimuli [25].

Although reactivation of epicardial-EMT process contributes to disease pathogenesis, redirection of disease-related epicardial-EMT stimulates cardiac regeneration. G protein-coupled receptor (GPCR) signaling controls EMT during heart development, and may redirect EMT after myocardial infarction to regenerate heart.

GPCR signaling

Another aspect strongly associated with cardiac development and defects is G protein-coupled receptors (GPCRs) that are also

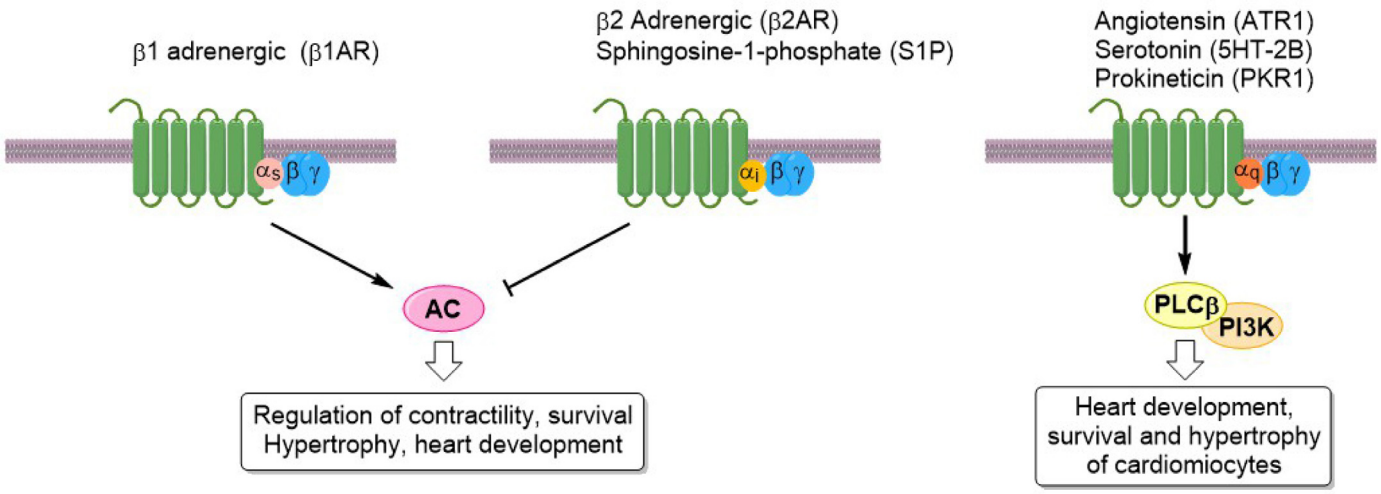

Fig 4. GPCRs in heart development and diseases. β1-adrenergic receptor via Gαs activates adenylate cyclase (AC), however β2-adrenergic (β2-AR) and Spingosine-1 phosphate (S1P1R) receptors couple to Gαi, and inhibit AC. Angiotensin receptor (ATR1) serotonin (5-HT2B) and prokineticin (PKR1) receptors uses Gαq/11 to activate phosphor lipase C (PLC) and phospho inositol 3 kinase (PI3K). These receptors are involved in heart development, regulation of contractility, survival and hypertrophic pathways.

called seven transmembrane helical (7TM) receptors [26]. GPCRs transduce extracellular signals from endogenous hormones and neurotransmitters or from exogenous factors, such as photons of light, odorants, and tastants (chemosensory receptors). GPCRs are classified into 6 subgroups based on the sequence homology [26]. These subgroups are Class A (rhodopsin-like receptors), Class B (secretin receptor family), Class C (metabotropic, glutamate receptors), Class D (pheromone receptors), Class E (cyclic AMP receptors) and Class F (frizzled receptors). Among the GPCRs, circulating catecholamines (Class A) play an important role in the control of cardiovascular function, via their adrenergic receptors, by mediating the actions of sympathetic nervous system activation. In cardiovascular diseases, the most used GPCR-targeted drugs are the blockers of β-adrenergic (β-AR) and angiotensin (AngII) receptors. AngII receptor blockers have been used for the treatment of hypertension and cardiovascular disorders [27]. During heart failure, β1-ARs are hyper-stimulated, which induces a cardiotoxic effect. However, β2-ARs exert cardioprotective roles, counteracting the deleterious effects of chronic sympathetic stimulation in failing hearts. Thus, β1-specific ARs antagonist together with β2-AR agonist have been used for treatment of heart failure [28]. Some of the GPCRs are involved in heart development such as prokineticin receptor-1 (PKR1), sphingosine-1-phosphate (S1P) 1 receptor (S1P1R) and serotonin (5-HT)-2B receptors (Fig. 4). Here we discuss mainly these 3 GPCRs that are involved in heart development and diseases.

Prokineticin receptors in heart development and disease

Prokineticins as angiogenic and anorectic hormones, exert their biological activity by binding to their cognate GPCRs; namely, PKR1 and PKR2 [29]. A critical role of epicardial-PKR1 signaling during cardiac development has been recently demonstrated. Mice lacking PKR1 in their Wt1$^+$ epicardial cells showed partial embryonic lethality, due to impaired EMT in their hearts [30]. PKR1 signaling promotes the proliferation and EMT of epicardial cells of the Wt1$^+$ lineage and their subsequent differentiation into endothelial and vascular smooth muscle cells during heart development. PKR1 activation or overexpression induces changes in embryonic epicardial cell morphology, actin cytoskeleton remodeling, and EMT-gene expression profile [30].

PKR1 orchestrates epicardial-cardiomyocyte interactions in the developing heart. In mice, inactivation of PKR1 in epicardial-derived cells also causes epicardial detachment and a reduction of the adjacent myocardium compact zone, impairing myocardial growth [30]. Although myocardial expression of PKR1 induces coronary vessel formation by a paracrine process [31], a reciprocal interaction between the epicardium and cardiomyocytes via PKR1 signaling has also been shown to be involved in EPDC function and myocardial development and function [30].

EMT/MET plays important roles in stem cell differentiation and de-differentiation or reprogramming [32]. Prokineticin-2/PKR1 signaling in hEPDCs controls a switch between formation of EAT and vasculogenesis via inhibiting EMT (Fig. 3). Prokineticin/PKR1-mediated inhibition of EMT allows the regaining of epithelial features with self-renewal and rapid generation of vascular precursors [25]. A newly described epigenetic route involving histone modifications by KDM6A overcomes the intrinsic limitations of differentiating hEPDCs into vasculogenic cells. Activation of KDM6A by PKR1 signaling plays a key role in the demethylation of H3K27me3, leading to promoter derepression and induction of lineage-specific marker expression for endothelial cells and smooth muscle [25]. Prokineticin-2/PKR1-mediated KDM6A activity is also essential for the inhibition of adipogenesis in response to adipocyte induction in hEPDCs, by inhibiting EMT, and stabilizing cytosolic β-catenin levels, thereby blocking PPARγ activity.

Supporting these *in vitro* findings, epicardial-specific PKR1 knockout mice have been shown to have an imbalance between adipogenic and vasculogenic transformation following exposure to a high-fat diet (HFD), leading to systolic and diastolic left ventricular dysfunction and severe arrhythmia [30]. Mice lacking PKR1 in their tcf21$^+$ cardiac fibroblast progenitors displayed low capillary formation. However, such mice fed a high fat diet exhibited an increased epicardial adipose tissue (EAT) and a severe regression of blood vessels, leading to cardiac dysfunction [33]. Overall, these data show that prokineticin-2/PKR1 signaling plays an important role in regulating epicardial fate via epigenetic control from adipogenesis towards vasculogenesis *in vitro* and *in vivo*. Thus, the control of epicardial-EMT/MET program is a potentially valuable target for future applications in cardiac tissue engineering.

Sphingosine-1-phosphate (S1P) receptor signaling in heart development and disease

S1P is a lysophospholipid that uses GPCRs to promote cellular differentiation, proliferation, migration, cytoskeletal reorganization,

and apoptosis [34]. S1P receptors (S1PRs) are composed of five subtypes, S1P1R to S1P5R [35]. The deletion of the S1P1R in mice ($S1P1R^{-/-}$) leads to embryonic lethality between embryonic days E13.5 and E14.5 due to several defects in the developing heart. These defects are atrioventricular canal cushion and vascular maturation defects, and malformed myocardium [36]. The heart condition in $S1P1R^{-/-}$ hearts may also be due to the disruption of fibronectin (FN) in the epicardium due to altered EMT [37]. This disrupted epicardial layer due to impaired EMT may explain the disorganized myocardium observed in the compact layer of $S1P1R^{-/-}$ hearts. Further analysis of the role of S1P1R signaling during epicardial development is needed to confirm this possibility.

Serotonin receptor signaling in heart development and disease

The serotonin (5-hydroxytryptamine, 5-HT) regulates cardiovascular functions during embryogenesis and adulthood [38]. There are at least 15 receptor subtypes that belong to four populations namely, 5-HT1/5, 5-HT2, 5-HT3, and 5-HT4/6/7 subtypes. The 5-HT2 receptors are composed of three subunits: 5-HT2A, 5-HT2B, and 5-HT2C [39]. The serotonin 2B receptor and serotonin uptake inhibitors are involved in heart development and diseases. Inactivation of 5-HT2B receptor leads to embryonic midgestation lethality due to a lack of trabeculae in the heart [40,41]. All surviving newborn mice display a severe ventricular hypoplasia caused by impaired proliferative capacity of myocytes, leading to neonatal lethality [42]. This phenotype is similar to defective EMT-mediated heart malformations. A selective serotonin reuptake inhibitor (SSRIs) fluoxetine used for treatment of gestational depression. It causes dramatic postnatal mortality of the offspring with severe heart failure due to dilated cardiomyopathy in rodents [43]. This suggests that the 5-HT system is involved in heart development and that fluoxetine treatment during fetal development affects the heart, resulting in dilated cardiomyopathy. Major cardiac malformations have also been associated with prenatal SSRIs in human practice, although most of the cardiac malformations were observed after prenatal SSRI treatment [44]. Moreover, a meta-analysis of clinical trials has shown that prenatal SSRIs significantly increased the risk for spontaneous abortion, which is also observed in mice [44]. Nevertheless, more research is necessary to confirm the effects of SSRI and serotonin receptor ligands on cardiac development- and diseases-related EMTs.

Other GPCRs that regulate heart development and disease

A chemokine, Apelin, and its receptor, Agtrl1b (Angiotensin II receptor-like 1 receptor) has been found to regulate blood pressure [45] and to induce a positive inotropic effect in humans [46]. Apelin has also been shown to be required for normal vascular development in frog embryos [47]. The loss of Agtrl1b in mice leads to embryonic lethality due to growth retardation and cardiac malformations similar to that observed in mice having defective EMT [48]. The earliest ligand for Agtrl1b called ELABELA promotes endoderm differentiation and subsequent cardiogenesis. Loss of ELABELA causes a rudimentary heart or no heart in embryos [49].

Several orphan GPCRs have emerged as novel therapeutic targets to treat heart failure. Two such candidates, GPR37L1 (downregulated in cardiovascular diseases) and GPR35 (upregulated in myocardial infarction), were identified by correlating gene expression with clinical parameters, such as pulmonary artery pressure, left ventricular ejection fraction, and brain natriuretic peptide mRNA levels [50]. However their role in heart development and disease-related EMT have not been studied yet.

Concluding remarks and future perspectives

EMT is a key player for heart development during embryogenesis and after the cardiac injury, however, without EMT heart defects and impaired cardiac regeneration occur. Targeting cardiac EMT/MET could hold a great potential to redirect the fate of cardiac stem/progenitor cells. Tracking EMT/MET in vivo in humans by imaging techniques could be a new approach to delineate the disease stage. In animals it would be useful for cell tracing studies. The therapeutic manipulation of EMT/MET can also be a therapeutic approach for treatment of heart diseases.

GPCRs are the largest family of signaling receptors and the major targets of new and approved pharmaceuticals. Indeed, GPCR-targeted drug discovery still successfully continues. Newly approved 19% of therapeutics target GPCRs, including the antithrombotic drug (Plavix) that targets platelet P2Y12 adenosine receptors, the antidepressant drugs that are selective serotonin reuptake inhibitors (SSRIs) and act agonists or antagonists of serotonin receptors, and the anti-insomnia drug (Tasimelteon) that is a melatonin receptor agonist.

GPCRs can be a valid target for redirecting and epigenetic reprogramming EMT/MET to stimulate regeneration in the injured heart. Given the central role of the GPCR signaling pathways in both health and disease, their role in tissue engineering and modeling needs to be further explored. The efforts in discovering and developing compounds such as antibodies, allosteric modulators and biased agonists that modulate GPCRs may open a new possibility to more precisely controlling receptor signaling and ultimately therapeutic effects. Recently, the sequencing of the human genome revealed new members of the GPCR family, which brings new opportunities for developing novel therapeutics targeting these new GPCRs.

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