Role of the Notch1 signaling pathway in ischemic heart disease (Review)

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Abstract. Ischemic heart disease (IHD) is a prevalent cardiovascular disease characterized by the formation, progression and rupture of atherosclerotic plaque. The Notch signaling pathway is a key mechanism facilitating intercellular coordination. An increasing number of studies have revealed the significance of Notch signaling, particularly as regards Notch1. Of note, the existence of aberrant Notch1 signaling in IHD is universal, suggesting clinical significance. Thus, the present review summarizes the implications of Notch1 signaling in endothelial cells, vascular smooth muscle cells and macrophages in association with the development of IHD. The present review also examined the effects of Notch1 signaling on various remodeling stages of IHD consisting of reendothelialization, neovascularization, and myocardial fibrosis. Moreover, the participation of Notch1 signaling in conventional reperfusion treatments and cardiac regeneration therapies is discussed. On the whole, the present review aims to outline Notch1 signaling as a novel target which may be used to enhance the treatment efficacy for patients with IHD.

Contents

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1. Introduction

Ischemic heart disease (IHD) causes a heavy disease burden worldwide. Its underlying pathogenesis consists of coronary atherosclerosis characterized by the formation of atherosclerotic plaque. Gradual increases in plaque size can lead to coronary artery stenosis and an impaired blood supply, which subsequently induces clinical manifestations, such as angina pectoris. A ruptured plaque can induce thrombus formation, leading to myocardial infarction (MI) and ultimately triggering severe hemodynamic deterioration or sudden death (1).

The development of atherosclerotic plaque is a multi-stage process. At first, THE continuous exposure to pathogenic factors can initiate vascular endothelial activation or dysfunction. The resulting hyperpermeable endothelial cells (ECs) allow monocyte adhesion and infiltration. Subsequent monocyte-to-macrophage differentiation, macrophage polarization and foam cell conversion contribute to building a lipid-rich core in the developing plaque. Concomitantly, various growth factors and cytokines from microenvironments at injury sites stimulate vascular smooth muscle cells (VSMCs) to migrate into the intima vascular layer, and the accumulation of these translocated cells induces neointima formation and luminal stenosis. Furthermore, the phenotypic switch of VSMCs enhances extracellular matrix synthesis and fibrous cap formation (2). The histopathological characteristics of MI include necrotic and apoptotic cardiomyocyte death accompanied by a series of remodeling stages, intertwined with compensatory myocardial hypertrophy, myocardial fibrosis and intense angiogenic response. These alterations are highly detrimental and cause progressive cardiac dysfunction (3).

In mammals, Notch receptors include the four isoforms Notch 1-4, while Notch ligands include Jagged 1 and 2 and Dll (Delta-like) 1, 3 and 4. Notch signaling activation requires direct molecular interactions between Notch receptors and ligands. Such interactions occur between adjacent signal-receiving and sending cells. Upon receptor-ligand engagement, the Notch receptor is subjected to protein cleavage performed by a disintegrin and metalloprotease (ADAM), followed by a presenilin-dependent γ-secretase complex. The cleavage location by ADAM is at the extracellular S2 site, while the cleavage by γ-secretase first occurs at the intracellular S3 site and subsequently, at the S4 site. Proteolytic cuts at sites S2, S3 and S4 allow for the untethering of the active of Notch, the Notch intracellular domain (NICD). As regards

canonical Notch signaling, NICD translocates to the nucleus and subsequently forms a complex with DNA-binding protein recombination signal binding protein-J (RBP-Jκ in mammals; CSL from CBF1 in vertebrates, suppressor of hairless in *Drosophila* and Lag-1 in *Caenorhabditis elegans*), as well as with the coactivator Mastermind-like 1-3 (MAML1-3). This NICD/RBP-Jκ/MAML transcriptional activator complex is able to recruit additional co-activators, such as p300 and PCAF to induce the transcription of the Notch target gene Hairy-and-enhancer of split (Hes) and Hairy-related transcription factor (Hrt, also known as Hey) families (4) (Fig. 1).

As a highly conserved signaling pathway throughout species evolution, Notch signaling is broadly involved in a wide array of cellular events, such as cell fate determination, development, differentiation, proliferation and apoptosis (4). The significance of Notch signaling in cardiovascular development, including the atrioventricular canal, outflow tract, valves, chambers, conduction system and blood vessels, has been reported (5). Of note, a number of studies have described the role of Notch, particularly Notch1, in IHD (6-10). The present review aimed to comprehensively elucidate the implication of Notch1 signaling in ECs, VSMCs and macrophages, which are interwoven together to facilitate the development of atherosclerosis. Furthermore, the influence of Notch1 signaling during the intricate remodeling phases of IHD, including reendothelialization, neovascularization and myocardial fibrosis is summarized. Finally, the literature that elucidates the significance of Notch1 signaling in reperfusion treatments and cardiac regenerative therapies is assessed.

2. Role of Notch1 signaling in atherosclerosis

Role of Notch1 signaling in ECs. In early-stage atherosclerosis, ECs selectively express an array of adhesive molecules for the recruitment of leucocytes to the luminal surface. The findings from the study by Nus *et al* (11) indicated that Notch inactivation attenuated leucocyte recruitment and the inflammatory status in ECs. More specifically, NICD was shown to function as a transcriptional co-factor with non-canonical nuclear factor κB (NF-κB) to promote the nuclear translocation and retention of NF-κB. By contrast, other researchers have proposed that Notch1 acts as an antagonist in signal transducer and activator of transcription 3 (STAT3)-mediated endothelial inflammation during atherosclerosis (6). Vascular inflammation may be induced by low shear stress, and Notch1 has been found to be modulated by shear stress, partly due to the caveolin-1/Notch1/NF-κB inhibitor α/NF-κB pathway (12). In summary, the inconsistent effects of Notch1 on endothelial inflammation may reflect the functional diversity of Notch1 signaling.

The endothelial-mesenchymal transition (EndMT) of ECs in terms of morphology and function has been confirmed to drive the progression of atherosclerosis. Both *in vitro* and *in vivo*, Notch1 has been found to promote EndMT during atherosclerosis, as manifested by oppositional changes in EC and interstitial markers (13,14). Indeed, during the hypoxia-induced EndMT of human cardiac microvascular ECs, Notch1 signaling and its downstream effector, runt-related transcription factor 3 (RUNX3), stabilize NICD to become activated (15).

Aged arteries are partially characterized by senescent vascular ECs, which can serve as a substrate to accelerate the deterioration of atherosclerotic lesions. Notch1 signaling can cause EC dysfunction by facilitating cell telomere shortening-induced replicative senescence, and the Notch target gene, HeyL is considered to be key in this outcome (16). Venkatesh *et al* (17) provided evidence to support the hypothesis that Notch activation boosted two major cell cycle-related pathways, namely p53/p21 and p16-Rb, through the mitogen-activated protein kinase kinase 1 (MEK1)/extracellular signal-regulated kinase (ERK) pathway, thus resulting in the senescence-like growth arrest of ECs.

There is also evidence to suggest the participation of Notch1 in the apoptosis of ECs, acting in histone acetylation. Mechanistically, NICD complexes with histone acetylase general control non-depressible 5 and thus affects the transpriction of neuregulin-1. The increased expression of neuregulin-1 then inhibits EC apoptosis (18). The direct interaction of peptidylprolyl isomerase and Notch1 has also been proven to promote the apoptosis of ECs, which may be attenuated by resveratrol (19). Finally, loss-of-function of Krev interaction trapped protein 1 induces the redox-sensitive downregulation of Notch1 signaling, which facilitates EC apoptosis (20) (Table I).

Some efforts have been made to recognize available inhibitors of Notch1 signaling in ECs. Apart from resveratrol mentioned above (19), it has been shown that Xuan Bi Tong Yu Fang, a well-known traditional Chinese medical prescription, promotes EC-mediated angiogenesis in rats with myocardial ischemia by inhibiting the Dll4/Notch1 pathway (21). The anticoagulant drug, sulodexide (22), and the vasodilator, pentoxifylline (23), have also been found to inhibit the Dll4/Notch1 pathway to affect angiogenesis in mouse proepicardial explant cultures. The Notch1/NF-κB pathway has been confirmed to be inhibited by niacin to alleviate EC inflammation (24) (Table II).

Taken together, it is suggested that the atheroprotective or atherogenic effects of Notch1 signaling are dependent on external factors, the cellular context, as well as on its own signaling complexity. Thus, the further exploration of the exact functions of Notch1 in ECs during atherosclerosis is highly warranted.

Role of Notch1 signaling in smooth muscle cells. Unlike terminally differentiated skeletal and cardiac muscle cells, quiescent VSMCs in the tunica media can switch phenotypes when exposed to various stimuli during atherosclerosis. More specifically, VSMCs downregulate the expression of genes required for maintaining the contractile phenotype. This induces transformation into a synthetic phenotype, whereby VSMCs proliferate, migrate from the medial layer to the intima and increase the expression of extracellular matrix genes to crucially initiate neointimal hyperplasia (25).

Noseda *et al* (26) reported that a direct combination of the NICD/CSL complex with smooth muscle α-actin (SMα-actin) promoter can induce SMα-actin expression. However, these effects can be antagonized by inducing the expression of Hrt1 and Hrt2, thus characterizing a negative feedback loop and fine-tuning SMα-actin expression (27). Furthermore, it has reported been that Notch/RBP-Jκ/Hrt1, 2 and 3 signaling is

Table I. Role of Notch1 signaling in endothelial cells.

EC phenotype	Signaling pathway	Effect of Notch1 signaling on the phenotype	(Refs.)
Inflammation	NICD/IKKα/IKBα/NICD-RBP-Jκ-NF-κB	Promotion	(11)
	Ox-PAPC/STAT3/NICD	Inhibition	(6)
	Fluid shear stress/CAV1/NICD/IKBα/NF-κB/ NICD-RBP-Jκ-NF-κB	Promotion	(12)
Endothelial-mesenchymal transition	/	Promotion	(13)
	Hypoxia/NICD/RUNX3/Snail-Slug	Promotion	(15)
Senescence	NICD/HeyL/telomerase activity	Promotion	(16)
	NICD-RBP-Jκ/MEK1/ERK/p53/p21	Promotion	(17)
	NICD-RBP-Jκ/MEK1/ERK/p16-Rb/CyclinD1	Promotion	(17)
Apoptosis	NICD/GCN5/H3K9Ac/Nrg1	Inhibition	(18)
	Pin1/Notch1	Promotion	(19)
	KRIT1/Notch1	Inhibition	(20)

EC, endothelial cell; NICD, Notch intracellular domain; IKKα, inhibitor of κB kinase α; IKBα, NF-κB inhibitor α; RBP-Jκ, recombination signal sequence binding protein Jκ; NF-κB, nuclear factor κB; ox-PAPC, oxidized-1-palmitoyl-2-arachidonyl-sn-glycerol-3-phosphocholine; STAT3, signal transducer and activator of transcription 3; CAV1, caveolin-1; RUNX3, Runt-related transcription factor 3; HeyL, hairy and enhancer of split-related with YRPW motif-like; MEK1, mitogen activated protein kinase kinase 1; ERK, extracellular signal-regulated kinase; Rb, retinoblastoma tumor susceptibility gene; GCN5, general control non-depressible 5; H3K9Ac, histone H3 acetyl K9; Nrg1, neuregulin-1; Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; KRIT1, Krev interaction trapped protein 1.

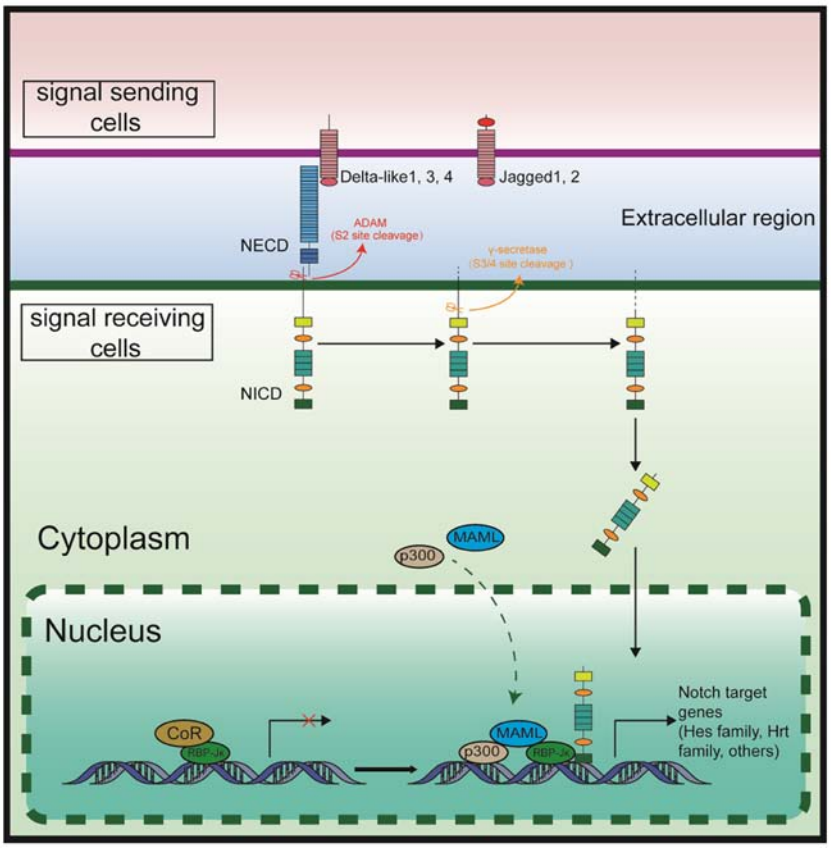

Figure 1. Schematic diagram of the Notch signaling pathway. In total, five different Notch ligands (Jagged1, 2 and Delta-like 1, 3 and 4) are expressed in the signal sending cells and Notch receptors are expressed in the adjacent signal receiving cells. Notch signaling is initiated by interactions between Notch ligands and receptors. Receptor-ligand engagement triggers two sequential proteolytic cleavages of the Notch receptor by the ADAM (S2 site) and by the presenilin-dependent γ-secretase complex (S3, S4 site), releasing NICD into the nucleus. The complex of NICD and RBP-Jκ displaces CoR and recruits the coactivator MAML and additional co-activators such as p300, converting RBP-Jκ from a transcriptional repressor into a transcriptional activator. This NICD/RBP-Jκ/MAML/p300 complex activates the transcription of target genes, including Hes and Hey family members. NICD, Notch intracellular domain; NECD, Notch extracellular domain; RBP-Jκ, recombination signal sequence binding protein Jκ; ADAM, a disintegrin and metalloprotease; MAML, Mastermind-like; Hes, hairy-and-enhancer of split; Hrt, hairy-related transcription factor (also known as Hey); CoR, corepressor.

Table II. Chemical activators/inhibitors of Notch1 signaling in ECs, VSMCs and macrophages.

Name	Signaling pathway	Activator/ inhibitor of Notch1 signaling	Affected cell phenotype	(Refs.)
Resveratrol	Pin1/Notch1	Inhibitor	EC apoptosis	(19)
Xuan Bi Tong Yu Fang	Dll4/Notch1	Inhibitor	EC angiogenesis	(21)
Sulodexide	Dll4/Notch1	Inhibitor	EC angiogenesis	(22)
Pentoxifylline	Dll4/Notch1	Inhibitor	EC angiogenesis	(23)
Niacin	Notch1/NF-κB	Inhibitor	EC inflammation	(24)
Indoxyl sulfate	miR-34a/Notch1	Activator	VSMC proliferation/migration	(35)
Resveratrol	Notch1	Inhibitor	VSMC phenotypic switching	(36)
Sodium ferulate	Notch and Wnt signaling	Inhibitor	VSMC phenotypic switching	(37)
Curcumin	CAV1/Notch1/myocardin	Inhibitor	VSMC phenotypic switching	(38)
Melatonin	Notch1/Hes1	Activator	VSMC apoptosis	(39)
EtOH	γ-Secretase/NICD	Inhibitor	VSMC proliferation	(40)
Acetaldehyde	Notch1/Hrt1,2,3	Activator	VSMC proliferation	(40)
Ganoderma lucidum triterpenoids and polysaccharides	Dll4/Notch1	Inhibitor	Macrophage phenotypic polarization (M1)	(50)
Ganoderic acid A	Notch1/PPARγ/CD36	Inhibitor	Macrophage phenotypic polarization (M1)	(51)
Celery seed extract	Notch1/NF-κB	Inhibitor	Macrophage phenotypic polarization (M1)	(52)
Niacin	Notch1/NF-κB	Inhibitor	Macrophage phenotypic polarization (M1)	(24)

ECs, endothelial cells; VSMCs, vascular smooth muscle cells; Dll4, Delta-like 4; PPARγ, peroxisome proliferator-activated receptor γ; CAV1, caveolin-1; NICD, Notch intracellular domain.

enhanced in VSMC phenotypic switching, as indicated by inducing the downregulation of myosin and smoothelin, which further confirms the positive effects of Hrt on VSMC phenotypic switching (25).

To maintain the contractile phenotype, there is a requirement for serum response factor (SRF) and its coactivator, the myocardin-dependent transcriptional program. Proweller *et al* (28) described that this contractile phenotype was modulated by NICD, since an increased Hrt2 expression suppressed the transcription of VSMC-restricted genes via its capability to impede the function of the myocardin-SRF complex. Hrt1 can also physically interact with SRF to interfere with subsequent SRF/DNA binding (29). Collectively, these findings indicate a balance between Notch and Hrt to modulate the VSMC phenotypic change (25-29).

Notch1 is also extensively involved in the dynamics of VSMC growth, proliferation, migration and apoptosis. The constitutive expression of active Notch 1 and 3 receptors induces the prominent upregulation of Hes5 and Hrt1, concomitant with the increased growth, and the suppressed migration and apoptosis of VSMCs (7). Previous research (30) has revealed that the effects of Hrt1 on VSMC proliferation and apoptosis are respectively owed to the inhibition of cell cycle inhibitor-$p21^{WAF1=CIP}$ and the induction of protein kinase B (Akt). Moreover, Hrt2 has been shown to directly interact with the promoter of cyclin-dependent kinase inhibitor $p27^{kip1}$ to repress its transcription and induce a hyperproliferative state in VSMCs (31). Another study revealed that Hrt2-deficient VSMCs exhibited a diminished growth and migration associated with decreased lamellipodia formation and membrane ruffling, due to the blunted activation of the small GTPase Ras-related C3 botulinum toxin substrate 1 (Rac1) and the expression of Rac guanine exchange factor Son of sevenless homolog 1 (32). That study clarified the association between Hrt2 and migration-related cytoskeleton reorganization (32).

The inhibition of the Jagged1-Notch1 interaction between ECs and VSMCs may impair cell-matrix focal adhesion, strengthen intercellular junctions and cause defects in VSMC migration toward arterial injury areas (33). These observations broaden the relevance of Notch signaling for vascular cell adhesion and migration (33). In addition, a circ_TNPO1/microRNA 181b (miR-181b)/Notch1 axis has been shown to induce the proliferation and migration of VSMCs (34). The miR-34a/Notch1 axis involved in VSMC proliferation and migration has also been implicated in the atherogenic effect of indoxyl sulfate (35) (Table III).

Research has also provided new paradigms for drug development aiming at VSMC phenotypic switching. For example, the negative effects of the polyphenolic compound, resveratrol, on VSMC phenotypic switching have been confirmed to occur mainly through the blockage of NICD release (36). There is a simultaneous suppressive effect of sodium ferulate on both Notch and Wnt signaling, which may indicate a frequent crosstalk of these two pathways in VSMC phenotype remodeling (37). The natural polyphenolic compound, curcumin, can enhance the contractile phenotype of VSMCs through the caveolin-1/Notch1/myocardin pathway (38). Other chemical

Table III. Role of Notch1 signaling in smooth muscle cells.

SMC phenotype	Signaling pathway	Effect of Notch1 signaling on the phenotype	(Refs.)
Phenotypic switching	NICD-RBP-Jκ/SMα-actin promoter	Inhibition	(26)
	Hrt1, Hrt2/NICD-RBP-Jκ/SMα-actin promoter	Promotion	(27)
	NICD-RBP-Jκ/Hrt1,2,3	Promotion	(25)
	NICD-RBP-Jκ/Hrt2/myocardin-SRF	Promotion	(28)
	NICD-RBP-Jκ/Hrt1/myocardin-SRF	Promotion	(29)
Proliferation	NICD-RBP-Jκ/Hes5, Hrt1	Promotion	(7)
	NICD-RBP-Jκ/Hrt1/$p21^{WAF1=CIP}$	Promotion	(30)
	NICD-RBP-Jκ/Hrt2/$p27^{kip1}$	Promotion	(31)
	NICD-RBP-Jκ/Hrt2/Sos1/Rac1	Promotion	(32)
	Circ_TNPO1/miR-181b/Notch1	Promotion	(34)
	miR-34a/Notch1	Promotion	(35)
Apoptosis	NICD-RBP-Jκ/Hes5, Hrt1	Inhibition	(7)
	NICD-RBP-Jκ/Hrt1/Akt	Inhibition	(30)
	miR-34a/Notch1	Inhibition	(35)
Migration	NICD-RBP-Jκ/Hes5, Hrt1	Inhibition	(7)
	NICD-RBP-Jκ/Hrt2/Sos1/Rac1	Promotion	(32)
	Jagged1/NICD-RBP-Jκ/cell-matrix adhesion, intercellular junction	Promotion	(33)
	Circ_TNPO1/miR-181b/Notch1	Promotion	(34)
	miR-34a/Notch1	Promotion	(35)

SMC, smooth muscle cell; SMα-actin, smooth muscle α-actin; Hrt, hairy-related transcription factor; SRF, serum response factor; Hes, hairy-and-enhancer of split; Sos1, son of sevenless homolog 1; Rac1, small GTPase Ras-related C3 botulinum toxin substrate 1; miR, microRNA; Akt, protein kinase B; NICD, Notch intracellular domain; RBP-Jκ, recombination signal sequence binding protein Jκ.

substances can also regulate Notch1 signaling in VSMCs. Melatonin is able to attenuate VSMC apoptosis by activating Notch1/Hes1 signaling pathway (39). Ethanol can inhibit Notch signaling by inhibiting γ-secretase cleavage activity, so as to hinder VSMC proliferation, while its metabolite, acetaldehyde, stimulates Notch/Hrt signaling to promote VSMC proliferation (40) (Table II).

Overall, enhanced Notch1 signaling appears to intensify the negative role of VSMCs during atherosclerosis. However, it is worth noting that Notch1 and its effector gene, Hrt, antagonize phenotypic transformations, while the Hrt and Hes genes exert contradictory effects on certain VSMC behaviors.

Role of Notch1 signaling in macrophages. When an injury occurs, monocytes attach to the inflamed endothelium through adhesion molecules expressed by ECs, penetrate the subendothelium guided by chemokines and differentiate into two polarized macrophages subpopulations induced by distinct effectors. Activating factors including, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and bacterial lipopolysaccharide (LPS) can induce pro-inflammatory M1 macrophages that become more common as the plaque progresses. By contrast, anti-inflammatory M2 macrophages, which are a subtype enriched in regressing plaques, can be primed by inhibitory cytokines, such as interleukin (IL)-4 and IL-13. Pro-inflammatory mediators secreted by M1 macrophages include inducible nitric oxide synthase, IL-6, monocyte chemotactic protein-1 and TNF-α, among others, while M2 macrophages secrete anti-inflammatory factors, such as IL-10, IL-1RA and arginase-1 enzyme (41,42). These subintimal heterogeneous macrophage groups uptake native and modified low-density lipoprotein particles, and ultimately transit into cholesterol-laden foam cells, which are recognized as the hallmark of atherosclerosis (42).

The involvement of Notch1 in macrophage phenotypic polarization has been explored (43). It has been found that macrophage activation induced by LPS and/or IFN-γ results in a p38 mitogen-activated protein kinase (MAPK)-dependent increase in Notch1 and Jagged1 expression. The resulting expression of Hes1 mediates the crosstalk between NICD and activating protein 1 (AP-1)/STAT1/3-dependent transcription. Thereafter, altered AP-1/STAT1/3-dependent gene expression drives the formation of M1 macrophages. It has also been reported that blocking the Notch1 pathway enhances M2 macrophage polarization, attenuates pro-inflammatory signals and promotes anti-inflammatory responses in THP-1 cells (41) and primary human monocytes (44).

Fukuda *et al* (45) described that, through the NF-κB axis, the Dll4-Notch axis led to incremental susceptibility to the M1 phenotype. Members of the interferon regulatory factor (IRF) family proteins are transcriptional regulators of macrophage polarization. Xu *et al* (46) reported that a complex signaling cascade consisting of the Notch1/interleukin-1 receptor-associated kinase 2 axis and downstream MEK/MAPK (p38 and

Table IV. Role of Notch1 signaling in macrophages.

Macrophage phenotype	Signaling pathway	Effect of Notch1 signaling on the phenotype	(Refs.)
Macrophage phenotypic polarization (M1)	LPS, IFN-γ/p38 MAPK/NICD/Hes1/AP-1, STAT1, STAT3	Promotion	(43)
	/	Promotion	(41)
	/	Promotion	(44)
	Dll4-Notch1/NF-κB	Promotion	(45)
	Notch1/IRAK2/MEK/MAPK (p38 and ERK)/MNK1/eIF4E/IRF8	Promotion	(46)
	NICD/NF-κB	Promotion	(8)
	/	Promotion	(8)
	NICD/proteasome/IKBα/NF-κB	Promotion	(47)
	NICD/IKKβ/IKBα/NF-κB	Promotion	(48)
Interaction between macrophages and adventitia stem/progenitor cells (differentiation into VSMCs)	Macrophage-derived MMP8/ADAM10/Notch1	Promotion	(49)
Interaction between macrophages and VSMCs (VSMC hyperplasia)	Macrophage-derived MMP8/ADAM10/Notch1	Promotion	(49)

LPS, lipopolysaccharide; IFN-γ, interferon-γ; MAPK, mitogen-activated protein kinase; AP-1, activating protein 1; Dll4, delta-like 4; IRAK2, interleukin-1 receptor associated kinase 2; MNK1, mitogen-activated protein kinase interacting kinases 1; eIF4E, eukaryotic translation initiation factor 4E; IRF8, interferon regulatory factor 8; MMP8, matrix metalloproteinase 8; ADAM10, a disintegrin and metalloprotease 10; VSMCs, vascular smooth muscle cells; NICD, Notch intracellular domain; Hes, hairy-and-enhancer of split; STAT3, signal transducer and activator of transcription 3; IKKα, inhibitor of κB kinase α; IKBα, NF-κB inhibitor α.

ERK)/MAPK interacting kinases 1/eukaryotic translation initiation factor 4E (eIF4E)/IRF8 pathway induced the expression of a subset of M1 effector molecules.

The communication between Notch and the inflammatory hub, i.e., NF-κB signaling within macrophages is frequent and promotes macrophage polarization. A recent study revealed that the inhibition of NF-κB decreased NICD, which in turn downregulated the M1-like MAC387$^+$ macrophage differentiation of THP-1 cells (8). Another study identified the positive regulatory effects of Notch on NF-κB signaling in macrophages derived from patients with atherosclerosis. Specifically, Notch1 inhibition led to the inactivation of NF-kB signaling via the proteasome and other NF-κB signaling components, which decreased the expression of downstream pro-inflammatory factors (47). Such interactivity is again verified in the macrophage-like cell line, RAW264.7, in which Dll4-Notch1 signaling promotes IκB kinase β activation, subsequently inducing the activation of NF-κB (48). Therefore, the interaction between Notch and NF-κB signaling pathways in macrophages (8,47,48) may present a parallel with what is reported in ECs (11).

Notch1 plays a critical role in facilitating the interaction between macrophages and other cells involved in atherosclerosis. Matrix metalloproteinase (MMP)8 is expressed by macrophages within atherosclerotic plaques and promotes plaque rupture. Yang *et al* (49) found that macrophage-derived MMP8 promoted the VSMC differentiation of adventitia stem/progenitor cells via the activation of ADAM10/Notch1 signaling. In the context of arterial remodeling, macrophage-derived MMP8 also increases neointimal VSMCs hyperplasia in a manner dependent on ADAM10/Notch1 signaling (49) (Table IV).

Unlike the undefined effects of Notch1 signaling on ECs and VSMCs, the negative role of Notch1 signaling in macrophages has been verified by a series of studies performed by different groups, as described above. As such, *Ganoderma lucidum* triterpenoids and polysaccharides targeting the Notch1-Dll4 axis (50) or ganoderic acid A targeting the Notch1/peroxisome proliferator-activated receptor gamma/CD36 axis (51) have been proven to attenuate atherosclerosis. Celery seed extract can inhibit the Notch1/NF-κB pathway to block peroxide injury in macrophages (52). The Notch1/NF-κB pathway is also inhibited by niacin to alleviate the inflammation of macrophages (24). These findings suggest that pharmacological intervention which inhibits Notch1 signaling in macrophages holds great potential as a promising strategy with which to improve the outcomes of patients afflicted by atherosclerosis (Table II).

3. Role of Notch1 signaling in reendothelialization and neovascularization

Reendothelialization is often defined as an endothelial compensation at the injured sites that enhances endothelial recovery and restrains neointimal thickening during atherosclerosis (53). Ii *et al* (53) found opposite effects for cholesterol (positive) and Notch1 (negative) in endothelial progenitor cell (EPC) activity, eventually influencing reendothelialization during arterial injury in hypercholesterolemic mice.

VSMC-EC co-culture increases the bone morphogenetic protein receptor 2-dependent deposition of collagen IV in ECs. Such an accumulation triggers the downstream integrin-linked kinase/phospho-c-Jun N-terminal kinase/presenilin1/Notch1 axis, which enhances the glucose metabolism and acetylation level of both Notch1 and MYC gene enhancers. These effects promote the expression of genes critical in EC regeneration and the maintenance of endothelial monolayer integrity following arterial injury (54).

Postnatal angiogenesis and vasculogenesis are two main forms of neovascularization, which act to bypass blocked arteries and maintain heart perfusion following MI. Angiogenesis refers to the process of the formation of new blood vessels from pre-existing ones via budding. In parallel, vasculogenesis is a process of the *de novo* formation of blood vessels and is slower than angiogenesis. These procedures are partially mediated by pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor. Therapeutic angiogenesis for revascularizing ischemic tissues is considered a promising strategy with which to facilitate the remodeling of cardiac blood supplies (55). Of note, hyperglycemia in diabetic mice has been found to increase the expression of Notch pathway proteins (Notch1, Hes1 and Hes5) in bone marrow EPCs with reduced colony-forming, differentiation, mobilization and migratory capabilities, while the inhibition of the Notch pathway restores such vasculogenic dysfunction (56). Jiang *et al* demonstrated that deficiency in cathepsin K impaired Notch1 intramembranous cleavage and downstream signaling transduction (Hes1, Hey1/2, VEGF and p-Akt), thus attenuating EC/EPC neovascularization in response to hypoxic stress (57).

Several studies have emphasized the distinct roles of Dll4 and Jagged1 as regards physiological angiogenesis. The expression of Dll4 in endothelial tip cells is considered to activate Notch signaling and suppress the tip phenotype in adjacent stalk ECs. This in turn suppresses the emergence of excessive sprouting and maintains intact and functional vascular networks. The consequential downregulation of VEGF receptor (VEGFR) and the reduced responsiveness to VEGF are the main mechanisms underlying the activity of Dll4. By contrast, Jagged1 has been found to promote tip cell formation and sprouting by antagonizing Dll4-Notch signaling in angiogenic endothelium (58). These antagonistic conditions regulated by Jagged1 and Dll4 in neovascularization have aroused immense interest. The deacetylative ability of sirtuin 1 facilitates an increased expression of nicotinamide phosphoribosyltransferase/nicotinamide adenine dinucleotide in EPCs (55). This causes a response to ischemia-induced energy stress, inhibits anti-angiogenic Dll4-Notch1 signaling, and thereby promotes the response to VEGF via upregulating VEGFR-2 and VEGFR-3 (55). Furthermore, a simultaneous increase in the sensitivity to Jagged1 jointly contributes to enhanced EPC mobilization, proliferation, migration and tube formation (55). Similarly, the suppressive effects of Matrix Gla protein on Jagged1 expression reinforce the resolution phase of angiogenesis and vascular stabilization (58). In bone marrow microenvironments, Jagged1 signaling is pivotal for the functional kinetics of bone marrow-derived EPCs, which leads to a more participatory role of EPCs in ischemic neovascularization (59). The effect of blood flow on angiogenesis in response to hypoxic stimulation also requires the participation of Dll4/Notch signaling since blood flow was shown to suppress vascular Notch signaling in zebrafish embryos via a transcriptional downregulation of Dll4. The absence of blood flow offsets the excessive angiogenesis driven by hypoxia signaling (60).

In peripheral ischemic mouse models, Dll4 has been found to be upregulated and its inhibition causes a chaotic orientation of capillary sprouts and induces the formation of an profuse, yet inefficient angiogenesis (9). Beyond that, blocking the Dll4/Notch interaction has been found to cause excessive leukocyte homing due to elevated release of both chemoattractant CXC ligand 1 in a mouse model and its human functional homolog IL-8, which further suggests a diverse role of Dll4/Notch signaling to coordinate interactions between inflammation and angiogenesis under reparative courses (9).

Notably, in human umbilical vein ECs, Dll4 expression is induced by VEGFA-VEGFR2 binding and has been shown to strengthen the paracrine activation of Notch signaling in adjacent ECs. These stimulated neighboring cells increase the expression of fatty acid-binding protein 4, which promotes the subsequent pro-angiogenic behaviors of ECs unexpectedly. This suggests an indirect pro-angiogenic effect of the well-known angiogenesis-restricting role of Dll4-Notch signaling (61).

In addition to EPCs and ECs, other types of cells participate in neovascularization. Xu *et al* found that simvastatin robustly enhanced the differentiation of bone marrow stromal cells into functional ECs via the activation of Notch signaling components, such as Dll4, Presenilin-1, Notch1, Notch4 and Hes5 (62). The co-culture of human bone marrow-derived EPCs/human bone marrow-derived mesenchymal stem cells has been found to enhance cell proliferation and angiogenic capacity, and the underlying mechanism was attributed to the crosstalk between platelet-derived growth factor and Notch1 (63).

Notch1 signaling is widely involved in reendothelialization and neovascularization, while its functions are slightly different or sometimes contradictory. Differences are mainly due to the diversity of upstream stimulatory signals, the cellular context and induced downstream pathways. Even with respect to the well-known neovascularization balance fine-tuned by the Jagged1-DLL4 system, the outputs are somewhat elusive due to different effectors being recruited downstream (61). Nevertheless, the ubiquity of Notch1 signaling and its sensitive response to various types of stimuli from cell microenvironments indicate its critical role in vascular network reconstitution in IHD.

4. Role of Notch1 signaling in myocardial fibrosis

Upon the establishment of MI, numerous cardiomyocytes die from ischemia. Being restricted by their limited regeneration capacity, the majority of these necrotic or apoptotic cardiomyocytes in the infarct area are replaced by a fibrotic scar in a process known as replacement fibrosis. Moreover, myocardial tissues located at the infarct boundary and remote to the infarction undergo reactive fibrosis. Both forms of fibrosis are mediated by cardiac fibroblasts. Initially, quiescent fibroblasts are stimulated by ischemia to proliferate, migrate and transform into myofibroblasts. This serves to maintain cardiac integrity, whereas it results in pathological cardiac remodeling (64). Recent research indicates that pro-fibrogenic transforming growth factor-β1 (TGF-β1)/mother against decapentaplegic homolog 3 (Smad3) signaling is antagonized by an interaction between NICD and Smad3, which impedes cardiac fibroblasts to differentiate into myofibroblasts and limits excessive myocardial fibrosis (65).

In agreement with the role of Notch signaling (10,65-68), the injection of cell-free self-assembling peptide hydrogels containing a peptide mimic of Jagged1 into rats immediately post-MI has been shown to benefit the heart via ameliorating cardiac fibrosis (69). However, a recent finding confirmed that oxymatrine, a component of the Chinese herb, Sophora japonica, exerted anti-fibrotic effects by blocking the TGF-β1-induced Notch activation in cardiac fibroblasts isolated from neonatal rats, suggesting the potential synergistic effects of Notch and TGF-β signaling during fibroblast-myofibroblast transition (70).

In the majority of cases, the activation of Notch1 signaling inhibits myocardial fibrosis, particularly through TGF-β. Nonetheless, it is worth noting that Notch1 and TGF-β signaling are not always antagonistic. In fact, the overexpression of Notch1 has been reported to promote lung fibroblast transition into myofibroblasts (71) and to cooperate with TGF-β1 signaling to aggravate kidney fibrosis (72,73). These data suggest that Notch1 and other fibrosis-related signaling molecules may crosstalk to positively or negatively regulate fibrosis in different contexts.

5. Role of Notch1 signaling in ischemia-reperfusion injury

Timely and effective reperfusion treatments, such as thrombolytic therapy, percutaneous coronary intervention and coronary bypass surgery have been extensively employed as major therapeutic approaches to restore blood supply and alleviate ischemic injury. However, reperfusion itself exacerbates myocardial injury in a process known as MI/reperfusion injury (MI/RI). The mechanisms of MI/RI are multifactorial, essentially consisting of nitroxidative stress, inflammation and intracellular and mitochondrial Ca^{2+} overload. These processes result in mitochondrial dysfunction, lipid peroxidation, and DNA and protein damage that can trigger cardiomyocyte apoptosis or necrosis (74,75). Currently available methods for the treatment of MI/RI are ineffective and their underlying mechanisms have not yet been fully elucidated. For instance, relaxin has been shown to facilitate the upregulation of Notch1 signaling, and decrease cardiac muscle cell apoptosis and nitroxidative damage (76), while microgravity can ameliorate MI/RI via the restriction of Notch1 signaling (77). Overall, these studies support the protective role of Notch1 inhibition in MI/RI.

There is extensive literature to indicate that Hes1 can bind to tumor suppressor gene phosphatase and tensin homology deleted on chromosome 10 (PTEN) promoter and thus inhibit its activity. A previous study characterized a PTEN/Akt-mediated anti-oxidative and anti-nitrative mechanism employed by Notch1 to decrease MI/RI (74). In diabetic rats, polydatin administration was shown to protect against oxidative/nitrative stress during MI/RI via the Notch1/Hes1-mediated activation of PTEN/Akt signaling (78).

In non-diabetic rats undergoing MI/RI surgery and high-glucose infusion treatment, Yu *et al* (79) revealed that acute hyperglycemia aggravated MI/RI, whereas melatonin reversed this effect. The underlying mechanism was attributed to the Notch1/Hes1/Akt pathway and its downstream thioredoxin antioxidant system (79). As a pivotal member of enzymatic antioxidant defenses, manganese superoxide dismutase expression has been shown to be enhanced by Notch1/Janus activated kinase signal transducer 2/STAT3 signaling in the rat myocardium following burn injury, which is a model that shares a similar pathogenesis with the ischemia-reperfusion model (80).

Serving not only as the main source, but also as targets for reactive oxygen species (ROS)-induced damage, the mitochondria have emerged as major contributors to the pathogenesis of MI/RI. Pei *et al* (81) indicated that melatonin preserved mitochondrial integrity and function by modulating the Notch1/mitochondrial fusion-associated protein 2 (Mfn2) pathway, which positively disturbed the vicious cycle of oxidative stress occurring in mitochondria during MI/RI. Notch1/Keap/Nuclear factor E2-related factor 2 signaling can protect the heart against MI/RI by inhibiting mitochondrial ROS generation and improving mitochondrial bioenergetics (82).

Being mainly regulated by mitochondrial dynamics (fission and fusion) and mitophagy, mitochondrial quality control also affects mitochondrial homeostasis in MI/RI (83). Indeed, Zhou *et al* (83) reported that Notch1 overexpression improved cell viability and adenosine triphosphate production, increased mitochondrial fusion, and inhibited mitochondrial fission and mitophagy. This was attributed to the inhibition of PTEN-induced putative kinase 1/Mfn2/Parkin signaling induced by Notch1 overexpression (83).

Endoplasmic reticulum (ER) stress is another key component of the pathogenesis of MI/RI, in which the protective unfolded protein response aims to attenuate cell damage (84). Notably, Zhang *et al* (84) revealed that 2,3,5,4'-tetrahydroxy stilbene-2-*O*-β-D-glucoside reduced ER stress by activating Notch1/Hes1 signaling, with the downstream ER stress-related signal cascade being affected.

Contrary to the aforementioned protective role of Notch1 signaling in MI/RI, curcumin has been suggested to attenuate the oxidative stress and apoptosis of H9C2 cells undergoing hypoxia/reoxygenation through an unexpected inhibition of Notch signaling. Treatment with Jagged1 has been shown to reverse this effect (85).

Several microRNAs (miRNAs/miRs) also participate in MI/RI by regulating Notch1. For example, when subjected to hypoxia/reoxygenation, the inhibition of miR-449a has been

found to upregulate Notch1/Hes1 signaling to ameliorate cell apoptosis and necrosis (86). Likewise, miR-322, which is mainly produced by ECs, increases the level of NICD in the myocardium, thus eliciting cardioprotection (87). Upon MI/RI, the elevated level of miR-208a downregulates the expression of the chromatin remodeling protein, CHD9, and consequently activates Notch/NF-κB signaling to promote cell apoptosis (88). In parallel, miR-374 has been found to block the Notch1 axis by downregulating cell signaling-related cytoplasmic protein dystrobrevin α to protect against MI/RI in rats (89). The upregulation of long non-coding RNA-zinc finger antisense 1 has been demonstrated to facilitate Notch1 downregulation due to DNA methylation, thus triggering cardiomyocyte apoptosis and ROS production during MI/RI (90). These observations suggest a promising, yet but unclear participation of Notch1 epigenetic processes in the development of IHD.

Ischemic pre-conditioning (IPC) and ischemic post-conditioning (IPost) have been proven to activate various pro-survival signaling molecules that provide cardioprotection in MI/RI. Yu and Song (91) reported that Notch1 signaling decreased cardiomyocyte apoptosis in IPost by regulating mitochondrial-mediated apoptosis. Further investigations have clarified that an elevated Hes1 expression in IPost is dependent on PTEN so as to influence the activity of the reperfusion injury salvage kinase pathway (92) and STAT3 (93). Notch1 also mediates cardioprotection due to IPC by regulating STAT3 phosphorylation (94). The Notch1/Hes1 signaling pathway is activated by IPC/IPost and has been confirmed to directly downregulate the expression of voltage-dependent anion channel 1 and relieve MI/RI (95).

In summary, the effects of Notch1 signaling on MI/RI mainly involve the regulation of nitroxidative stress-related signaling, mitochondrial homeostasis and ER stress. However, there is still a pressing need for the clarification of the participation of Notch1 signaling in other pathological mechanisms underlying MI/RI.

6. Role of Notch1 signaling in cardiac regeneration

Cardiac regenerative therapies, such as cell-based therapeutics, tissue engineering and reprogramming of scar fibroblasts have gained increasing attention as promising treatments for the regeneration of myocardial tissues in IHD (96). Among the various approaches, stem cell therapies are extremely attractive. Embryonic stem cells (97) and multiple adult stem cells, including bone marrow-derived stem cells (BMCs), such as bone marrow-derived hematopoietic stem cells (98), bone marrow-derived mesenchymal stem cells (BM-MSCs) (99), bone marrow-derived EPCs (BM-EPCs) (100), as well as adipose-derived stem cells (ASCs) (101) have been extensively investigated. However, current obstacles in stem cell therapies, such as ineffectiveness in cell preparation, engraftment, survival, host immune rejection and the insufficient understanding of underlying mechanisms have all severely hindered the progress of regenerative therapy.

Role of Notch1 signaling in embryonic stem cells. Embryonic stem cells can be readily isolated from the inner cell mass of blastocysts and can be maintained indefinitely *in vitro* (102). Embryonic stem cells have immense potential in the field of regenerative medicine, as they are able to differentiate into every type of cell and tissue in the body, including cardiomyocytes (97). Nemir *et al* (102) suggested that Notch1 activation can shift the differentiation of embryonic stem cells into neuroectodermal fates, instead of cardiomyocyte fates. This conclusion is partly consistent with observations of the biphasic effect caused by Notch activation (103), in which cardiac differentiation is hampered at the pluripotent state, but is reinforced at cardiovascular progenitor stages under the precise induction of microparticle-based Notch-signaling biomaterials. Embryonic stem cells and induced pluripotent stem cell transplantation into a post-infarction mouse model with doxorubicin-induced cardiomyopathy have been shown to stimulate Notch1/Hes1/PTEN/Akt signaling and ameliorate myocardial apoptosis and fibrosis (104). Tsang *et al* (105) indicated that hypoxia-mediated embryonic stem cell differentiation into functional arterial ECs occurred due to the activation of the hypoxia-inducible factor-1α (HIF-1α)/ETS variant transcription factor 2/Notch1 signaling axis.

This temporally dependent biphasic effect exerted by Notch1 signaling over the course of cardiac differentiation suggests that the timing of Notch1 signaling activation according to the developmental stage contributes to embryonic stem cell fate decisions.

Role of Notch1 signaling in BM-MSCs. BM-MSCs can differentiate into multiple lineages, including cardiogenic cells and can be easily obtained and handled. Therefore, BM-MSCs have been widely investigated for stem cell therapy (106). Ding *et al* (107) observed that in c-Kit^{POS}/Nkx2.5^{POS} bone marrow stem cells, the targeted activation of Notch1 signaling promoted their differentiation into cardiac lineages, particularly cardiomyocytes. The classic cell-to-cell interactive manner of Jagged1/Notch1 signaling activation contributes to the differentiation of mesenchymal stem cells into cardiomyocytes *in vitro* and *in vivo* (99). Boopathy *et al* (106) reported that oxidative stress induced the expression of Notch1 and its downstream targets, Hes5, Hey1 and Wnt11, thus increasing the expression of cardiogenic genes.

In addition to cardiomyocyte differentiation, other biological behaviors of MSCs are also regulated by Notch1. For instance, HIF-1α overexpression promotes NICD cleavage and SUMOylation, thus promoting the Notch1-dependent migration and invasiveness of MSCs (108). The global hemizygous deletion of Notch1 in bone marrow-derived cells also decreases the recruitment, proliferation and survival of MSCs in the infarcted zone (109).

In summary, Notch1 exerts a relatively clear effect on promoting activity and cardiomyocyte differentiation of MSCs. This suggests that stimulating Notch1 signaling in MSCs may be conducive to translational stem cell therapies in MI.

Role of Notch1 signaling in BM-EPCs. The therapeutic application of BM-EPCs from peripheral blood in cardiac regeneration has been demonstrated. Specifically, is has been demonstrated that the co-culture of EPCs with neonatal cardiomyocytes induces the activation of Notch1 signaling by cell-to-cell communication (99); subsequently, activated Notch1, with the assistance of Wnt proteins, promotes the expression of the cardiac markers in EPCs (100). Although

the incidence of the cardiomyogenic commitment of EPCs is relatively low, the full clarification of the molecular pathways related to cardiac differentiation, such as Notch1 signaling, may help to amplify the cellular repair capacity.

Role of Notch1 signaling in ASCs. Another easily accessed type of stem cell, ASCs, also has the potential to differentiate into cardiomyocytes (101,110). The differentiation of ASCs into cardiomyocyte-like cells is enhanced by miR-1 overexpression, which stimulates Notch1/Hes1 signaling (101). It has been confirmed that serum exosomes isolated from mice that experienced MI can be internalized by ASCs, and that miR-1956, which is enriched in MI serum exosomes, is transferred into adipose tissue-derived mesenchymal stem cells. Such transference thus promotes stem cell-mediated angiogenesis through Notch1/VEGF signaling (111). However, ASCs result in a limited renewal of impaired myocardium, given their lower differentiation efficiency. Thus, targeting Notch1 signaling may be beneficial for enhancing the efficacy of ASCs to regenerate cardiac tissue in MI.

Role of Notch1 signaling in cardiomyocyte regeneration. The limited regeneration of cardiomyocytes has been shown to occur in adult mammals following cardiac injury (112). Further studies have assessed the effects of Notch1 in cardiomyocyte regeneration. In the border zone of the infarct region, a complex network containing hepatocyte growth factor/c-Met, Notch/Hes1 and phosphatidylinositide 3-kinase/Akt signaling axes endows injured cardiomyocytes with pro-survival benefits, as indicated by improved cardiac function and proliferative signaling (113). Similarly, the induction of supplemental intracellular Notch1 signaling in the adult mouse myocardium post-MI reveals a positive influence by promoting cardiomyocyte survival (114). The comparability of the infarct size and cardiac function between cardiac-specific Notch1 knockout mice and control mice following left anterior coronary artery ligation also indirectly supports the aforementioned notions (109). However, contrary to these observations, the reactivation of the Notch1 pathway using viral vectors in the cardiomyocytes of adult mice post-MI is largely ineffective to stimulate cardiomyocyte proliferation, which is attributed to permanent epigenetic modifications at Notch responsive promoters (115).

Unlike mammals, zebrafish exhibit a complete regenerative capacity of their hearts following damage. This renders the taxa a model species for exploring the molecular mechanisms of cardiomyocyte regeneration. Preceding heart regeneration, there is a marked Notch1 activation throughout the endocardium of the ventricle in zebrafish (116). In a zebrafish model undergoing ventricular amputation, robust cardiac regeneration has been observed after Notch signaling is activated in the endocardium and epicardium (117). The cryoinjury-based treatments of zebrafish hearts indicate that Notch and serpine1 signaling participate in cardiac regeneration and affect cardiomyocyte proliferation in adjacent tissues (118). Zhang *et al* (119) reported that the *in vivo* destructive ablation of zebrafish ventricular cardiomyocytes induced atrial-to-ventricular cardiomyocyte trans-differentiation through Notch1 signaling activation in the atrial endocardium, which potentially introduced a novel endogenous source for regenerative therapy.

These zebrafish-based cardiomyocyte regeneration studies provide an excellent platform for the investigation of determinants for cardiomyocyte proliferation. Furthermore, experiments targeting Notch1 signaling have been performed and should continue to provide an excellent reference for its value in cardiomyocyte renewal of the mammalian heart.

7. Conclusions and future perspectives

The present review identified Notch1 signaling as an ubiquitous mediator that widely participates in the development of atherosclerosis, cardiac remodeling and the modulation of MI/RI, and is possibly a novel target which can be used improve cardiac regeneration. The responses of ECs, VSMCs and macrophages dominate the dynamics underlying the progression of atherosclerosis with the participation of Notch1 signaling. Notch1 signaling is also associated with a series of complicated remodeling processes following MI, including myocardial fibrosis and vascular remodeling. Furthermore, the effects of Notch1 signaling on MI/RI and emerging regenerative therapy have been discussed in detail. Accumulating evidence underlines a promising approach of targeting Notch1 signaling for the treatment of IHD.

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Authors' contributions

All authors (XP, SW, HC and MC) contributed to conceptualization, designing, writing, drafting, revising, editing and reviewing of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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