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Immune Regulator Retinoic Acid-Inducible Gene I (RIG-I) in the Pathogenesis of Cardiovascular Disease

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Retinoic acid-inducible gene I (RIG-I) is a cytosolic pattern recognition receptor that contains two CARD domains, an RNA helicase domain, and a C-terminal domain. RIG-I initiates antiviral innate immunity by recognizing exogenous viral RNAs/DNAs. However, some studies have reported that RIG-I activation leads to damage in various organs and tissues in diverse circumstances. Recent studies have shown that RIG-I is involved in cancer, lupus nephritis, immunoglobulin A nephropathy, Crohn's disease, and atherosclerosis. These reports indicate that RIG-I not only participates in antiviral signaling pathways but also exerts an influence on non-viral infectious diseases. RIG-I is widely expressed in immune and non-immune cells including smooth muscle cells, endothelial cells, and cardiomyocytes. A succinct overview of RIG-I and its signaling pathways, with respect to the cardiovascular system, will aid in the development of novel therapeutics for cardiovascular diseases. In this review, we summarize the structure, activation, signaling pathways, and role of RIG-I in cardiovascular diseases.

Keywords: RIG-I, activators, signal pathway, inflammation, cardiovascular diseases

INTRODUCTION

The innate immune response serves as the first line of defense against pathogens and transfers signals to activate the adaptive immune system to eliminate invading pathogens (1). Short-term activation of the innate immune system is beneficial for the elimination of pathogenic microorganisms, and tissue repair. However, sustained or excessive innate immune activation is unfavorable and detrimental to organs (2–4). Pattern recognition receptors (PRRs) expressed in the innate immune cells mediate innate immune responses (5) and accelerate inflammation. PRRs are divided into four groups: Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), and C-type lectin receptors (CLRs) (6). RLRs play a crucial role in recognizing viruses and triggering inflammation (7).

RLRs include MDA5 (melanoma differentiation-associated factor 5), LGP2 (laboratory of genetics and physiology 2), and RIG-I (retinoic acid-inducible gene I) (8). RIG-I is the first identified RLR and is induced by all-trans retinoic acid in acute promyelocytic leukemia cells (9). Thus far, RIG-I has been of interest and explored; it can detect RNA virus infection and induce production of interferon (IFN), inflammatory cytokines, and chemokines (10) *via* stimulation of transcriptional factors, including interferon regulatory factor (IRF), nuclear factor-κB (NF-κB), and activator protein-1 (AP-1). To date, the structure, activation, signaling pathways, and function of RIG-I in innate immunity have been well documented (11). However, many new insights into the other biological functions of RIG-I have emerged to extend the role of RIG-I as a PRR. Accumulating evidence has shown that RIG-I participates in cellular damage and the occurrence and development of many diseases, such as acute myeloid leukemia (AML), hepatocellular carcinoma, lupus nephritis, immunoglobulin A nephropathy, Crohn's disease, rheumatoid arthritis, and cardiovascular diseases (CVD) (12–18).

CVD is one of the main causes of death worldwide and imposes a heavy economic burden on families and society (19). The pathogenesis of CVD is complex. It involves many pathological processes including endothelial cell dysfunction, proliferation and migration of vascular smooth muscle cells (VSMCs), apoptosis, cardiomyocyte hypertrophy, fibrosis, and heightened inflammatory response. Experimental studies have focused on the effect of RIG-I-mediated inflammation in the development and complications of human cardiovascular diseases (20), indicating the potential of RIG-I as a therapeutic target in the treatment of cardiovascular diseases. This review elucidates the role of RIG-I in the etiology of cardiovascular dysfunction and the pathogenesis of cardiovascular disease.

THE STRUCTURE OF RIG-I

Human RIG-I is encoded by DDX58, which maps to chromosome9p21.1 and comprises 18 exons. RIG-I is a cytosolic protein containing 925 amino acids and the length of its mRNA is 2775 bp (21). It is a member of the RLR family and contains two N-terminal caspase active recruitment domains (CARDs), a catalytic helicase core consisting of two RecA-like domains (Hel1 and Hel2), and a C-terminal domain (CTD) (22, 23). The two N-terminal CARDs are essential for initiating downstream antiviral signaling molecular transduction by binding to the mitochondrial antiviral signaling protein (MAVS). The catalytic helicase core has ATPase and translocase activities, which are essential for binding RNA and catalyzing ATP hydrolysis. The C-terminal domain (CTD), also known as the repressor regulatory domain (RD), is necessary for RNA-terminus recognition (24–26).

THE ACTIVATION OF RIG-I

As a key intracellular viral RNA sensor, RIG-I is activated by short (<300bp) double-strand RNA and 5'-triphosphate single-strand RNA to promote the formation of interferons that trigger and mediate antiviral responses (27–29). RIG-I can specifically distinguish cytosolic viral dsRNAs from self-RNAs, with its ATPase activity playing a crucial role in this discrimination (30). Self RNAs do not activate RIG-I signaling because their 5'ppp is capped by 2'O-methylation (31, 32). Moreover, deficiencies in these aspects cause autoimmune disease *via* self-RNAs that activate RIG-I signaling (33, 34). Other studies have shown that RIG-I can detect single-strand RNA (ssRNA) viruses to mediate antiviral responses during infection (28, 35, 36). Saito et al. found that the hepatitis C virus could also be detected by RIG-I *via* binding to the A/U-rich motif in the 3′-untranslated region of the genome (37). In addition to viral RNAs, many analogs of double-stranded RNA, including poly(I: C) and poly (A: U) are specifically recognized by RIG-I (38). A recent study reported that mitochondrial RNA triggers a RIG-I-MAVS-dependent immune response (39).

Several DNA sensors including TLR9, AIM2, and cGAS have been identified (40–42). RIG-I, a cytosolic RNA receptor, also recognizes cytosolic DNA to selectively activate the expression of type I IFN genes (43). Furthermore, studies have shown that apart from RNA/DNA, lipopolysaccharide (LPS) (44), interferon-gamma (45), interleukin (IL)-1β (46), and TNF-α (47) also activate RIG-I signaling to mediate the inflammatory response. Furthermore, RIG-I mediates LPS- or IFN-γ-induced inflammation in endothelial cells and vascular smooth muscle cells, indicating that RIG-I is crucial in non-antiviral inflammation-related diseases. Considering the pathogenic roles of these new RIG-I activators in the elderly, patients in ICU, patients with organ transplantation, and patients with immune deficiency (48–51), targeting RIG-I could be a therapeutic option for these patients. These activators of RIG-I are summarized in **Table 1**. The above-mentioned studies indicate the pleiotropic functions of RIG-I.

The Antiviral Signaling Pathway of RIG-I

Studies on virus infection provide fundamental information on the RIG-I signaling pathway. RIG-I is an auto-regulated protein that exhibits auto-inhibition of the interaction between the CTD and CARD domains. During viral infection, viral dsRNA binds to the CTD domain and the N-terminal CARD is exposed for downstream signaling (23). RIG-I then interacts with the adaptor protein MAVS through a CARD-CARD interaction. MAVS is also known as a virus-induced signaling adaptor (VISA), CARD adaptor inducing IFN-β (Cardif), and IFN-β promoter stimulator (IPS-1). MAVS is located in the mitochondrial outer membrane *via* its C-terminal transmembrane (TM) domain (52). It interacts with RIG-I *via* CARD-CARD domains (53).

The RIG-I/MAVS signaling pathway is divided into two branches, with one branch inducing the production of type I interferons and other inducing the production of pro-inflammatory cytokines. During the production of type I interferons, MAVS recruits TANK-binding kinase 1(TBK1) and inhibitor of κB kinase (IKKε) to phosphorylate the transcription factors, interferon regulatory factors IRF-3 and IRF-7, to phosph-IRF3 and phosph-IRF7, respectively. The

TABLE 1 | Activators of RIG-I.

Categories	Activators
RNA	dsRNAs; 5'-triphosphate single-stranded RNA; poly I:C; poly(rU): poly(rU) RNA; mitochondrial RNA
DNA	DNA
Others	LPS; IFN-γ; IL-1β; TNF-α

phosphorylated factors translocate to the nucleus and induce the production of type I interferons (54). On the other branch, MAVS recruits IKKα, IKKβ, and IKKγ to induce the phosphorylation and destruction of IκBs for the activation of nuclear factor 'kappa-light-chain-enhancer'(NF-κB), which promotes the expression of pro-inflammatory cytokines (55).

Unlike the RNA-RIG-I pathway, the DNA-RIG-I pathway can interact directly with DNAs or an RNA intermediate derived from DNA through RNA polymerase III transcription (43, 56). The recognition of DNAs or DNA-derived RNA intermediate depends on the type of cell line and the structure of the DNA and DNA-derived RNA. The RNA-RIG-I pathway can activate IRF3/7 and NF-κB for inducing production of type I interferons and pro-inflammatory cytokines, respectively; whereas, the DNA-RIG-I pathway primarily activates the transcription factor IRF3 to generate type I IFNs. These results indicate the diverse role of RIG-I in the response to RNA- or DNA-containing pathogens. The RIG-I antiviral signaling pathway is shown in **Figure 1**.

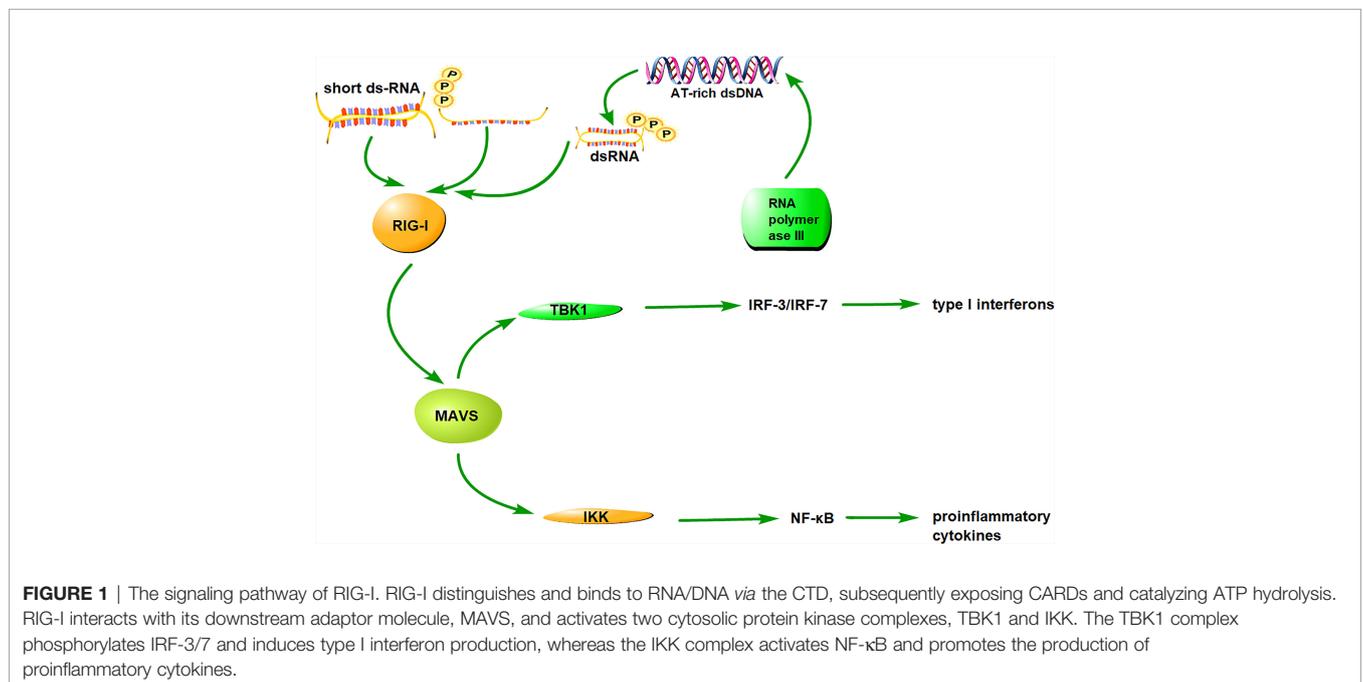## RIG-I in Regulating the Function of Cardiovascular Cells and Macrophages

It is known that both the injury of the cardiovascular cells and the activation of inflammatory cells contribute to the pathophysiology of cardiovascular system. During the occurrence and development of cardiovascular diseases, RIG-I

in cardiovascular cells and macrophages was reported to be of importance in the disease pathology.

RIG-I in Endothelial Cell Dysfunction

The endothelium, which lines the interior surface of blood vessels plays an important role in controlling vascular permeability. Vascular endothelial cells have an essential function in restraining inflammation and avoiding thrombosis (57). Thus, they play a critical role in acute and chronic inflammation (58, 59). Vascular endothelial cells participate in immune and inflammatory reactions by inducing the expression of various cytokines and adhesion molecules. Additionally, the inflammatory response of endothelial cells leads to a pro-thrombotic state (coagulopathy, increased vascular permeability, arterial hypotension, and organ dysfunction) and increases the risk of cardiovascular diseases (60).

Studies have shown that RIG-I activates innate immunity and inflammation to promote endothelial cell (EC) dysfunction. Dengue virus (DENV) induces RIG-I activation in microvascular endothelial cells to increase the production of type I IFN, ICAM-1, and other pro-inflammatory cytokines, resulting in endothelial injury (61). In porcine circovirus disease (PCVD), porcine circovirus type 2 (PCV2) upregulates the production of inflammatory factors in arterial endothelial cells *via* the RIG-I signaling pathway, which eventually leads to endothelial dysfunction and vascular system disorders (62). In addition, RIG-I activation by RIG-ligand 3p-RNA induces endothelial damage by enhancing reactive oxygen species (ROS) formation and pro-inflammatory cytokine release, contributing to atherogenesis (63). Poly (I:C), an analog of double-stranded RNA, impairs sodium nitroprusside (SNP)-induced rat superior mesenteric artery relaxation by activating the RIG-I/NF-κB/iNOS pathway (64). The above studies suggest

FIGURE 1 | The signaling pathway of RIG-I. RIG-I distinguishes and binds to RNA/DNA *via* the CTD, subsequently exposing CARDs and catalyzing ATP hydrolysis. RIG-I interacts with its downstream adaptor molecule, MAVS, and activates two cytosolic protein kinase complexes, TBK1 and IKK. The TBK1 complex phosphorylates IRF-3/7 and induces type I interferon production, whereas the IKK complex activates NF-κB and promotes the production of proinflammatory cytokines.

that the antiviral process mediated by RIG-I signaling could be accompanied by inflammatory injury in endothelial cells. Thus, it is imperative to consider targeting RIG-I as a therapeutic strategy for the treatment of virus-related diseases.

As mentioned previously, RIG-I activation by viral RNA or RNA analogs induces endothelial damage. RIG-I activation by non-viral ligands also plays an important role in mediating endothelial injury. For example, LPS induces the expression of RIG-I in endothelial cells, and RIG-I overexpression selectively upregulates the expression of COX-2, which participates in inflammation and vascular injury (44). Moreover, LPS activates RIG-I to upregulate the expression of proinflammatory molecules in endothelial cells to mediate sepsis (65, 66). In addition, Imaizumi et al. observed that IFN-γ induced RIG-I expression, which mediated immunological reactions and inflammatory responses in HUVECs, leading to endothelial damage (45). Furthermore, Wang et al. showed that 25-hydroxycholesterol promoted inflammation in HUVECs *via* the IRF1/RIG-I axis, which contributed to atherosclerosis (20). These results indicated that activation of RIG-I by non-viral ligands promotes endothelial damage by enhancing the inflammatory response. Moreover, in addition to the effect of RIG-I on inflammation-mediated endothelial dysfunction, a study demonstrated the effect of RIG-I on the pro-thrombotic state. They found that dsDNA poly(dA: dT) and hepatitis B virus induced the expression of prothrombotic proteins in vascular endothelial cells, which accelerated microvascular thrombus formation *in vivo* and promoted upregulation of von Willebrand factor (vWF) and platelet tethering *via* RIG-I signaling (67).

Taken together, these studies demonstrate that RIG-I activation leads to endothelial cell injury and dysfunction by enhancing inflammation and thrombosis. Blockade of RIG-I signaling in non-viral diseases associated with inflammatory injury of endothelial cells might be beneficial for maintaining the integrity of the endothelium.

RIG-I in Vascular Smooth Muscle Cell Dysfunction

Smooth muscle cells (SMCs) are one of the major components of the vascular wall and involved in vascular disorders such as vasospasm, hypertension, and atherosclerosis. Proliferation, migration, dedifferentiation, and apoptosis of vascular SMCs contribute to the pathogenesis of vascular diseases (68). A recent report showed that IFN-γ induced RIG-I expression in SMCs *in vivo* and *in vitro* (69). A previous study also found that G3BP1 interacts with RIG-I and further activates MAVS to act on aortic SMCs and drive aortic calcification. Accordingly, a G3BP antagonist downregulated RIG-I-stimulated G3BP1 methylation; hence, RIG-I and MAVS deficiency reduced osteogenic signals in VSMCs, attenuating arteriosclerosis (70). Another study showed that lncRNA growth-arrest-specific transcript 5 (GAS5) induced SMC apoptosis and subsequent abdominal aortic aneurysm (AAA) by activating the zeste homolog 2 (EZH2)-mediated RIG-I signaling pathway in angiotensin II-induced AAA mouse models (71). These evidences highlight that RIG-I activation contributes to SMC dysfunction and vascular diseases, including aortic calcification

and abdominal aortic aneurysms. Further research on the detailed mechanisms of RIG-I in SMC dysfunction and related diseases is required.

RIG-I in Cardiac Cell Pathology

Cell death including apoptosis, necrosis, and pyroptosis, are well-documented in heart disease (72). A previous study showed that RIG-I activator TNF-α upregulated the expression of RIP3, which was sufficient to induce necroptosis of cardiomyocytes during myocardial infarction (73). However, another study reported that TNF-α played a protective role in the early-stage of myocardial infarction in line with the regulation of autophagy and apoptosis (74). As for the role of another RIG-I activator IFN-γ in cardiomyocyte death is unclear. Considering the importance of cardiomyocyte death under various insults and the established role of IFN-γ in cell death (75), it would be worthwhile to further explore the role of RIG-I in IFN-γ associated-cardiomyocyte death. In cardiac fibroblasts, stimulation of RIG-I promoted the production of pro-inflammatory cytokines such as IL-6 and IL-8, contributing to heart injury and cardiomyopathy (76). This evidence suggests a pathogenic role for RIG-I in heart disease. However, in a pressure overload-induced cardiac hypertrophy and heart failure model, the RIG-I signaling pathway mediated the protective role of ADRB3 depletion by enhancing the innate immune response in the heart (77). Another study demonstrated the remodeling of scar fibroblasts into cardiomyocytes and thereby defined the protective role of RIG-I in heart repair. Hu et al. observed that a stabilized RNA, ICR2, increased the level of cardiomyocyte-specific genes in reprogrammed "fibroblasts" and enhanced their ability to differentiate into cardiomyocytes *via* the RIG-I and TLR3 pathways (78). In addition to the discrepancy in the above findings, the role of RIG-I in cell senescence is also controversial. Some studies have reported that RIG-I mediates senescence-associated inflammation (79, 80), while another study suggested that RIG-I inhibited cellular senescence by negatively regulating the integrin β3/p38 MAPK pathway (81). Therefore, the role of RIG-I in cardiac cell senescence requires further investigation. Overall, these controversial findings related to the role of RIG-I in cardiac cells under pathological conditions could be due to heterogeneity in the experimental settings and pathological conditions. Further studies are required to better define the function and underlying mechanisms of RIG-I in cardiac cell injuries.

RIG-I in Macrophage Activation

Macrophage activation is not only involved in the innate immune system but also in immune-related cardiovascular diseases. RIG-I plays an important role in the antiviral innate immune response by inducing the production of type I IFN and pro-inflammatory cytokines in macrophages, as previously described. Imaizumi et al. found that RIG-I was expressed in macrophages of human atherosclerotic lesions, indicating that RIG-I may play a role in the differentiation and activation of macrophages in atherosclerosis (16). Another study found that RIG-I was significantly upregulated in LPS-stimulated primary human monocytes infected with dengue virus (DENV), resulting

in vascular injury (82). These studies demonstrate that RIG-I expressed in macrophages participates in vascular injury and atherosclerosis. However, the function and related mechanism of RIG-I in macrophage activation-mediated cardiovascular diseases remain unclear and need to be explored.

RIG-I in Cardiovascular Diseases

It is well known that inflammation plays a critical role in eliminating viruses and repairing damaged tissues. However, chronic inflammation often induces organ injury and triggers the onset of various diseases, including cardiovascular disease. Emerging studies have shown that RIG-I is involved in the pathogenesis of cardiovascular diseases.

RIG-I in Atherosclerosis

Atherosclerosis is a progressive inflammatory disorder of the arterial wall that underlies hypertension, heart attack, and stroke (83). The study by Imaizumi et al. revealed RIG-I expression in foamy macrophages within atherosclerotic lesions, as well as IFN-gamma-induced RIG-I expression in macrophages, thereby suggesting the effect of RIG-I on the regulation of differentiation and activation of macrophages and induction of atherosclerosis (16). Another study showed that enhanced expression of RIG-I correlated with augmented lesions in atherosclerosis induced by organic pollutants (84).Wang's study further revealed that 25-hydroxycholesterol induced higher expression of RIG-I in endothelial cells and macrophages, thereby contributing to atherosclerotic inflammation (20). RIG-I or MAVS deficiency reduced osteogenic signals in aortic vascular smooth muscle (VSM). Moreover, Blockage of RIG-I/MAVS signaling decreased aortic calcium accumulation in MAVS-deficient LDLR$^{-/-}$ mice (70). These results provide new insights into the role of RIG-I in the pathogenesis of atherosclerosis and its therapeutic potential.

RIG-I in Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA) is an inflammatory vascular disease that is common in the elderly. AAA is characterized by an inflammatory immune response and abdominal aorta dilation (85). The RIG-I gene expression in the aortic wall and blood of patients with AAA has been investigated. A previous study reported that RIG-I mRNA levels were enhanced in the circulation of patients with AAA compared with that in healthy subjects. RIG-I appears to be a promising biomarker for diagnosis and disease progression of AAA (86). Evidence from Ang II-induced AAA mouse models also revealed elevated RIG-I mRNA and protein levels. Moreover, animal experiments have shown that RIG-I overexpression by a lentivirus expression system resulted in the apoptosis of SMCs, which promoted AAA progression (71). The above studies suggest that RIG-I could serve as a promising biomarker for predicting the disease progression of AAA. Inhibition of this pathogenic signaling might be beneficial in retarding the progression of AAA.6

RIG-I in Cardiac Dysfunction

Heart failure (HF) is one of the leading causes of death worldwide. Hypertensive heart disease, dilated cardiomyopathy, ischemic heart disease, and chronic obstructive pulmonary disease are the main causes of HF. Cardiac hypertrophy is the primary pathological change in hypertensive heart disease, however, its underlying molecular mechanisms remain unknown. Using an animal model with transverse aortic constriction (TAC), the authors observed that enhanced expression of RIG-I mediated the protective role of ADRB3 depletion in cardiac hypertrophy and heart failure (77). Such protection can be mediated by the enhancement of the innate immune response. In dilated cardiomyopathy, *in vitro* cell experiments showed that activation of RIG-I leads to higher production of pro-inflammatory cytokines such as IL-6 and IL-8, in human cardiac fibroblasts (76). This suggests the inflammatory function of RIG-I in the progression of dilated cardiomyopathy. Another study showed that ICR2 (a stabilized RNA) enhanced the ability of cardiac fibroblasts to reprogram into cardiomyocytes *via* the RIG-I pathway without inducing inflammatory events (78). These results reveal the controversial role of RIG-I in cardiac dysfunction caused by different stimuli and requires further research to validate the phenotypes and underlying mechanisms.

RIG-I in Other Cardiovascular Diseases

Coronary artery disease (CAD) is a heart disease with a high morbidity rate. A study aimed at identifying potential biomarkers of CAD progression showed that genes enriched in the RIG-I-like receptor signaling pathway were possible candidates (87), and may be involved in the pathology of CAD. Although direct evidence of the role of RIG-I in hypertension is absent, RIG-I-like receptors might be involved in the pathological process of Ang II-induced hypertension (88). Considering the importance of inflammation in cardiovascular injury and the established role of RIG-I in inflammation, it would be worthwhile to further explore the role of RIG-I in CAD, hypertension, and other cardiovascular diseases.

In summary, these results indicate that RIG-I plays diverse roles in cardiovascular diseases by inducing endothelial injury, SMC apoptosis, reprogramming of heart fibroblasts, and macrophage activation (**Figure 2**).

CONCLUSION AND FUTURE PERSPECTIVE

Accumulating evidence highlights the critical role of RIG-I in the innate immune and inflammatory responses involved in the pathogenesis of cardiovascular disease and this review adds substantial knowledge to existing literature. The role of RIG-I in the pathogenesis of cardiovascular disease, and the potential of RIG-I signaling as a biomarker for predicting the occurrence and progression of cardiovascular diseases has been established. However, more studies are required to validate the phenotypes
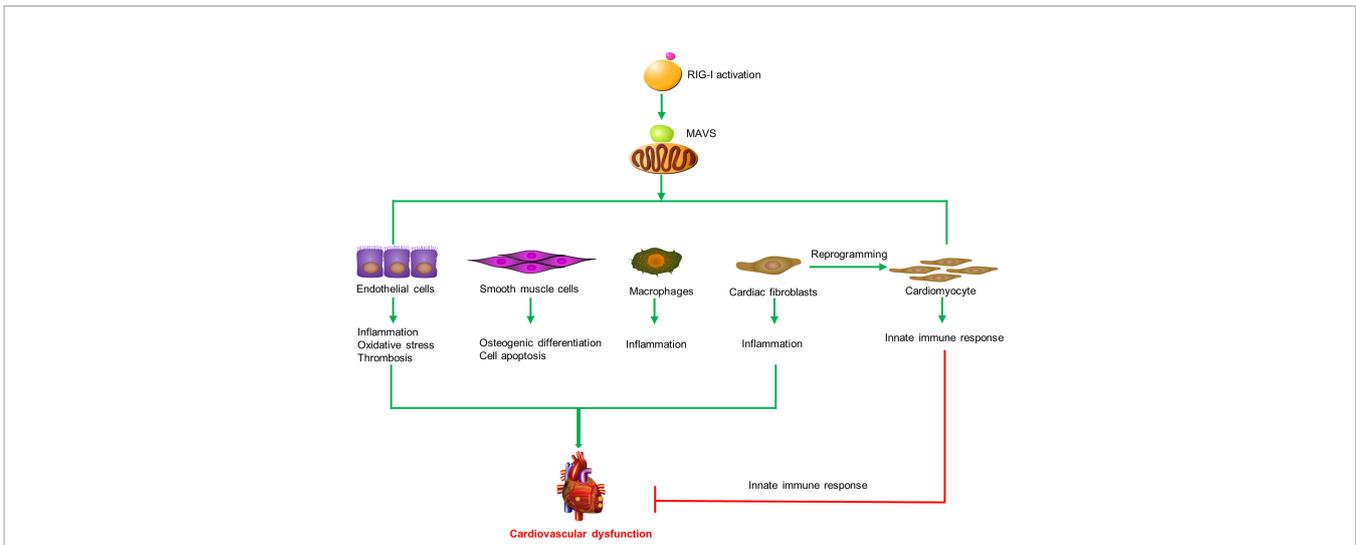
FIGURE 2 | RIG-I triggers the innate immune response and participates in cardiovascular diseases. RIG-I is activated by activators and interacts with MAVS to trigger inflammatory responses, cell apoptosis, oxidative stress, prothrombotic proteins expression, osteogenic differentiation in macrophages, endothelial cells, smooth muscle cells, and cardiac fibroblasts to promote cardiovascular dysfunction. Otherwise, RIG-I activation mediates the remodeling of scar fibroblasts into cardiomyocytes and prevents cardiac hypertrophy by enhancing the innate immune response.

of RIG-I in different cardiovascular diseases, as well as the underlying mechanisms. The development and application of RIG-I agonists and inhibitors could provide novel therapeutics that target the RIG-I signaling pathway for the treatment of cardiovascular diseases.

AUTHOR CONTRIBUTIONS

WX, HC and ZJ conducted the review, and WX, HW, and JY wrote the manuscript. XG and WS contributed to the revision of the manuscript. All the authors have reviewed and approved the manuscript.

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