

REVIEW

The interferon regulatory factors as novel potential targets in the treatment of cardiovascular diseases

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The family of interferon regulatory factors (IRFs) consists of nine members (IRF1–IRF9) in mammals. They act as transcription factors for the interferons and thus exert essential regulatory functions in the immune system and in oncogenesis. Recent clinical and experimental studies have identified critically important roles of the IRFs in cardiovascular diseases, arising from their participation in divergent and overlapping molecular programmes beyond the immune response. Here we review the current knowledge of the regulatory effects and mechanisms of IRFs on the immune system. The role of IRFs and their potential molecular mechanisms as novel stress sensors and mediators of cardiovascular diseases are highlighted.

LINKED ARTICLES

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Tables of Links

TARGETS	
Catalytic receptors^a	Enzymes^b
IFN- α/β receptor	HAT, histone acetyltransferase
IFN- γ receptor	HDAC, histone deacetylase
NLR, NOD-like receptors	TBK1, TANK binding kinase 1
PRR, pattern recognition receptors	GPCRs^c
TLR3	Angiotensin AT ₂ receptors
TLR4	
TLR7	
TLR9	

LIGANDS
Angiotensin II
Chemokine CXCL10
IFN- β
IFN- γ
Isoprenaline

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Pawson *et al.*, 2014) and are permanently archived in the Concise Guide to PHARMACOLOGY 2013/14 (^{a,b,c}Alexander *et al.*, 2013a,b,c).

Abbreviations

ATF3, activating transcription factor 3; CBP, CREB-binding protein; cDCs, conventional dendritic cells; CLL, chronic lymphocytic leukaemia; CMPs, common myeloid progenitor cells; CREB, cAMP-responsive element-binding protein; Dock2, dedicator of cytokinesis 2; dsRNA, double-stranded RNA; ECM, extracellular matrix; ET-1, endothelin-1; GSK3 β , glycogen synthase kinase 3 β ; GWAS, genome-wide association studies; HATs, histone acetyltransferases; HDACs, histone deacetylases; I/R, ischaemia/reperfusion; IAD, IRF-associated domain; IFN, interferon ; IGF-I, insulin-like growth factor I; iNOS, inducible NOS; IRFs, interferon regulatory factors; MAVS, mitochondrial antiviral signalling protein; MDA5, melanoma differentiation-associated gene 5; MyD88, myeloid differentiation primary-response protein 88; PCAF, p300/CBP-associated factor; pDCs, plasma cytoid dendritic cells; PRR, pattern recognition receptor; RIG-I, retinoic acid-inducible gene I; SLE, systemic lupus erythematosus; SRF, serum response factor; TAD, transcription activation domain; TBK1, TANK-binding kinase 1; TG, transgene; TIRAP, TIR domain-containing adaptor protein; TLRs, Toll-like receptors; TRAF, TNF receptor-associated factor; TRAM, TRIF-related adaptor molecule; TRIF, TIRAP-inducing IFN- β ; Tyk2, tyrosine kinase 2; VSMCs, vascular smooth muscle cells

Introduction and background

The interferon regulatory factor (IRF) family was first described as transcriptional regulators of the type I interferon (IFN) system. Since 1988, when the first IRF was identified (Miyamoto *et al.*, 1988), most studies of IRFs have focused on their functions in immunity. Abnormalities in IRFs are associated with changes in both innate and adaptive immune responses to cellular and environmental stimuli in a wide variety of pathways. Now, more recent evidence has revealed the remarkable contributions of IRFs to other diseases, such as cardiovascular diseases (Guo *et al.*, 2014; Jiang *et al.*, 2014d; Zhang *et al.*, 2014a), metabolic diseases (Eguchi *et al.*, 2008; 2011; Wang *et al.*, 2013c,d; 2014) and oncogenesis (Yanai *et al.*, 2012). In this review, as documented elsewhere, the roles of IRFs in immune responses are only briefly summarized and discussed. Instead, we focus on the essential and distinct functions of IRFs, as novel stress sensors and

regulators in cardiovascular diseases to provide a systematic understanding of their therapeutic promise for cardiac remodelling, stroke and vascular injury. A summary of IRFs and their functions in the immune and cardiovascular systems are shown in Table 1.

Structural basis of IRFs

The first IRF, IRF1, was originally identified as a protein binding to the virus-inducible elements of the human *IFN- β* gene (Miyamoto *et al.*, 1988). IRF2 was recognized in the following year through cross-hybridization with *IRF1* cDNA (Harada *et al.*, 1989). As shown in Figure 1, IRF1 and IRF2 have 62% homology located at their amino-terminal regions, which comprise a DNA-binding domain (DBD) with five highly conserved tryptophan repeats (Harada *et al.*, 1989). Using three of the five tryptophan repeats, the DBDs of IRF1 and IRF2 form a helix-turn-helix motif to recognize and bind a consensus DNA sequence known as the IRF-element (IRF-E)

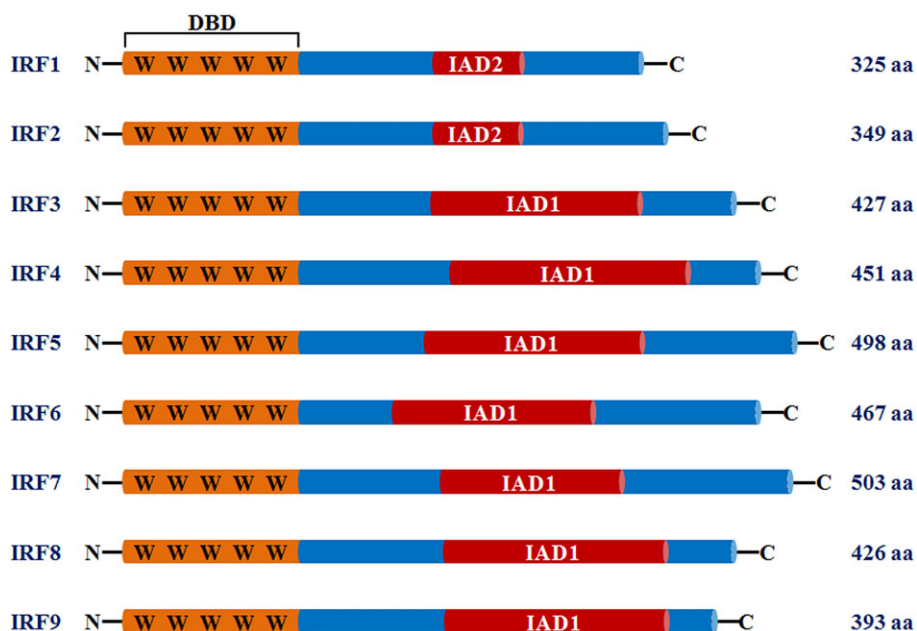


Figure 1

Schematic illustration of mammalian IRFs (IRF1–IRF9). All of the IRFs possess a homology spanning 115 amino acids in their N-terminal regions, including a DBD characterized by five highly conserved tryptophan repeats. In the C-terminal region, the IRFs, except for IRF1 and IRF2, contain IAD1, while IRF1 and IRF2 share IAD2.

Table 1

A summary of IRF family members and their functions in the immune system and the CVS

IRF	Expression	Related diseases	Functions	Typical targets	References
IRF1	Ubiquitously in most cell types and organs	Chronic hepatitis B and C, heart failure, ischaemic stroke, AS, AAA	Antiviral and bacterial responses; induction of cell cycle arrest and apoptosis; required for NK cells development and the differentiation of CD8 ⁺ T-cells; promotes Th1 differentiation; suppresses Th2 differentiation; accelerates cardiac remodelling; exacerbates ischaemic stroke; protects against neointima formation	IFN-inducible genes, iNOS, IL-4, IL-12, IL-15, CD40, PPAR γ	Liu <i>et al.</i> , 2000; Taniguchi <i>et al.</i> , 2001; Watford <i>et al.</i> , 2003; Wessely <i>et al.</i> , 2003; Mellor and Munn, 2004; Passiura <i>et al.</i> , 2005; Tamura <i>et al.</i> , 2005; Caso <i>et al.</i> , 2007; Schmitz <i>et al.</i> , 2007; Li <i>et al.</i> , 2009; Korachi <i>et al.</i> , 2013; Jiang <i>et al.</i> , 2014a
IRF2	Widely in various cells and organs	Unknown	Accentuates type I IFN response; essential for CD4 ⁺ DC differentiation and NK cells development; promotes Th1 differentiation; suppresses Th2 differentiation	IRF1, IRF9, IL-4, IL-12	Taniguchi <i>et al.</i> , 2001; Ichikawa <i>et al.</i> , 2004; Jia and Guo, 2008
IRF3	Most cell types and organs	Dilated cardiomyopathy, hypertrophic cardiomyopathy, stroke, AS, AAA	Induces type I IFNs; reduces cardiac hypertrophy; indispensable for TLR ligands pretreatment-induced tolerance to stroke; exacerbates outcomes of stroke; inhibits neointimal formation	IFN- α , IFN- β , PPAR γ , ERK2	Holland <i>et al.</i> , 2008; Stevens <i>et al.</i> , 2011; Lu <i>et al.</i> , 2013a; Sasai and Yamamoto, 2013; Zhang <i>et al.</i> , 2014b
IRF4	Constitutive in cardiocytes, neurons, macrophages and DCs, abundant in lymphocytes	Recurrent bronchitis, atopy, CLL, AS, AAA	Retards interactions of IRF5 with MyD88 and reduces TLR-dependent inflammation; required for differentiation of CD4 ⁺ DCs, pDCs and macrophages; exacerbates cardiac remodelling; improves stroke outcomes; required for B-lymphocytes development	IRF5, IL-4, CREB, SRF	Pernis, 2002; Schiavoni <i>et al.</i> , 2002; Lehtonen <i>et al.</i> , 2003; Kanno <i>et al.</i> , 2005; Negishi <i>et al.</i> , 2005; Tamura <i>et al.</i> , 2005; Di Bernardo <i>et al.</i> , 2008; Jiang <i>et al.</i> , 2013; Pinto <i>et al.</i> , 2013; Guo <i>et al.</i> , 2014
IRF5	Mainly in B-cells and DCs; expressed in the heart	SLE, cardiac hypertrophy	Stimulates type I IFNs and immune responses upon virus infection	IFN- α , IFN- β , IL-6, TNF- α	Brown <i>et al.</i> , 2011
IRF6	Constitutive in skin	Unknown	Required for keratinocyte differentiation	Unknown	Restivo <i>et al.</i> , 2011; Biggs <i>et al.</i> , 2014
IRF7	Most cell types and organs	Influenza infection, SLE, heart failure, stroke, AS, AAA	Positively regulates TLR-dependent proinflammatory responses; suppresses cardiac remodelling; required for TLR ligands pretreatment-elicited neuroprotection; alleviates ischaemic stroke; inhibits neointimal formation	IFN- α , IFN- β , IKK β , ATF3	Erickson and Gale, 2008; Holland <i>et al.</i> , 2008; Stevens <i>et al.</i> , 2011; Sasai and Yamamoto, 2013; Jiang <i>et al.</i> , 2014b
IRF8	Expressed in cardiocytes, neurons, and lymphocytes	Heart failure, ischaemic stroke, AS, AAA	Promotes type I and II IFNs; required for CD8 ⁺ DCs and pDCs differentiation; promotes macrophage differentiation; promotes myeloid apoptosis; essential for B-cells development; alleviates cardiac hypertrophy; reduces stroke-induced infarct lesions; accelerates vascular hyperplasia	IFN- α , IFN- β , Bcl211, Nf1, Bax, iNOS, IL-12, NFATc1, SRF	Lehtonen <i>et al.</i> , 2003; Kanno <i>et al.</i> , 2005; Tamura <i>et al.</i> , 2005; Huang <i>et al.</i> , 2007; Yang <i>et al.</i> , 2011; Scheller <i>et al.</i> , 2013; Jiang <i>et al.</i> , 2014d; Xiang <i>et al.</i> , 2014; Zhang <i>et al.</i> , 2014a
IRF9	Broadly in various cells and organs	Heart failure, MI, stroke, AS, AAA	Forms ISGF3 to promote type I IFN-inducible genes; anti-hypertrophy; promotes myocardial I/R responses; aggravates stroke responses; augments intimal hyperplasia	IFN- α , IFN- β , SRF, Sirt1	Chen <i>et al.</i> , 2014; Jiang <i>et al.</i> , 2014c; Zhang <i>et al.</i> , 2014c

AAA, abdominal aortic aneurysm; AS, atherosclerosis; MI, myocardial infarction.

(Tanaka *et al.*, 1993; Fujii *et al.*, 1999). In the carboxyl-terminal region, IRF1 contains many acidic amino acids and serine-threonine residues, whereas IRF2 is relatively rich in basic amino acids (Harada *et al.*, 1989), suggesting that these factors have distinct functions.

Following the identification of these two structurally related factors, numerous approaches have been taken to explore additional IRF factors, and seven other mammalian IRFs have been identified: IRF3, IRF4 (*LSIRF*, PIP, MUMI or ICSAT), IRF5, IRF6, IRF7, IRF8 (ICSBP) and IRF9 (*p48* or *ISGF3 γ*) (Taniguchi *et al.*, 2001; Honda and Taniguchi, 2006b). Like IRF1 and IRF2, these members of the IRF family showed a homology of over 115 amino acids in their amino-terminal regions with five well-conserved tryptophan repeats and the helix-turn-helix DNA-binding motif, suggesting similar, if not identical, DNA recognition sequences, for example, IRF-E (Lallemant *et al.*, 2007), IFN-stimulated response element (ISRE) (Guillot *et al.*, 2005), IFN consensus sequence (Ko *et al.*, 2002), and positive regulatory domain (PRD) (Hiscott, 2007). The carboxyl-terminal regions of the IRF family, which contain transcriptional activation domains, might constitute regulatory regions. Except for IRF1 and IRF2, IRFs exhibit homology to the C-terminal domains of the SMAD family and contain an IRF-associated domain 1 (IAD1), while IRF1 and IRF2 share IAD2 (Eroshkin and Mushegian, 1999; Yanai *et al.*, 2012). The protein–protein interactions that are dependent on these domains may define the binding sites and functions of the protein complex, as a transcriptional activator or repressor.

Cellular events of IRFs

A given transcription factor mediates the associated genetic regulatory network by activating, suppressing and/or interacting with its target genes. The specific regions of IRF members allow them to bind to corresponding motifs of their modifiers, co-activators and co-repressors, leading to diverse and specific molecular events, depending on the cell types and variations in stimuli. Accumulating studies have indicated that, following various extracellular and intracellular stimuli, IRFs activate and expand immune responses through various molecular events, especially the IFN and pattern recognition receptor (PRR) signalling pathways (Taniguchi *et al.*, 2001; Honda and Taniguchi, 2006b). These molecular events are summarized in Figure 2.

IRFs in IFN signalling. IFNs are the central mediators of innate immunity. Two types of IFNs, type I IFNs (IFN- α and IFN- β) and type II IFNs (IFN- γ), have been identified. The type I IFNs are crucial mediators of antiviral responses in a variety of cells following viral infection and are principally regulated by IRFs, whereas type II IFNs are mainly produced by activated T-cells and NK cells (Taniguchi *et al.*, 2001). In the type I IFN system, the binding of ligands with the IFN- α/β receptor activates JAK1 and tyrosine kinase 2 (Tyk2). Following tyrosine phosphorylation of residue 455 (Y455) of the intracellular domain of IFN- α/β receptor 1 through JAK1 and Tyk2, STAT2 is recruited to this Y455 *via* its SH2 domain, whereas STAT1 is recruited by IFN- α/β receptor 1 through its interaction with phosphorylated STAT2. These phosphorylated STAT factors, in combination with IRF9, form a heterotrimeric complex, ISGF3, that subsequently translocates to the nucleus and

binds to ISRE or IRF-E, leading to the activation of several IFN-inducible genes (Taniguchi *et al.*, 2001; Honda and Taniguchi, 2006b).

As in the IFN- α/β receptor signalling pathway, stimuli on the IFN- γ receptor may induce formation of the STAT1/STAT2/IRF9 and STAT1/STAT1/IRF9 heterotrimeric complex. Additionally, the dimerization of phosphorylated STAT1 undergoes conversion into the transcriptionally active form, IFN- γ -activated factor/IFN- α -activated factor, and binds to the IFN- γ -activated site (GAS) in the IRF1 promoter, inducing transcription of the *IRF1* gene (Takaoka and Yanai, 2006). The IRF family members are thus pivotally involved in IFN signalling from both the α/β and the γ receptors.

IRF1 and IRF2 are ubiquitous and expressed at low levels in various cell types in normal physiological conditions. However, after stimulation with viral infection and immune factors, for example TNF- α , IL-1 β , IL-6 and IFNs, the expression of IRFs, particularly IRF1, is dramatically up-regulated concomitant with posttranslational modification, for example phosphorylation, allowing functional changes from steady-state levels (Taniguchi *et al.*, 2001). The serine-phosphorylation of IRF1 by PKA, PKC, and casein kinase II is one of the most common phenomena during IRF-regulated molecular events (Taniguchi *et al.*, 2001). Phosphorylated IRF1 activates IFN- α/β promoters and induces endogenous *IFN- α* and *IFN- β* genes through the mediation of STAT and NF- κ B transcription factors (Sato *et al.*, 2000; Taniguchi and Takaoka, 2002; Honda *et al.*, 2006a). In contrast to IRF1, phosphorylated IRF2 represses both ISRE- and IRF-E-regulated transcriptional activation, thereby weakening IRF1-induced IFN- α/β signalling (Hida *et al.*, 2000; Jia and Guo, 2008). Thus, IRF1 and IRF2 function as a transcriptional activator and attenuator of IFNs respectively.

IRF3 and IRF7 are ubiquitously expressed in a variety of cells and have very similar structures. These IRFs are best known for their critical roles as transcriptional regulators promoting activation of type I IFN by binding to IRF-E and ISRE after homo- or hetero-dimerization (Holland *et al.*, 2008). Under normal conditions, these factors reside in the cytoplasm; however, upon viral infection, IRF3 and IRF7 are activated, phosphorylated, polymerized and then translocate to the nucleus to regulate IFN production (Taniguchi *et al.*, 2001). After treatment with IFNs, IRF3 expression is constitutive and remains essentially unaffected, whereas the level of IRF7 is dramatically enhanced in IFN- α/β signalling, indicating that IRF7 could be considered as an IFN-stimulated gene (ISG) triggering and augmenting IFN expressions to further activate systemic IFN-induced antiviral defences (Taniguchi *et al.*, 2001; Prakash *et al.*, 2005; Erickson and Gale, 2008; Chen *et al.*, 2013a). The dominant effect of IRF7 in activating IFN- α/β was demonstrated by the evidence that the induced expression of IFNs in wild-type mice is similar to that of *IRF3*^{-/-} following viral infection, whereas in the *IRF7*^{-/-} and *IRF3*^{-/-} *IRF7*^{-/-} mice, dramatically lower levels of IFN- α/β expression were obtained (Chen *et al.*, 2013a). In *IRF7*^{-/-} mouse embryonic fibroblasts (MEFs), the induction of IFN- β mRNA was markedly inhibited and the residual mRNA induction was blocked with an additional deficiency of *IRF3*, suggesting synergistic effects of IRF3 and IRF7 in the induction of IFNs (Honda *et al.*, 2005). *In vivo* studies demonstrated that the combined absence of *IRF3* and *IRF7* resulted in

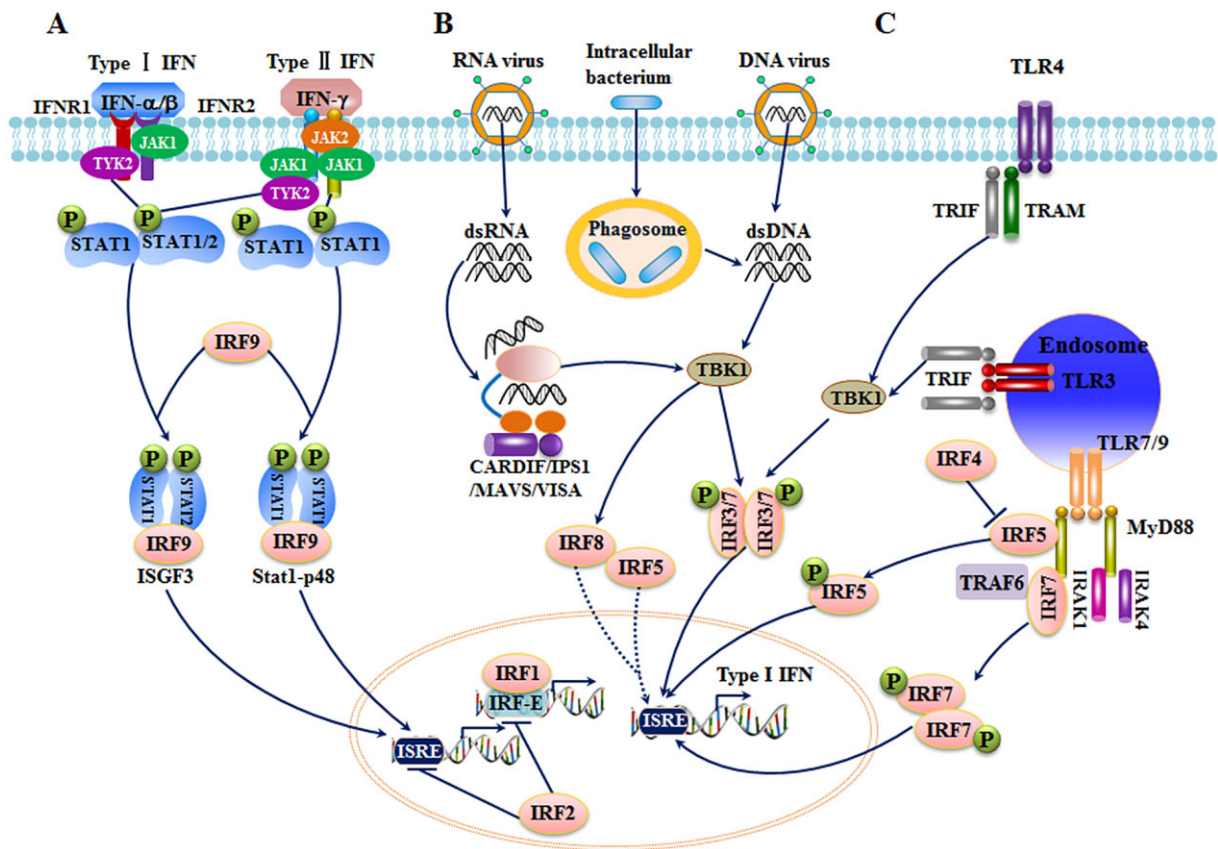


Figure 2

Schematic representation of molecular events involving IRFs in immune responses. (A) Role of IRFs in IFN signalling. In type I IFN responses, IFN- α/β binds to its receptor and activates JAK1/Tyk2, leading to the recruitment and phosphorylation of STAT2/STAT1. IRF9 forms a complex with the phosphorylated STAT factors, translocates to the nucleus, and activates IFN-inducible genes. In type II IFN signalling, the STAT1/STAT2/IRF9 and STAT1/STAT1/IRF9 complexes form in a similar pathway. (B) IRFs in cytosolic PRRs. In response to viral infection, RIG-I or MDA5 recognizes viral RNA and binds to CARDIF/IPS1/MAVS/VISA, leading to the phosphorylation of IRF3 and IRF7 through TBK1. The phosphorylated IRF3 and IRF7 undergo homo- or hetero-dimerization and nuclear translocation, thereby binding to ISRE DNA sequences and activating IFNs and other target genes. In some cases, IRF5 and IRF8 also participate in PRR signalling. (C) IRFs in TLR signalling. Depending on adaptor types, TLR signalling is divided into MyD88-dependent and TRIF-dependent pathways. TLR3 and TLR4 respond to stimuli and activate IRF kinase TBK1 mainly through a MyD88-independent pathway. TBK1 subsequently phosphorylates IRF3 and IRF7, resulting in their dimerization and translocation to the nucleus. In contrast to IRF3 and IRF4, TLR7 and TLR9 trigger IRF activation mainly through a MyD88-dependent pathway. IRF5 and IRF7 directly bind to MyD88 or TRAF6, dimerize, and translocate to the nucleus. IRF4 inhibits the interaction of IRF5 with MyD88.

uncontrolled viral burdens, higher inflammatory responses, and more rapid death of *IRF3*^{-/-}*IRF7*^{-/-} mice compared with the individual single IRF knockout (KO) mice, directly confirming the mutually enhanced effects of IRF3 and IRF7 (Daffis *et al.*, 2007; 2008; 2009; 2011; Murphy *et al.*, 2013).

In contrast to the ubiquitous expressions of other IRF members, IRF4 and IRF8 are preferentially expressed in cells responsible for immune responses (Lehtonen *et al.*, 2003; Kanno *et al.*, 2005). In the presence of a high level of IFN- α , the expression of IRF4 is strongly up-regulated, whereas the expression of IRF8 is induced by IFN- γ , rather than by IFN- α/β (Tamura and Ozato, 2002; Wang and Morse, 2009). These two IRFs regulate cellular immunity by directly binding to IRF-E or ISRE motifs in the target gene promoters or *via* their indirect interaction with composite motifs that can be recognized by the Ets transcription factors PU.1 and Spi-B (Honma *et al.*, 2005; Lu, 2008). The phosphorylated serine residue in the

PEST region of PU.1 provides a binding site that is required for the PU.1-IRF4/IRF8 interaction (Escalante *et al.*, 2002). Similarly, IRF4/IRF8 forms a complex with Spi-B, a factor that is closely associated with PU.1, on an Ets-IRF composite element. Moreover, several other factors regulate the functions of IRF4 and IRF8 in IFN signalling. STAT4, an essential signalling protein for Th1 responses, binds to the GAS-like element in the promoter region of IRF4. In a yeast two-hybrid analysis, the immunophilin FKBP52-binding protein 52 (FKBP52) post-translationally regulated and interacted with IRF4, thereby inhibiting the DNA-binding activity of IRF4 (Mamane *et al.*, 2000).

As mentioned earlier, IRF9 was originally discovered as a DNA-binding subunit of the transcription factor ISGF3, whose formation is triggered by activation of IFN- α/β receptors, resulting in the induction of various IFN-inducible genes. The details of the molecular events involving IRF9 in this pathway have yet to be investigated.

IRFs in PRR signalling. Since the discovery of PRRs, a family that links innate and adaptive immunity, IRFs have received much more attention as regulators of immune responses (Honda and Taniguchi, 2006b). Two classes of PRRs, the cytosolic PRRs and the transmembrane Toll-like receptors (TLRs), have been defined (Savitsky *et al.*, 2010).

IRFs in cytosolic PRR signalling. Cytosolic PRRs comprise three major types: the retinoic acid-inducible gene I (RIG-I) family, IFN-inducible double-stranded RNA (dsRNA)-dependent PKR, and nucleotide-binding oligomerization domain (NOD) proteins (Janeway and Medzhitov, 2002; Akira *et al.*, 2006), among which the RNA helicase enzymes in the RIG-1 family, RIG-I and melanoma differentiation-associated gene 5 (MDA5), are essential receptors for the recognition of viral RNA and the activation of downstream signalling pathways (Savitsky *et al.*, 2010). In the early phase of viral infection, RIG-I or MDA5 interacts with the mitochondrial antiviral signalling protein MAVS (also known as IPS-1, VISA or CARDIF) *via* the physical binding of their N-terminal caspase-recruitment and activation domains (Seth *et al.*, 2005). The signals are then relayed to TANK-binding kinase 1 (TBK1) and induce the phosphorylation of IRF3 and IRF7 on serine residues, resulting in their homo- or heterodimerization and nuclear translocation (Kawai *et al.*, 2004). After binding to the target ISRE DNA sequences, this complex transcriptionally activates type I IFNs and other target genes, such as the chemokine CXCL10. The secreted IFNs bind to IFN receptors in an autocrine or paracrine manner and positively activate the TBK1-IRF3/7-IFN loop, leading to the expression of large amounts of IFN α/β proteins in a positive feedback mechanism (Honda *et al.*, 2006a). Four IRF members, IRF3, IRF5, IRF7 and IRF8, are clearly involved in the RIG-I/MDA5-regulated PRR signalling pathways.

The IRF3 and IRF7-related cytosolic PRR events are mediated by various molecules. *Igp2*, a gene that belongs to the DExD/H-box-containing RNA helicase family together with RIG-1 and MDA5, might compete with RIG-1 and MDA5 for engagement with viral RNA, thereby negatively regulating the RIG-I- and MDA5-signalling pathways (Yoneyama *et al.*, 2005). Cyclophilin B, TNF receptor-associated factor 3 (TRAF3) and the ubiquitin ligase mind bomb, positively regulate TBK1-activated IRFs, whereas the suppressor of I κ B-kinase ϵ might function as a negative regulator (Huang *et al.*, 2005; Heineke and Molkenin, 2006; Oganessian *et al.*, 2006; Li *et al.*, 2011b). Additionally, cAMP-responsive element-binding protein (CREB)-binding protein (CBP) or p300, as co-activator, promotes the phosphorylation process and forms a holocomplex with IRF3 and IRF7 (Mori *et al.*, 2004; Panne *et al.*, 2007). In contrast, the HCV NS3/4A serine protease blocks the phosphorylation and functions of IRF3 (Foy *et al.*, 2003). The prolyl isomerase, PIN1 (peptidylprolyl *cis-trans* isomerase, NIMA-interacting 1), could also blunt or even terminate the action of IRF3 by binding to phosphorylated IRF3 in the nucleus, facilitating the polyubiquitin-dependent degradation of IRF3 (Saitoh *et al.*, 2006). After the elimination of virus, the IFN response should subside before it becomes deleterious to the host. This attenuation may occur partly through the translational-suppressive functions of 4E-BPs on IRF7 mRNA translation, thereby decreasing IFN production and the innate immune response (Erickson and Gale, 2008).

Although IRF3 and IRF7 exert significant effects on IFN production, sustained production of type I IFN was still found with the combined absence of *IRF3* and *IRF7* under the control of MAVS signalling. However, the simultaneous loss of *IRF3*, *IRF5* and *IRF7* (*IRF3/5/7-TKO*) in mice yields immune responses relatively equivalent to those seen in *MAVS*^{-/-} mice (Lazear *et al.*, 2013). Like IRF3 and IRF7, IRF5 can be phosphorylated by TBK1 and translocated into the nucleus to induce IFN activation following viral infection (Savitsky *et al.*, 2010). Lazear *et al.* (2012) indicated that the RIG-I like receptor adaptor protein MAVS could induce ISGs through an IRF5-dependent but IRF3- and IRF7-independent pathway. However, gene-disruption studies of IRF5 have reached disparate conclusions in terms of IFN production and antibody responses. The identified spontaneous genomic duplication and frameshift mutation in the guanine exchange factor, dedicator of cytokinesis 2 (Dock2), might explain the discrepancies among the published results. Dock2 has emerged in a subset of circulating *IRF5*^{-/-} mice and inadvertently to homozygosity. *IRF5*^{-/-} mice lacking the mutation in Dock2 exhibited largely intact type I IFN responses and relatively normal antibody responses to viral infection (Purtha *et al.*, 2012). IRF8 is also essential for IFN- α/β induction in virus stimulated immune cells by directly binding to promoters of type I IFN genes or *via* participation in the IRF7-mediated amplifying phase of IFN transcription (Tamura *et al.*, 2008).

IRFs in TLR signalling. The TLR family, which consists of 10 functional members in humans (13 in mice), plays a pivotal role in the activation of both the innate and adaptive immune responses. All TLRs contain extracellular leucine-rich repeats that recognize pathogen-associated molecular patterns, whereas the transmembrane and cytoplasmic Toll/IL-1 receptor (TIR) domains transmit intracellular signals by recruiting TIR-containing adaptor proteins (Takeda and Akira, 2004; Kawai and Akira, 2006). Depending on their adaptor types, that is myeloid differentiation primary-response protein 88 (MyD88), TIR domain-containing adaptor protein (TIRAP), TIRAP-inducing IFN β (TRIF) or TRIF-related adaptor molecule (TRAM), the TLR signalling pathways can be divided into a MyD88-dependent pathway, which is shared by all TLRs, and a TRIF-dependent pathway (MyD88-independent pathway), which is specific to TLR3 and TLR4 (Tamura *et al.*, 2008). TLR3, TLR4, TLR7 and TLR9 are the major TLRs responsible for the activation of IRF-engaged molecular events through both the MyD88- and TRIF-dependent pathways.

TLR3, which is expressed at the cell surface of endothelial and NK cells or in the membrane of endosomes and phagosomes, employs a TRIF-dependent pathway to induce type I IFN (Akira *et al.*, 2006). In response to stimuli from dsRNA or other pathogens, TLR3 interacts directly with TRIF to trigger the IRF kinase TBK1, which subsequently phosphorylates IRF3 and IRF7, the essential factors in IFN production mediated by TLR pathways (Sasai and Yamamoto, 2013). Similarly to TLR3, TLR4 can induce IFN gene expression in a MyD88-independent and TRIF- and TBK1-dependent pathway; however, this induction is limited to the gene encoding IFN- β and excludes IFN- α (Piao *et al.*, 2013). Using the intracellular adaptor protein, IRF4 interacts with TRAM-TRIF, which recruits TBK1 through NF- κ B activating kinase-

associated protein 1 and TRAF3 (Clark *et al.*, 2011). The activated TBK1 phosphorylates IRF3 and IRF7, facilitating their dimerization and translocation to the nucleus, inducing the genes that encode IFN- β . Gene deletion studies have indicated that IRF3, rather than IRF7, is required for the MyD88-independent TLR4 signalling pathways (Shaik-Dasthagirisaheb *et al.*, 2014).

In contrast to TLR3 and TLR4, TLR7 and TLR9 regulate IRFs mainly *via* MyD88-dependent signalling. With the stimulation of TLR7/9 ligands, IRF7 directly interacts with the death domain of MyD88 or is activated by a kinase cascade involving IRAK4, IRAK1 and IKK α (O'Neill and Bowie, 2007). Utilizing the TLR7/9–MyD88–IRF7 signalling pathway, a positive feedback loop can be activated, thereby stimulating robust type I IFN production (Colonna, 2007). Similarly to IRF7, IRF5 could bind to and is activated by MyD88 and TRAF6. Following its interaction with an intermediary and part of the TIR domain of MyD88, activated IRF5 dimerised and then translocated to the nucleus (Brown *et al.*, 2011). The binding of IRF5 to MyD88 can be retarded by IRF4, because IRF4 binds to MyD88 in the region overlapping that of IRF5 (Negishi *et al.*, 2005). IRF8 is also involved in TLR9 signalling, amplifying the type I IFN response by interacting with TRAF6 or directly activating the transcription of pro-inflammatory cytokine genes (Lande and Gilliet, 2010).

Ubiquitination of IRFs. During molecular events involving IRFs, ubiquitination, like phosphorylation, is an efficient cellular process that is responsible for many signal transductions and drives various immunity-related regulatory events. These two protein-modification events can occur rapidly through dedicated enzymes, and often act cooperatively in mobilizing particular cellular pathways in response to extracellular signals (Ben-Neriah, 2002; Wang and Maldonado, 2006). For IRF1, under certain stress conditions, the C-terminus of Hsc70-interacting protein binds to and forms a stable complex with IRF1, allowing an increase in IRF1 ubiquitination and a decrease in IRF1 steady-state levels (Narayan *et al.*, 2011). Following the removal of the C-terminal 70 amino acids from IRF1, which could be recognized by an E3 ligase, its degradation and polyubiquitination can be inhibited, suggesting that the C-terminal of IRF1 promotes ubiquitination. Conversely, the enhancer domain *in trans* inhibits endogenous E3 ligase-regulated IRF1 ubiquitination (Pion *et al.*, 2009). For IRF2, two binding sites on IRF2 have been identified for the interaction of IRF2 and Mdm2, leading to the ubiquitin-induced degradation of IRF2 and the retardation of IRF2-attenuated IFNs activity (Pettersson *et al.*, 2009).

To protect the host from excessive or even uncontrollable immune responses after viral infection, the activations of IFNs will be limited directly or indirectly through polyubiquitination and subsequent proteasomal degradation, especially of IRF3 and IRF7. Viral proteins have been considered as E3 ubiquitin ligases and target IRFs for proteasomal degradation under the regulation of various factors. Bauhofer and Hilton research groups (Hilton *et al.*, 2006; Bauhofer *et al.*, 2007) demonstrated that the pestiviruses, classical swine fever virus and bovine viral diarrhoea virus, could interact with IRF3 through the protein N^{pro}, prior to its phosphorylation-induced activation, resulting in polyubiquitination and subsequent proteasomal degradation of IRF3,

which could be abolished through thermal inactivation of the E1 ubiquitin activating enzyme (Chen *et al.*, 2007). The non-structural protein 1 and bICP0 (BHV1-ICP0) could directly mediate the degradation of IRF3 in a proteasome-dependent manner, thus inhibiting the IFN- β promoter (Barro and Patton, 2005; Graff *et al.*, 2007; Saira *et al.*, 2007). Additionally, several other proteins, for example viral protein R, viral infectivity factor, RBCC protein interacting with PKC1, and caspase-8 have been found to catalyse, maybe not directly promote, the ubiquitination and degradation of IRF3 (Melroe *et al.*, 2007; Okumura *et al.*, 2008; Zhang *et al.*, 2008; Sears *et al.*, 2011). For the regulation of IRF7 degradation, N-Myc and STATs interactor, a negative regulator of the virus-triggered type I IFNs, was found to promote K48-linked IRF7 ubiquitination (Wang *et al.*, 2013a). Notably, among those factors responsible for the ubiquitination and degradation of IRFs, Ro52 (TRIM 21) has been highlighted not only for its direct effects on diminishing the transcriptional activities of IRFs, but also for dual functions in their activation (Higgs *et al.*, 2008; 2010). In certain cell types and conditions, Ro52 may sustain IRF3 and IRF8 activity by facilitating interactions with their co-activators, whereas under other conditions, Ro52 promotes the inactivation of IRF3, IRF5, IRF7 and IRF8 (Kong *et al.*, 2007; Yang *et al.*, 2009; Oke and Wahren-Herlenius, 2012). Further evidence to substantiate that the protein degradation is not the only outcome of ubiquitination can be found in ubiquitin-mediated IRF7 activity. For instance, following Lys⁶³-linked ubiquitination stimulated by TRAF6 and the viral oncoprotein latent membrane protein 1, the activation of IRF7 is enhanced (Kawai *et al.*, 2004; Huye *et al.*, 2007).

The ubiquitination-controlled activities of other IRFs have remained poorly understood until recently. Among the cellular events regulating IRF5 activity, TRAF6-mediated K63-linked polyubiquitination also occurred and is required for nuclear translocation and activation of IRF5 (Balkhi *et al.*, 2008). For IRF8, Cb1 is likely to be the ubiquitin-protein isopeptide ligase and could form a complex with IRF8, contributing to its degradation (Xiong *et al.*, 2005). As ubiquitination plays multiple roles in IRF activations, related factors and mechanisms of this molecular programme require further investigation.

Acetylation of IRFs. Acetylation has pivotal roles in activating cytokine receptors and their downstream signalling pathways. Acetylation of diverse domains of IRF members leads to their conformational change and thus influences their DNA-binding activities (Tang *et al.*, 2007b). Generally, acetylation in DBD represses DNA binding, whereas acetylation adjacent to DBD enhances DNA binding (Masumi, 2011). Therefore, it is not surprising that both transcriptional activating and silencing can be mediated through the orchestra of acetylation-associated enzymes and IRFs.

Modification of reversible histone acetylation and deacetylation processes is governed by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). These enzymes have emerged as major regulators of the expression and acetylation activation of genes (Feng *et al.*, 2010). Both IRF1 and IRF2 can be acetylated by forming a multiprotein complex with HATs such as p300/CBP and PCAF (p300/CBP-associated factor), enabling the crosstalk

between IRFs and cell apoptosis or growth-regulated promoters (Masumi *et al.*, 2003; Marsili *et al.*, 2004). Lys⁷⁸ of helix α 3 within DBD is the major acetylation site for both IRFs, while Lys⁷⁵ is specific for IRF2 (Qi *et al.*, 2012). Acetylated IRF2, but not IRF1, inhibits p300-mediated acetylation of core histones; IRF2 thus possibly acts as a substrate for histone acetylases, competitively inhibiting histone acetylation (Masumi, 2011).

For IRF3 and IRF7, the HATs (including p300, PCAF and GCN5) and the corresponding acetylation are crucial for the DNA binding of their homo- or hetero-complex, which are responsible for IFN transcriptional activation (Masumi, 2011). Like IRF1 and IRF2, the single lysine-residue target of IRF7 for acetylation is a helix- α 3 lysine, Lys⁹², which is located in the DBD and conserved throughout the entire IRF family. Acetylated IRF7 exhibits an impaired DNA-binding capacity (Caillaud *et al.*, 2002; Masumi *et al.*, 2003).

The HAT-regulated acetylations of other IRFs, including IRF4, IRF5 and IRF9, are inducible upon viral infection or IFN treatment. Under the indicated conditions, IRF4 binds to and could be acetylated by GCN5 (Kikuchi *et al.*, 2014), while IRF5 is reversibly acetylated by p300 and CBP (Feng *et al.*, 2010). In response to IFN stimulus, IFN- α/β receptor 2 and IRF9 undergo CBP-mediated acetylation and activate ISGF3. All of the acetylated lysine sites of IRF9 are highly conserved and reside within the N-terminal domain (Tang *et al.*, 2007b). These results collectively demonstrate that the activation and functions of the IRF family are intricately regulated by diverse and/or overlapping molecular programmes, the in-depth investigation of which will greatly expand our understanding of their broad functions in related diseases.

Implication of IRFs in immunity

Benefiting from emerging molecular biotechnological approaches, genetic techniques and network analysis, the responses of IRFs involved in classic molecular responses to internal and external stimuli have been expanded to their roles in the development and functioning of several cell lines of immunological importance, including dendritic cells (DCs), myeloid cells, NK cells, T-cells and B-cells.

DCs, comprising conventional DCs [cDCs, including CD4⁺ DCs, CD8 α ⁺ DCs and CD4⁻CD8 α ⁻ (double-negative, DN) DCs] and pDCs, are crucial for mounting both the innate and adaptive immune systems (Geissmann *et al.*, 2010; Mildner *et al.*, 2013). The development of DCs is mediated by several IRFs, among which IRF4 and IRF8 initially emerged as key players. Studies on *IRF4*^{-/-}, *IRF8*^{-/-} and *IRF4*^{-/-} *IRF8*^{-/-} mice have demonstrated that IRF4 and IRF8 are essential for the generation of CD4⁺ and CD8 α ⁺ DCs, respectively; while, in conventional DN DCs and pDCs, overlapping effects of IRF4 and IRF8 regulate cell development (Schiavoni *et al.*, 2002; Tamura *et al.*, 2005; Hambleton *et al.*, 2011). Also, IRF4 and IRF8 are functionally separated in DC differentiation, which occurs in a subset-selective manner in response to two different growth factors, Flt3 ligand (Flt3L) and GM-CSF (Gilliet *et al.*, 2002; Tamura *et al.*, 2005). IRF1 and IRF2 also regulate DCs development and differentiation. *IRF1*-KO mice exhibit reduced numbers of CD8 α ⁺ DCs (Gabriele *et al.*, 2006), whereas *IRF2*^{-/-} DCs display a significant defect in CD4⁺CD8 α ⁻ DCs (Ichikawa *et al.*, 2004). Additionally, IRF1 may inhibit the immunosuppressive features of DCs, as indicated by the

failure of *IRF1*^{-/-} splenic DCs to mature in response to viral or bacterial stimuli (Mellor and Munn, 2004).

Common myeloid progenitor cells (CMPs) give rise to granulocytes (neutrophils) and macrophages. Clinical and experimental studies have shown that IRF4 and IRF8 function as notable effectors in the development, growth and apoptosis of myeloid cells. Although IRF4 is expressed at a much lower level than IRF8 in granulocyte-macrophage progenitors, both of these IRFs strongly promote the differentiation of CMPs to macrophages. However, neutrophilic differentiation is inhibited by the ectopic expression of IRF4 or IRF8, possibly as a result of altered PU.1 expression (Yamamoto *et al.*, 2011; Becker *et al.*, 2012). Presumably because of the lower expression level, *IRF4*^{-/-} mice, but not *IRF8*^{-/-} mice, exhibit no obvious abnormality in the development of myeloid cells compared with their wild-type controls (Yamamoto *et al.*, 2011). Additionally, IRF8 shows a potent ability to inhibit myeloid cell growth and to promote apoptosis potentially by regulating several key genes, for example *Bcl211*, *Nf1* and *Bax* (Huang *et al.*, 2007; Yang *et al.*, 2011; Scheller *et al.*, 2013). It was also reported that IRF1 stimulates cell differentiation and mediates the N-ras-induced growth suppression of myeloid cells (Passioura *et al.*, 2005; Schmitz *et al.*, 2007).

Lymphocytes are a diverse group of cells that are central to the development of immunologic memory and tolerance. NK cells, originally identified as effector lymphocytes of innate immunity with constitutive cytolytic functions, are now known to have much more sophisticated biological functions, such as the early control of viral infection and the secretion of cytokines to shape T-cell responses (Vivier *et al.*, 2011). *In vivo* experiments have demonstrated that IRF1 robustly regulates the development and functions of NK cells, as suggested by the finding that IRF1 deficiency not only reduced the number of NK cells in the spleen and liver, but also abolished NK cell-mediated cytolytic activity. The impaired transcriptional induction of genes encoding IL-15 and IL-12, cytokines responsible for the development and functions of NK cells, might largely, if not entirely, account for the potent effects of IRF1 on NK cells (Liu *et al.*, 2000; Watford *et al.*, 2003). Interestingly, in contrast to the results seen with the reverse functions in IFN signalling, *IRF2*^{-/-} mice carry similar defects in the development and functions of NK cells compared with *IRF1*^{-/-} mice, whereas the number of NK cells was maintained at a normal level in *IRF2*^{-/-} mice (Taki *et al.*, 2005).

Mammalian adaptive immunity is regulated by two additional types of lymphocytes: B- and T-cells. After encountering antigens, naive B- and T-cells undergo cell division and maturation before exerting their effector functions (Vivier *et al.*, 2011). Among the discovered IRFs, most research on the functions of B- and T-cells has focused on IRF4 and IRF8, whose expression is largely restricted to lymphocytes. Molecular analysis indicated that IRF4 and IRF8 are required for the down-regulation of surrogate light-chain gene expression and its sequential DNA rearrangements during the development of B-lymphocytes (Lu *et al.*, 2003; Lazorchak *et al.*, 2006). Genetic studies also demonstrated that IRF4 is critical to mounting the antibody, cytotoxic or anti-tumour responses of mature B- and T-cell lineages, while IRF8 is partly involved in the transcriptional network governing B-cell

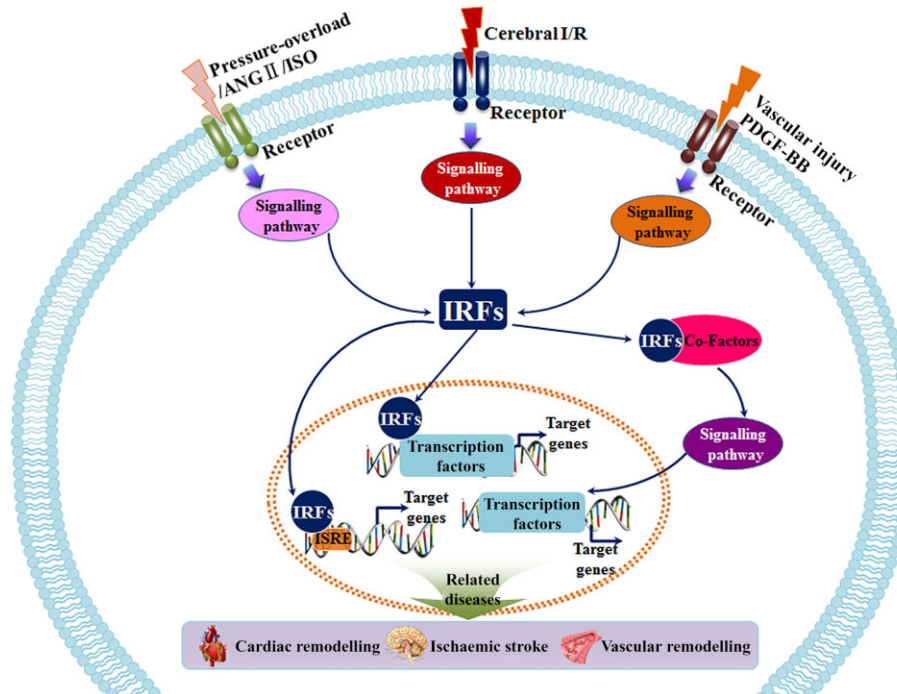


Figure 3

IRFs act as sensors and regulators of cardiovascular stress. Under physiological conditions, IRFs stay in a latent or stable form in the cytoplasm. After cardiovascular stress, such as cardiac pressure-overload, cerebral I/R and wire-induced vascular injury, IRF expression, structure and function are dramatically altered. IRFs convert upstream signalling to their co-activators, co-repressors or modifiers, triggering diverse and specific molecular events that further regulate the expression and activation of target genes. The dysfunction of these molecular programmes cause various cardiovascular diseases, for example cardiac remodelling, ischaemic stroke and vascular hyperplasia. Ang II, angiotensin II; ISO, isoprenaline.

specification, commitment, and differentiation (Pernis, 2002; Wang *et al.*, 2008). In addition to their involvement in B-cell development and functions, IRF8 and IRF4 promote the differentiation of Th1 and Th2 cells by regulating their promoting cytokines IL-12 and IL-4 respectively (Masumi *et al.*, 2002; Rengarajan *et al.*, 2002). In addition, IRF4 is an indispensable effector of IL-21-mediated induction, amplification and stabilization of Th17 phenotypes (Huber *et al.*, 2008; Zhou and Littman, 2009). Like IRF8, IRF1 is critical for IL-12-promoted Th1 cell differentiation, while IRF2 facilitates IL-12 production in cooperation with IRF1 (Elser *et al.*, 2002; Kano *et al.*, 2008). In addition to the extensively investigated IRFs, IRF7 governs the induction of CD8⁺ T-cell responses through the MyD88-IRF7 pathway (Honda *et al.*, 2005).

Given the diverse and essential molecular roles of IRFs in controlling the growth, differentiation and death of various cell types, it is reasonable that IRFs exert pivotal and versatile effects on human diseases, especially on immune diseases and oncogenesis, which have been well documented (Tamura *et al.*, 2008; Savitsky *et al.*, 2010; Yanai *et al.*, 2012). Interestingly, our recent studies and others have demonstrated that IRFs play intricate roles in cardiovascular diseases, especially cardiac remodelling, stroke and vascular injury. In this review, we summarize and discuss the regulatory effects of IRFs as critical novel stress sensors and regulators of the cardiovascular system, and the ways in which they exert their pathophysiological roles. Figure 3 summarizes the functions and potential mechanisms of IRFs in cardiovascular stress.

Functions of IRFs in cardiovascular diseases

IRFs in cardiac remodelling

Cardiac hypertrophy, typically initiated by ill-defined biomechanical stretch stress or neuroendocrine factors, is characterized by increased cardiomyocyte size accompanied by altered cardiac pump function and reduced ventricular wall tension (Sharif-Naeini *et al.*, 2010; Li *et al.*, 2014). Pathological cardiac hypertrophy is now recognized as the strongest predictor of the development of heart failure, arrhythmia and sudden death. Initially, compensatory hypertrophic growth allows the heart to cope with various pathogenic stimuli, but continuous pathological stimuli terminally convert this change into a maladaptive response with perturbed contractile performance and typical heart remodelling (van Berlo *et al.*, 2013).

In addition to ventricular and cellular remodelling, pathological cardiac hypertrophy involves molecular alterations such as the activation of neuroendocrine factors, the re-expression of fetal genes and changes in proteins involved in excitation-contraction coupling (Kehat and Molkentin, 2010). Angiotensin II, endothelin-1 (ET-1) and insulin-like growth factor I (IGF-I) are well-established neurohumoural and endocrine hormones that promote cardiac hypertrophy, while glycogen synthase kinase 3 β (GSK3 β), regulator of G-protein signalling 5, class II HDACs, PLA2 and the cyclic GMP-dependent PKGI have distinct anti-hypertrophic prop-

erties (Fiedler *et al.*, 2002; Sanbe *et al.*, 2003; Li *et al.*, 2010a,b; Yan *et al.*, 2011). Based on these critical molecules, numerous dominant signalling pathways regulating cardiac remodelling have been revealed, particularly the GPCR–calcineurin–NFAT pathway, Ras–MAPK signalling, and the IGF-I–PI3K–Akt/PKB–mammalian target of rapamycin/GSK3 β axis (Heineke and Molkentin, 2006; Huang *et al.*, 2010; Chen *et al.*, 2013b; Jiang *et al.*, 2014e; Liu *et al.*, 2014; Zhang *et al.*, 2014d). Experimental evidence from our laboratory and others' indicated the involvement of IRF1, IRF3, IRF4, IRF5, IRF7, IRF8 and IRF9 in the initiation and development of cardiac remodelling.

IRF1 is expressed ubiquitously, including in cardiomyocytes. In a well-established mouse model of cardiac hypertrophy induced by chronic aortic banding, IRF1 protein expression increases progressively during the early phase, and then dramatically decreases to below baseline levels during the later stage both in the animal model and in patients with dilated and hypertrophic cardiomyopathy. Gene-intervention studies have validated the profoundly detrimental effects of IRF1 in cardiac remodelling, as demonstrated by the accelerated ventricular hypertrophy and fibrosis in aortic banding-stimulated, cardiac-specific *IRF1*-transgene (TG) mice, with reverse phenotypes in *IRF1*^{-/-} mice and rats. However, neither IRF1 overexpression nor its deletion impair basal cardiac functions (Jiang *et al.*, 2014a). IRF1 functionally regulates inducible NOS (iNOS) expression by interacting with the binding site in the promoter region of the *iNOS* gene, which is significantly up-regulated in patients with heart failure (Huang *et al.*, 2011). The deletion of *iNOS* in IRF1-TG mice prevents the exacerbated heart remodelling and dysfunction (Jiang *et al.*, 2014a).

In contrast to IRF1, IRF3 and IRF7 function as negative regulators of pathological cardiac remodelling. *In vivo* chronic pressure overload and, *in vitro* isoprenaline stimulation could promote IRF3 phosphorylation and nuclear accumulation. Intriguingly, while sharing similar structures and phenotypes with IRF3, the IRF7 protein levels were markedly reduced in response to hypertrophic stimuli, possibly as a result of their disparate signalling pathways (Lu *et al.*, 2013a; Jiang *et al.*, 2014b). IRF3 directly interacts with ERK2 in cardiomyocytes, thereby inactivating the ERK1/2 signalling pathway (Lu *et al.*, 2013a). Alternatively, IRF7 directly interacts with IKK β by masking its kinase domain and then blocking IKK β –I κ B–NF- κ B-regulated cardiac remodelling and dysfunction (Jiang *et al.*, 2014b). Additionally, the functions of IRF3 in cardiac remodelling are disputed. Tsushima *et al.* (2011) reported that IRF3 regulates angiotensin II-induced cardiac fibrosis, but not hypertrophy. Different hypertrophic stresses and discrepant gene technologies might contribute to these seemingly paradoxical results. In Tsushima's study, ERK1/2 was also linked to angiotensin II-stimulated IRF3 activation, but located upstream of IRF3. Using a myxoma virus-infected non-permissive primary MEF model, Wang *et al.* (2004) also demonstrated the upstream regulatory effect of ERK1/2 on IRF3 activation. A conservative interpretation of these results suggests that, a negative feedback loop might exist in IRF3-to-ERK1/2 signalling for specific factors involved in cardiac remodelling. Collectively, the regulatory effects of IRF3 on cardiac remodelling in response to diverse stimuli are undefined, and the relationship between IRF3 and ERK1/2 remains to be rigorously clarified.

Although IRF4 and IRF8 were previously reported to be restricted to lymphocytes, our research group found that both of these transcription factors are highly expressed in human and animal hearts. Gain- and loss-of-function approaches have elucidated the exacerbating and alleviating effects of IRF4 and IRF8, respectively, on cardiac remodelling (Jiang *et al.*, 2013; 2014d). Previous experimental approaches have confirmed that the transcription factor CREB was necessary for activation of the fetal gene programme in cardiac hypertrophy (Kong *et al.*, 2006). In our recent studies, the CREB promoter was demonstrated to contain three IRF4 binding sites and to be responsible for the regulatory effects of IRF4 (Jiang *et al.*, 2013). Studies on the mechanisms of IRF8, however, highlighted a critical modulator of hypertrophic process, NFATc1, located downstream of IRF8. IRF8 shows a potent capacity to directly interact with NFATc1 depending on its IAD1 domain to prevent NFATc1 translocation to the nucleus and leading to at least partial inhibition of cardiac remodelling (Jiang *et al.*, 2014d).

As in the immune response, IRF5 is activated and translocated into the nucleus in the heart from tight skin (*Tsk*^{-/-}) mice with spontaneous heart failure. While total and phosphorylated IRF5 are comparable with their levels in the heart from WT controls, the total ubiquitin and K⁶³ ubiquitin levels of IRF5 are dramatically altered in the *Tsk*^{-/-} heart, suggesting that the structural modification of IRF5 might influence its function in pathological cardiac remodelling and heart failure. The treatment of apoAI mimetic 4E, a protein that could reduce inflammation by inhibiting IRF5 activation, delays the onset of heart failure (Xu *et al.*, 2012). Although the protective effect in heart remodelling might result from reduction of the inflammatory responses by IRF5, nuclear translocation of IRF5 did take place in the myocardium, indicating that IRF5 decrease-induced cardiac protection could arise through an immune-independent pathway. Nonetheless, the involvement of IRF5 in cardiac remodelling merits further exploration.

As noted earlier, in cardiac remodelling, crucial transcription factors, including NFAT, myocyte enhancer factor 2 (MEF2) and SRF, recruit co-activators or co-repressors to mediate the hypertrophic responses. IRF9 binds to the transcription activation domain (TAD) of myocardin, a co-activator of SRF, in response to aortic banding or to isoprenaline infusion, thereby strongly inhibiting CArG box-dependent reporters. Intriguingly, this anti-hypertrophic property of IRF9 is countered by p300, which also binds directly to TAD to activate myocardin. IRF9 protein expression is dramatically elevated in remodelled human and mouse hearts. Accordingly, IRF9-KO mice exhibited aggravated cardiac hypertrophy and fibrosis after hypertrophic stimuli, whereas the up-regulation of IRF9 expression alleviated these responses. Thus, IRF9 functions as a previously-identified negative regulator of cardiac remodelling (Jiang *et al.*, 2014c).

In addition to biomechanical and neuroendocrine stresses, myocardial ischaemia/reperfusion (I/R) injury also contributes to maladaptive cardiac damage (Timmers *et al.*, 2008; Xiao *et al.*, 2012; Frohlich *et al.*, 2013). Unexpectedly, our recent data indicate that, in contrast to the protective effect on the hypertrophic response, IRF9 functions as a promoter of myocardial I/R-derived cardiac dysfunction and

remodelling (Zhang *et al.*, 2014c). Unlike in cardiac hypertrophy, cardiomyocyte death and the inflammatory response are the dominant pathological factors during I/R injury (Hausenloy and Yellon, 2013). Thus the molecular mechanism by which IRF9 regulates myocardial I/R is likely to be different from that of cardiac hypertrophy. Our investigation indicated that the detrimental effect of IRF9 might depend on its modulation of Sirt1 expression and the corresponding apoptotic signalling. Further in-depth studies are needed to elucidate the underlying molecular events in IRF9-dependent myocardial I/R injury.

Functions of IRFs in stroke

Stroke usually arises from either ischaemia or haemorrhage, which interrupt blood flow to the brain. Ischaemic strokes account for approximately 87% of all of such cases (Candelario-Jalil, 2009; Go *et al.*, 2014). Once cerebral I/R occurs, a series of intricate and highly interconnected cellular and molecular events are initiated and ultimately disturb central autonomic control (Soros and Hachinski, 2012). In the early stage following ischaemic injury, metabolic compromise, calcium overload and oxidative stress rapidly lead to neuron death in the infarct core (Wang *et al.*, 2012). Compared with other organs, the brain is much more susceptible to oxidative attack as a result of its high content of polyunsaturated fatty acids, oxidative metabolic activity and low antioxidant capacity (Halliwell, 2006). In later events, the overly abundant oxygen radicals participate in signalling pathways of neuroinflammation and apoptosis, exacerbating the initial ischaemic damage and yielding penumbral tissue death (Candelario-Jalil, 2009; Lu *et al.*, 2013b; Wang *et al.*, 2013b). Stroke-induced cell death occurs preferentially *via* an apoptotic mechanism rather than necrosis. An alteration in genes encoding caspases and the Bcl family is involved in both the early and late phases of stroke (Stankowski and Gupta, 2011). In the inflammatory response, the TLR family exerts key functions and has attracted much more attention in recent years for its potential therapeutic roles in treating stroke. Generally, following the activation of TLRs, downstream signalling elicits the production and secretion of cytokines and chemokines, which initiate a severely detrimental inflammatory response to cerebral ischaemia (Tang *et al.*, 2007a; Ziegler *et al.*, 2007; Marsh and Stenzel-Poore, 2008). Paradoxically, emerging studies have suggested that the preconditioning by exogenous TLR ligands might confer robust neuroprotection against subsequent I/R injury (Marsh *et al.*, 2009b; Stevens *et al.*, 2011; Chamorro *et al.*, 2012). All of these phenomena appear to protect against or promote stroke at least partly by reprogramming the genomic response. The IRF family has been identified as one of these genetic factors.

The strong regulatory functions of IRFs in cerebral I/R were originally described in studies demonstrating that IRF1 expression was dramatically up-regulated in the ischaemic regions of a middle cerebral artery occlusion-induced mouse stroke model (Nguyen *et al.*, 1997; Iadecola *et al.*, 1999; Raghavendra Rao *et al.*, 2002). Iadecola and subsequent researchers (Alexander *et al.*, 2003) indicated that *IRF1* deletion was beneficial to the post-ischaemic brain, although the underlying mechanisms were largely unknown. Using a loss-of-function approach, Caso and colleagues (Caso *et al.*, 2007) observed that *TLR4*-deficient mice exhibit minor infarction

and inflammation after an experimental stroke. In these mice, IRF1 expression was significantly reduced compared with that of their wild-type littermates, explaining at least in part the neuroprotective effect of the *TLR4* deletion. IRF2 also showed potential involvement in the nervous system, given that IRF2 physically interacts with NF- κ B in neural cells (Drew *et al.*, 1995). However, the effects of IRF2 on stroke are obscure. Additional studies on the functions and underlying molecular mechanisms are required to clarify the modulatory effects of IRF1 and IRF2 on stroke.

Early studies with IRF3 and IRF7 found no direct evidence to indicate the involvement of these IRFs in stroke, but were focused on their essential roles in TLR ligand pretreatment-induced tolerance to ischaemic brain injury. Systemic preconditioning by LPS or the unmethylated CpG oligonucleotides provides neuroprotection against cerebral I/R injury by activating their receptors, TLR4 and TLR9 respectively (Marsh *et al.*, 2009a; Stevens *et al.*, 2011; Vartanian *et al.*, 2011). An analysis of the reprogrammed genes located downstream of TLRs indicated that IRFs are closely related to the beneficial effects on stroke of preconditioning by TLR ligands. A subsequent gene-disruption approach validated the indispensable roles of IRF3 and IRF7 in these cases (Stevens *et al.*, 2011). Most recently, Cui *et al.* (2013) demonstrated that pretreatment with chloroquine markedly suppressed the TLR3/IRF3-IFN- β signalling pathway, which was activated after global cerebral ischaemia in rats, thereby improving their spatial memory capacity. Additionally, TLR7 preconditioning also provided robust neuroprotection in response to stroke, an effect that was IRF7-dependent (Leung *et al.*, 2012). These protective effects seem to involve the IRFs that are related to immune/inflammatory responses. Notably, our laboratory recently generated a novel rat strain, *IRF3*-KO, and provided direct evidence that *IRF3* ablation attenuates stroke in rats, as indicated by blunted apoptosis (H. Li, unpubl. data). The direct effects of IRF3 on stroke in different experimental studies and the underlying mechanisms require further research.

In addition to the heart, IRF4 and IRF8 are also expressed constitutively in neurons and can be induced and suppressed, respectively, by cerebral ischaemia. Our recent investigations have demonstrated that neuron-specific *IRF4*-TG and *IRF8*-TG mice exhibited improved stroke outcomes and reduced infarct lesions, whereas these protective effects were reversed in *IRF4*-KO and *IRF8*-KO mice, respectively (Guo *et al.*, 2014; Xiang *et al.*, 2014). Mechanistically, SRF, a transcription factor that is essential for neuron survival, is required for the beneficial functions of IRF4, as indicated by the complete absence of phenotypes of *IRF4*-TG mice following SRF ablation (Guo *et al.*, 2014).

The influence of IRF9 on stroke has been reported recently by our research group. Promisingly, our studies indicated that IRF9 is a positive regulator of stroke by activating neuronal death-associated signalling pathways. After stimulation with cerebral I/R, *IRF9*^{-/-} mice showed markedly decreased neuronal death and neurological deficits, whereas IRF9 overexpression sensitized the neurons to death. Using a bioinformatic approach and genetic manipulation, the IRF9/Sirt1/p53 axis was identified as a crucial signalling pathway in stroke events. Our recent data suggest that, in response to acute I/R stress, IRF9 suppresses Sirt1 expression, followed by the activation of p53-regulated cell death signalling (Chen *et al.*, 2014).

IRFs involved in regulating vascular injury

Intimal hyperplasia, a prevalent form of severe arterial remodelling after vascular injury, is almost inevitable during various vascular diseases and their treatments, such as atherosclerosis, stenting, angioplasty and bypass surgery (Dzau *et al.*, 2002). This pathological condition consists of multifaceted interactions among vascular smooth muscle cells (VSMCs) and other cell types, as well as complex intracellular and intercellular regulatory mechanisms. In response to biomechanical injury or other stimuli, endothelial cells trigger and amplify inflammatory responses by recruiting inflammatory cells. Although this inflammation is initially a reparative mechanism, persistent inflammatory processes stimulate VSMC proliferation, migration, phenotypic switching and extracellular matrix (ECM) deposition, the most important pathological bases of neointimal thickening (Davis *et al.*, 2003; Inoue *et al.*, 2011). The deregulation of the VSMC is the central core of neointimal formation. Immediately after injury, VSMCs undergo phenotypic change, switching from a differentiated (or contractile) state to a de-differentiated (also termed 'synthetic') phenotype (Davis-Dusenbery *et al.*, 2011). The de-differentiated VSMCs, which are characterized by the reduced expression of contractile genes, are particularly susceptible to proliferation, migration, and ECM production (Alexander and Owens, 2012). These changes in VSMCs are regulated by a range of molecular pathways, especially growth factor/cytokine signalling (Dzau *et al.*, 2002; Li *et al.*, 2011a). Additionally, the involvement of immune mechanisms has also been demonstrated under these pathological conditions (Schiffrin, 2014). Several IRFs serve as crucial factors in vascular injury, not only through their participation in immune responses.

In the effort to explore the effects of IRF members on vascular injury, IRF1 has been studied more often than other IRFs and is deeply involved in vascular remodelling. IRF1 can be induced after IFN- γ stimulation both *in vitro* and *in vivo*. Horiuchi *et al.* (2000) indicated that IRF1, along with the JAK-STAT pathway, participates in the response to activation, by exogenous IFN- γ , of angiotensin AT₂ receptors, which are closely associated with cell growth, differentiation and injury. Increased level of IRF1 also partly mediates endogenous IFN- γ -promoted intimal thickening in immune-deficient Rag-1-KO mice (Dimayuga *et al.*, 2005; Kusaba *et al.*, 2007). In addition to IFNs, ET-1, a potent vasoconstrictor and growth-promoting mediator, can induce IRF1 activation in human VSMCs (Woods *et al.*, 2003). However, the beneficial or deleterious effects of IRF1 activation on intimal hyperplasia are less clearly defined. Experimental results from the Wessely and Li research groups (Wessely *et al.*, 2003; Li *et al.*, 2009) have provided direct evidence about the effects of IRF1 on vascular remodelling, indicated by the fact that vascular injury-stimulated neointimal formation was significantly aggravated in *IRF1*-deficient mice compared with wild-type mice. From a mechanistic standpoint, IRF1 exhibits pleiotropic anti-hyperplastic activities by regulating the expressions of various factors, such as AT₂ receptors, iNOS, mitogens, CD40 and PPAR γ , to attenuate endothelial dysfunction, cellular migration and VSMC proliferation (Wagner *et al.*, 2002; Wessely *et al.*, 2003; Lin *et al.*, 2004; Li *et al.*, 2009).

Consistent with the results from IRF1, our recent studies have indicated that both IRF3 and IRF7 act as inhibitors of neointimal formation, based on gain- and loss-of-function approaches in rodents and *in vitro* (Zhang *et al.*, 2014b). A significant down-regulation of IRF3 and IRF7 expression in VSMC was observed after carotid wire injury *in vivo* and stimulation by PDGF-BB *in vitro*. IRF3 binds to the AB domain of PPAR γ , a negative regulator of intimal hyperplasia (Lim *et al.*, 2006; Duan *et al.*, 2008), facilitating PPAR γ transactivation and the subsequent down-regulation of the expression of PCNA to ultimately suppress VSMC proliferation (Zhang *et al.*, 2014b). IRF7 is important for neointimal formation because of its ability to directly interact with the transcription factor ATF3 and to inhibit the ATF3-mediated induction of PCNA (L. Huang, submitted).

Several studies of the underlying mechanisms of VSMC phenotypic modulation have focused on another transcription factor, SRF. In addition to participating in cardiac hypertrophy and neuron survival, SRF and its co-activator, myocardin, play essential roles in SMC differentiation and phenotypic switching (Camoretti-Mercado *et al.*, 2003; Miano, 2003; Yoshida *et al.*, 2003). Recent studies from our group have demonstrated that IRF8 can act as an accelerated regulator of neointimal formation through a direct interaction with the SRF/myocardin complex, thereby regulating SRF transactivation to inhibit the expression of SMC-marker genes (Zhang *et al.*, 2014a).

Most recently, IRF9 was investigated in our research laboratory because of its regulatory effects on vascular remodelling in response to both *in vivo* and *in vitro* stimuli. Compared with controls, IRF9 protein expression is significantly higher in human femoral artery specimens with in-stent restenosis, a wire injury-induced neointimal formation mouse model, and PDGF-BB-stimulated VSMC. Furthermore, *IRF9* ablation attenuates VSMC proliferation and intimal thickening in response to injury, whereas IRF9 up-regulation results in the opposite phenotype, suggesting that IRF9 is an activator of intimal hyperplasia. Detailed mechanistic studies have indicated that IRF9 negatively regulates the transcription of a vascular protective factor, Sirt1, after vascular injury, and that IRF9-controlled intimal remodelling is dependent on Sirt1 deacetylase activity (S. M. Zhang, submitted).

Among vascular diseases that typically exhibit vascular remodelling, atherosclerosis and abdominal aortic aneurysm (AAA) present high-risk factors for other severe cardiovascular diseases. In our recent investigations, the regulatory functions of IRFs in these two diseases have been assessed. Several IRFs, including IRF1, IRF3, IRF4, IRF7, IRF8 and IRF9, are critically involved in the development of atherosclerosis and AAA (H. Li, unpubl. data). Further, more extensive studies of their underlying mechanisms are needed.

IRFs, the sensors and regulators of cardiovascular stress

As stress sensors and regulators, the involvement of IRFs in immunity, metabolism, and related diseases has been well documented (Zhao *et al.*, 2014). In the results summarized in this review, IRFs involved in cardiovascular diseases are expressed in a latent or stable form in the cytoplasm under normal conditions, but are dramatically altered in response to pathological cardiovascular stress or neuroendocrine factors,

other than viral infection, suggesting that IRFs might act as cardiovascular stress-inducible factors. Furthermore, IRFs respond to various intracellular or extracellular forms of stress, undergo structural/functional variation, and initiate corresponding signalling pathways to regulate a series of phenotypic alterations. From the published studies described in this review and unpublished data from our group, it is clear that the IRF family is intrinsically associated with and dramatically regulates the aetiologies of cardiac, neural and vascular diseases through its potent effects on cell dilation, proliferation, apoptosis, phenotype switching and inflammatory responses. Thus, IRFs have a much more complex role in these cardiovascular diseases and do not simply act through their mediation of the immune system. Interestingly, under basal conditions, neither the artificial up-regulation nor down-regulation of IRFs negatively affected the physiological functions of mice or cells. Rather, they exert significant influence only on pathological stimuli. These results suggest that the contributions of dysregulated IRFs might depend on their responses to detrimental cardiovascular states. Thus, in addition to their effects in the immune system, IRFs might also act as prominent stress sensors and regulators of cardiovascular disease.

Although the effects and mechanisms of IRFs have been systematically investigated, several important questions require further elucidation. For instance, other IRFs expressed in the cardiovascular system might have critical roles under pathophysiological conditions. Moreover, the timing and relative IRF protein levels and their relationships with functions should be determined. Additionally, many non-parenchymal cells in tissues exert important regulatory functions in response to environmental stimuli. The expression profiles and effects of IRFs in these non-parenchymal cells merit in-depth investigation. Our ongoing studies focus on these unresolved issues, the results of which will provide promising therapeutic targets for cardiovascular diseases.

Potential clinical applications of IRFs

Given the versatile and potent effects of IRFs, it is not surprising that this transcription factor family has a profound role in various diseases, especially in the related diseases in the immune and cardiovascular systems. In the recent years, genome-wide association studies (GWAS) have greatly facilitated wide screening and deep exploration of the latent associations between human diseases and specific genes. Utilizing this advanced technology, the preliminary clinical relevance of IRFs has been established. A recent study observed that *IRF1*, at positions -388 and -410, might be a candidate gene marker for chronic hepatitis B and C (Korachi *et al.*, 2013). Applying genome-wide SNP association study, Di Bernardo *et al.* (2008) demonstrated that *IRF4* is strongly associated with susceptibility to chronic lymphocytic leukaemia (CLL). The CLL risk loci were identified at 6p25.3 (rs872071, *IRF4*). Additionally, the SNP rs9378805 in *IRF4* is associated with recurrent bronchitis, as supported by the GWAS data set (Pinto *et al.*, 2013). In studies of the immune system, although cellular mechanisms that initiate pathogen recognition and IFN production are critical to protection against viral infection response, over-activation of these molecular events can contribute to adverse pathogenic effects charac-

teristic of autoimmune disorders. One representative example is systemic lupus erythematosus (SLE), a genetic and environmental factors-triggered disease marked by high levels of type I IFNs in serum (Banchereau and Pascual, 2006; Yang *et al.*, 2012). Several large-scale genetic association studies have shown that, the major alleles, rs2004640 and rs1131665 (412Q) in *IRF5* and *IRF7*, respectively, predispose the host to the development of SLE in several ethnic groups, cumulatively providing direct genetic evidence that IRFs are closely linked to human autoimmune diseases (Sigurdsson *et al.*, 2005; Graham *et al.*, 2006; Cunninghame Graham *et al.*, 2007; Fu *et al.*, 2011).

In terms of the relevance of IRFs to cardiovascular diseases, previous and ongoing studies have suggested the involvement of IRFs in cardiac remodelling, stroke and vascular injury, through the markedly altered expression levels of IRFs in response to the corresponding pathological cardiovascular conditions. For instance, *IRF1*, *IRF4* and *IRF8* are significantly down-regulated in failing human hearts compared with healthy controls (Jiang *et al.*, 2013; 2014a,d), whereas *IRF3* is profoundly up-regulated in the hearts of patients with dilated or hypertrophic cardiomyopathy (Lu *et al.*, 2013a). All of these alterations in patients are consistent with those seen in animal models of cardiac remodelling in the maladaptive stage. However, the alterations of IRF expression are not always consistent in the compensatory and maladaptive hypertrophy. For example the progressively increasing level of *IRF1* in the early stage and markedly reduced *IRF1* expression in the late stage of cardiac hypertrophy have not been observed and merit further investigation in human hearts. Furthermore, improved understanding of the timing of changes and the switches to turn on or turn off the expression and activation of IRFs in particular clinical diseases will provide promising bases for novel therapies.

Conclusions and perspectives

A growing number of studies have demonstrated that intricate signalling cascades converge on certain transcription factors that critically participate in the development of various diseases. Accordingly, an understanding of the regulatory mechanisms and counterbalancing molecules that selectively affect these specific transcriptional factors could be of great interest for preventing and treating these diseases. IRFs are a family of such transcription factors. The involvement of IRFs in the immune response has been known for a long time. Intriguingly, recent studies provide novel insights into the regulatory effects of IRFs on diseases of the heart, brain and vasculature. As cardiovascular stress-responsive regulators, IRFs undergo a series of structural and functional modifications to adapt or mediate environmental or intracellular stimuli-triggered pathological conditions, as described in this review. However, the functions of IRFs are much more extensive than earlier estimates. Our recent studies have also demonstrated potential functions of IRFs in metabolic diseases (Wang *et al.*, 2013c,d; 2014), and these studies are still ongoing. Future studies should examine the influences of the IRF family on other diseases, for example respiratory diseases, tuberculosis and diarrhoea. Although the growth of genetic approaches, bioinformatic methods and high-throughput techniques facilitate

our experimental studies, the molecular events underlying the IRF-regulated cellular responses are only partly understood and remain one of the most understudied areas in clinical and experimental research. Studies on the expression and function of IRFs raise a particularly interesting question: why are the trends in the altered expression of IRFs not consistent with their protective or deleterious effects? Among the divergent and overlapping molecular programmes of the IRF family, priorities for investigation should include the interplay of IRF members, the functional and physical interactions with their co-factors, and the bridges for the association of upstream or downstream events to IRFs. In addition, given that IRFs are shared by different signalling pathways under common pathological conditions, the governing effects of IRFs on these pathways are worthy of further validation and investigation. Most importantly, a deeper understanding of the precise regulatory effects and molecular mechanisms of these regulators will be crucial not only for disease treatment, but also for a global understanding of gene networks and cell behaviour.

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Conflict of interest

None.

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