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# Pattern-Recognition Receptors Sensing Viral Infection in Myocarditis and Inflammatory Heart Disease

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## 1. Introduction

Myocarditis is a potentially life-threatening heart disease affecting both children and adults which presents with a broad spectrum of clinical manifestations. Symptoms range from asymptomatic infection to a fulminant course that rapidly progresses to dilated cardiomyopathy (DCM) and heart failure. Viral infection of the heart is a major cause of acute myocarditis, leading to myocardial inflammation and tissue damage. Cellular infiltration in acute viral myocarditis may be caused by direct cytopathic effects of the virus, pathologic responses to persistent viral replication as well as autoimmunity triggered by the virus (Liu and Mason, 2001; Bowles and Vallejo, 2003; Linde et al., 2007; Rose et al., 2009; Rutschow et al., 2010). The cardiovirulence of the viral agent, together with the host's genetic susceptibility and the variability in the innate and acquired immune system, appear to determine the extent of the inflammatory reaction, thereby predicting clinical outcome (Kindermann et al., 2008).

Recently, meaningful advances have been made in our understanding of cellular mechanisms that are aimed to suppress viral propagation in inflammatory heart disease. In the first line of defense against viral replication, the host's innate immune system is activated by unspecific, albeit effective interactions of cellular receptors with distinct pathogen-derived ligands. A variety of pattern-recognition receptors have been shown to be implicated in the detection of invading microbial agents (Kawai and Akira, 2010; Takeuchi and Akira, 2010). Upon viral infection of the heart, different signal pathways initiate an inflammatory response and orchestrate the concerted anti-viral defense machinery in a complex manner. Toll-like and RIG-I-like receptors are essential for the recognition of pathogen-associated molecular patterns and their activation induces intracellular signalling pathways which lead to the production of pro-inflammatory cytokines, chemokines, and interferons (Bowles and Vallejo, 2003; Fairweather et al., 2005; Triantafilou et al., 2005; Frantz et al., 2007; Linde et al., 2007; Yajima and Knowlton, 2009; Kawai and Akira, 2010; Takeuchi and Akira, 2010; Yamamoto and Takeda, 2010; Zhu and Mohan, 2010). Vice versa, interferons appear to induce the expression of a subset of toll-like receptors (Khoo et al., 2011). Type I interferons execute anti-viral responses by modulating cell growth,

establishing an anti-viral state and influencing the activation of various immune cells. These potent anti-viral cytokines are best known for their role as innate immune mediators (Yajima and Knowlton, 2009). In the course of viral myocarditis, apoptotic signalling pathways are activated and modulate disease pathogenesis. However, cardiotropic viruses have evolved a battery of highly specific strategies to circumvent this innate protective response of the host and successfully replicate in cardiomyocytes (Versteeg and García-Sastre, 2010). Viral factors with or without homology to host proteins specifically target key components of the anti-viral defense machinery, some of which are transcription factors involved in establishing an anti-viral state.

In the present review we focus on the contribution of pattern-recognition receptors engaged in the early response cascade against cardiotropic viruses. In particular, we report on different signal transduction pathways emerging from membrane-associated and cytosolic receptors that inhibit viral dissemination and, furthermore, give a brief overview of the various adaptor molecules involved in these pathways. Not covered in this review are the diverse viral mechanisms for antagonizing the innate immune response and the precise cellular actions of cytokines in executing this anti-viral defense. Understanding the exact mechanisms by which viral components activate pattern-recognition receptors in the heart and modify gene expression profiles may help to improve novel therapeutic regimes for the treatment of viral myocarditis (Topkara et al., 2010).

## 2. Clinical course of myocarditis

Myocarditis is defined as a heterogeneous common disease pathway for myocardial inflammation resulting from a variety of infectious, immune and non-immune insults. The histopathologic hallmark of the disease is characterized by inflammatory infiltrates of the myocardium with concomitant necrosis or degeneration of adjacent cardiomyocytes in the absence of predominant ischemia. Despite this clear definition, the classification and diagnosis of myocarditis continue to present clinical problems. In recent years our understanding of the pathophysiology and natural clinical course of the disease has improved, probably because histological findings obtained from endomyocardial biopsies have routinely been combined with modern molecular biological and immunological tools in the detection of viral genomes persisting in the heart (Heidecker et al., 2011).

From epidemiological studies, it is known that viruses are the most frequent cause of myocarditis in Europe and North America although in rare cases bacteria, protozoa, and even fungi have also been implicated as infectious agents (Ellis and Di Salvo, 2007). Among the more common cardiotropic viruses are enteroviruses including Coxsackie virus, adenoviruses, parvovirus B19, hepatitis C virus, and human immunodeficiency virus (Kühl et al., 2005; Magnani and Dec, 2006; Mahrholdt et al., 2006; Noutsias et al., 2009; Rose, 2009; Pankuweit and Maisch, 2010). Other non-infectious etiologies of myocardial inflammation include hypersensitivity reactions against drugs, unexplained toxic reactions, and immunological syndromes including Churg-Strauss syndrome, giant cell myocarditis, systemic lupus erythematosus, sarcoidosis, Wegener's granulomatosis, and others (Magnani and Dec, 2006; Ellis and Di Salvo, 2007; Rose, 2009). Although infections with cardiotropic viruses are believed to be the most common cause of acute lymphocytic myocarditis, a large number of patients have no identifiable source of the illness (Liu and Mason, 2001; Rose, 2009). Particularly, when the inflammatory process in the myocardium is moderate, the diagnosis frequently remains a challenge for clinicians. The diagnostic sensitivity for viral

myocarditis is comparably low, even when applying modern molecular biological techniques, probably because, due to sampling error, the diagnostic accuracy of endomyocardial biopsy remains a significant limitation (Magnani and Dec, 2006; Ellis and Di Salvo, 2007). The Dallas criteria, originally proposed in an effort to standardize the histopathologic diagnosis of myocarditis, have been shown to be of limited use for epidemiological investigations (Magnani and Dec, 2006; Ellis and Di Salvo, 2007). Thus, despite recent advances in the recognition of myocardial inflammation, the true incidence and prevalence of acute viral myocarditis is still unknown.

The spectrum of clinical manifestations of viral myocarditis is extensive, ranging from asymptomatic infection to fever, myalgias, palpitations, exertional dyspnea, and hemodynamic collapse. Fulminant myocarditis may lead to systolic failure, malignant ventricular arrhythmias and sudden cardiac death (Baughman, 2005; Magnani and Dec, 2006; Rose, 2009, Blauwet and Cooper, 2010). The cardiac symptoms may also be present in more chronic forms of DCM, therefore contributing much to the difficulties in establishing the correct diagnosis. The main reason for the clinical variability appears to lie in the characteristics of the viral agent, together with the host's innate immune system and genetic susceptibility to infection. Given the diversity and insidious onset of clinical manifestations, endomyocardial biopsy in combination with other techniques such as immunohistochemistry, serological analyses, PCR and *in situ* hybridization remains the gold standard for the detection of virus-induced myocardial inflammation (Magnani and Dec, 2006; Rose, 2009).

Although, in severely affected individuals, fulminant viral myocarditis can lead to rapid progressive heart failure, the disease usually resolves spontaneously without persisting ventricular dysfunction (Baughman, 2005; Magnani and Dec, 2006; Rose, 2009, Blauwet and Cooper, 2010). Continuing cardiovascular symptoms in the absence of ventricular compromise may indicate that chronic persistent myocarditis has developed, which is characterized by the maintenance of lymphocytic infiltrates combined with foci of myocyte necrosis. Whereas it has been well-established that chronic active myocarditis can induce heart failure, there is still a controversy with respect to the causal relationship of asymptomatic viral infections for the pathogenesis of idiopathic DCM (Yajima and Knowlton, 2009). Several studies have suggested an association between viral persistence in the myocardium and the development of DCM. However, the etiologic significance of viral genomes detected in endomyocardial biopsies from DCM patients is currently unknown (Bock et al., 2010).

### 3. Toll-like receptors in the inflamed heart

Despite a wealth of information regarding the symptomatology and clinical course of the disease, the complex pathophysiological mechanisms underlying inflammatory heart disease are only partially understood. Lessons learned from transgenic mouse models have shed some light on the essential role of endogenous receptors and transcriptional regulators engaged in early anti-viral response. From clinical and animal studies we know that the host's innate immune system acts as the first line of defense against viral replication in a wide array of pathogenic viruses. The innate immune system, which senses pathogen invasion and primes antigen-specific adaptive immunity, has long been considered to be only non-specific and somewhat simpler than that of the adaptive system. However, recent findings on pattern-recognition receptors and their downstream signalling pathways have

led to a reconsideration of the role of innate immunity now seen as a highly potent defense apparatus against microbial pathogens which works in close cooperation with adaptive immunity.

Initial sensing of invading microorganisms by the innate immune system is mediated by pattern-recognition receptors (PRRs), which include toll-like receptors (TLRs), RIG-I-like-receptors, NOD-like receptors, and C-type lectin receptors (Akira et al., 2006; Bauer et al., 2009; Yajima and Knowlton, 2009; Kawai and Akira, 2010; Takeuchi and Akira, 2010). These four classes of germline-encoded PRR families are responsible for recognizing exogenous structures conserved among microbial species, which are called pathogen-associated molecular patterns (PAMPs). Currently, the paradigm of PRRs has changed, since it has been shown that PRRs also recognize endogenous molecules released from damaged cells, collectively termed damage-associated molecular patterns (DAMPs) (Piccinini and Midwood, 2010; Lamkanfi, 2011).

Among the PRRs, toll-like receptors and C-type lectin receptors are transmembrane glycoproteins, whereas retinoic acid-inducible gene (RIG)-I-like receptors and NOD-like receptors function as cytosolic PRRs (Figure 1). Toll-like receptors were first discovered in *Drosophila* as evolutionary ancient molecules that function as receptors for endogenous ligands such as proteolytically cleaved Spätzle protein, but later were found to be present also in the mammalian system where they respond to microbial components as well as endogenous ligands including heat shock proteins HSP60, HSP70, and gp96 (Medzhitov et al., 1997; Ohashi et al., 2000; Vabulas et al., 2002; Vabulas et al., 2002b; Kim et al., 2009; Arnot et al., 2010). Toll-like receptors are expressed on macrophages, dendritic cells, endothelial cells, and interestingly also on cardiac myocytes (Boyd et al., 2006). Structurally, they are characterized by a highly variable amino-terminal region containing a leucine-rich repeat (LRR) ectodomain, followed by a hydrophobic transmembrane region and a cytoplasmic toll/interleukin 1 receptor (TIR) homology domain, which mediates interaction between TLRs and downstream signalling molecules (Choe et al., 2005; Bell et al., 2006; Jin et al., 2007; Kang et al., 2009; Park et al., 2009). Ligand binding is mediated by the extracellular LRR ectodomain, which is composed of 19-25 tandem copies of the "xLxxLxLxx" motif (Jin and Lee, 2008). In humans, 10 members of the germline-encoded TLR family have been identified so far, TLR1-TLR9 being conserved in humans and mice. Due to a retroviral insertion, TLR10 is not functional in mice and the murine TLRs 11-13 are not present in humans (O'Neill, 2008; Kawai and Akira, 2010).

Ligand binding of PAMPs by TLRs occurs at the plasma membrane (TLR1, TLR2, TLR4-6) as well as in endolysosomal compartments and the endoplasmic reticulum (TLR3, TLR7-9) (Frantz et al., 2007; Kawai and Akira, 2010; Takeuchi and Akira, 2010; Yamamoto and Takeda, 2010). The difference in the downstream signalling cascades activated can be partly explained by the individual TLR molecule, which recognizes a specific subset of PAMPs and recruits different TIR domain-containing adaptors to the receptor. Ligands for TLRs include a broad range of various microbial components, such as bacterial lipoprotein moieties (TLR1-2, TLR6), lipopolysaccharide (TLR4), and flagellin protein (TLR5). Toll-like receptor 3, the first TLR family member to be implicated in the recognition of viral nucleic acids, binds to double-stranded RNA (dsRNA) molecules, which are produced as intermediates during the replication cycle of many viruses (Alexopoulou et al., 2001). TLR7 and TLR8 receptors recognize single-stranded RNA (ssRNA) and are expressed in a variety of immune cells, including dendritic cells, lymphocytes, monocytes, and NK cells (Bauer et al., 2008). Triantafilou and co-workers reported that inflammatory responses in human myocarditis

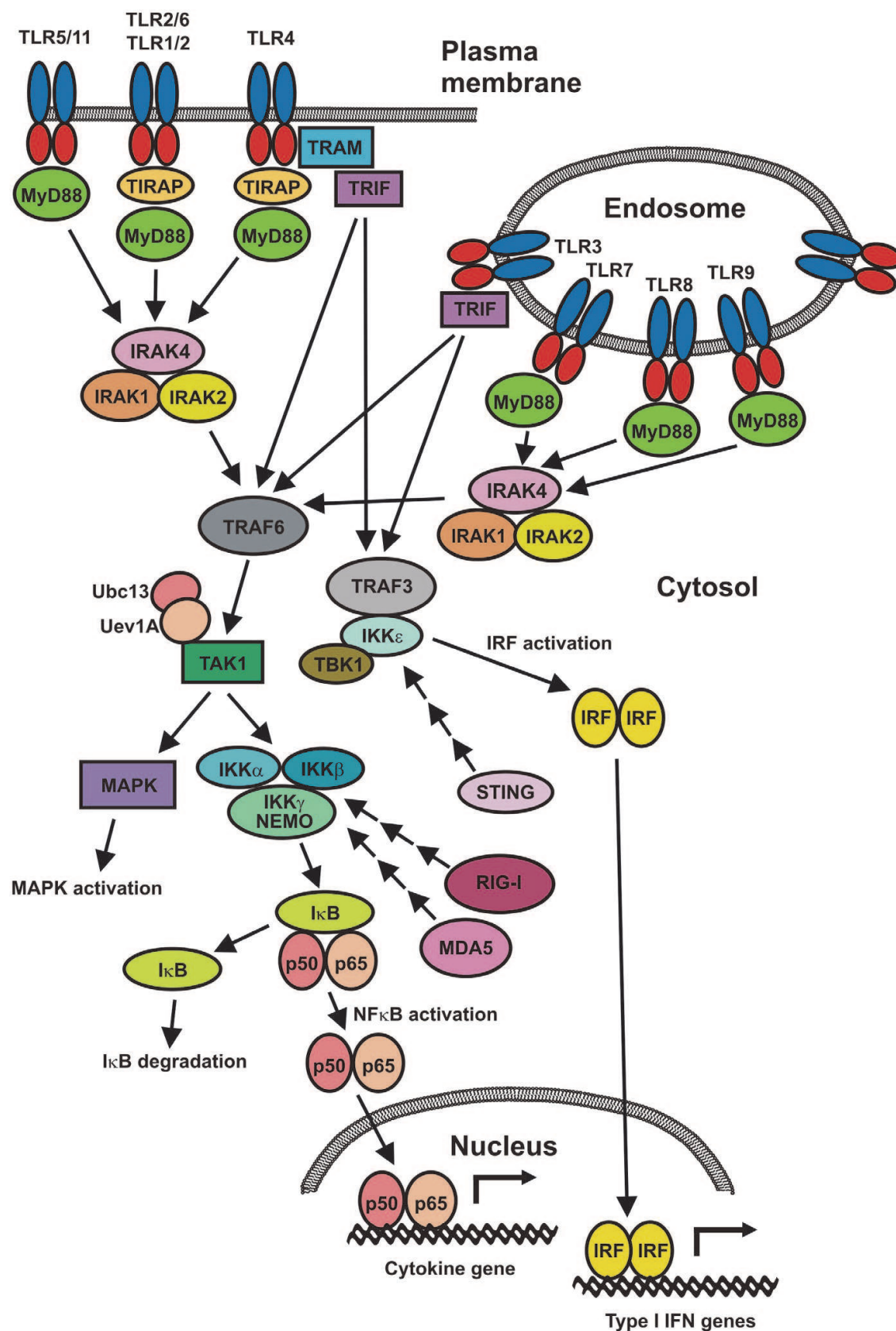


Fig. 1. Signalling pathways engaged in the detection of highly conserved, relatively invariant structural motifs of pathogens. Depicted are different pathways for the recognition

of microbial infection including toll-like receptor (TLR)-mediated MyD88-dependent and TRIF-dependent pathways as well as cytosolic sensors for foreign nucleic acid sequences (STING, RIG-I, and MDA5). For details on key receptors, their signalling adaptors and downstream mediators see text. **Abbreviations:** IKK; I $\kappa$ B kinase, IRAK; IL1-receptor-associated kinase, IRF; interferon-regulatory factor, MDA5; melanoma differentiation-associated gene 5, MyD88; myeloid differentiation primary response gene 88, NEMO; NF- $\kappa$ B essential modulator, NF- $\kappa$ B; nuclear factor- $\kappa$ B, RIG-I; retinoic acid-inducible gene-I, STING; stimulator of interferon genes, TAK1; transforming growth factor- $\beta$ -activated kinase 1, TBK1; TANK-binding kinase 1, TIRAP; toll-interleukin 1 receptor (TIR) domain-containing adaptor protein, TLR; toll-like receptor, TRAF; tumour necrosis factor receptor-associated factor, TRIF; TIR-domain-containing adaptor protein inducing interferon- $\beta$  (also known as TICAM), TRAM; TRIF-related adaptor molecule.

induced by Coxsackie virus B3 (CVB3) are mediated through TLR8 and to a lesser extent through TLR7 (Triantafilou et al., 2005). Elevated expression levels of TLR8 have been associated with heart failure and adverse clinical outcome in patients with enterovirus-associated dilated cardiomyopathy (Satoh et al., 2007). Toll-like receptor 9 functions as a sensor for unmethylated cytosine-phosphate-guanine (CpG) sequences in bacterial and viral DNA, which are rarely found in vertebrates (Barton et al., 2006; Guggemoos et al., 2008). Riad and colleagues demonstrated that, in the acute phase of CVB3-induced myocarditis, TLR9 knockout mice displayed improved LV function associated with reduced cardiac inflammation as compared to CVB3-infected wild-type mice. The cardioprotective effects due to TLR9 deficiency were associated with suppression of the TLR9 downstream pathway as indexed by reduced cardiac levels of the adapter protein MyD88 and the proinflammatory cytokine TNF- $\alpha$  (Riad et al., 2010).

In non-infected cells, TLR3 and TLR7-9 reside in the endoplasmic reticulum, whereas after uncoating and exposure to viral nucleic acids they traffic to the endosomal compartments, where they finally trigger a signal cascade resulting in the activation of the transcription factor NF- $\kappa$ B. The subcellular localization of the various TLR family members appears to be tightly regulated, probably because this avoids unbalanced activation to self-DNA in the absence of viral encounter. The diverse distributions of individual TLRs allow for the surveillance of different intracellular compartments, as viral entry usually occurs by receptor-mediated endocytosis and endosomal fusion or by direct fusion with the plasma membrane (Barton et al., 2006; Barton and Kagan, 2009).

Structural studies have revealed that the hydrophobic ligands of TLR1, TLR2, and TLR4 interact with internal protein pockets on the ectodomain, while hydrophilic dsRNA binds to the solvent-exposed surface of TLR3. Binding to cognate ligands induces homodimerization of the TLR ectodomains, whereas TLR2 forms heterodimers with TLR1 or TLR6 which interact with triacyl- and diacyl lipoproteins, respectively (Jin et al., 2007; Kang et al., 2009; Kawai and Akira, 2010). The membrane-adjacent carboxy-termini of the extracellular domains then converge and probably facilitate dimer formation of the cytoplasmic TIR domains to activate intracellular signalling.

Upon stimulation, the dimeric TLR molecules, except for TLR3, recruit a cytoplasmic adaptor called MyD88 (myeloid differentiation primary response gene 88), which is composed of a death domain (DD) in addition to a TIR domain (Muzio et al., 1997; Frantz et al., 2007; Kawai and Akira, 2010). CpG-DNA activates the TLR signaling pathway via MyD88 and TRAF6 (tumour necrosis factor receptor-associated factor 6), leading to

activation of kinases of the I $\kappa$ B kinase complex (Häcker et al., 2000). When infected with the spirochete *Borrelia burgdorferi*, mice deficient in MyD88 expression develop myocarditis and arthritis similar to the disease in wild-type mice (Liu et al., 2004). However, the pathogen burden was much higher in MyD88<sup>-/-</sup> mice than in wild-type mice, probably because degradation of the bacteria was critically impaired.

In response to stimulation with dsRNA, TLR3 recruits another adaptor molecule referred to as TRIF (TIR domain-containing adaptor protein inducing interferon- $\beta$ , also known as TICAM), which associates with TRAF6 and RIP1 (receptor interacting protein 1) (Yamamoto et al., 2003). TRIF plays a critical role in MyD88-independent TLR3 signalling via TRAF6 and TANK-binding kinase (TBK)-1, leading to the activation of two distinct transcription factors, NF- $\kappa$ B and interferon-regulatory factor 3 (Sato et al., 2003). Hardarson and colleagues reported that TLR3 is an essential component of the innate stress response in encephalomyocarditis virus (EMCV)-induced cardiac injury (Hardarson et al., 2007). Mice lacking TLR3 expression were more susceptible to EMCV infection and had a significantly higher viral load in the heart, but lesser inflammatory changes of the myocardium as compared to control mice. TLR3-deficient mice had impaired proinflammatory cytokine and chemokine production in the heart, while expression of interferon- $\beta$  was not impaired (Hardarson et al., 2007).

Satoh and colleagues reported that in 44 patients with myocarditis increased expression of TLR4 was associated with replication of enteroviral RNA and that these RNA levels were related to cardiac dysfunction (Satoh et al., 2003). In TLR4 signalling, the ligand-bound receptor utilizes MyD88 and TIRAP (toll-interleukin 1 receptor (TIR) domain-containing adaptor protein) for MyD88-dependent as well as TRIF and TRAM (TRIF-related adaptor molecule) for MyD88-independent pathways (Yamamoto et al., 2003b; Fitzgerald et al., 2003). The adaptor protein TRAM is required for activation of TRIF and recently a splice variant of TRAM called TAG (TRAM adaptor with GOLD domain) has been identified that acts as a negative regulator of TRIF-dependent signalling (Palsson-McDermott et al., 2009). TLR1, TLR2, TLR4, and TLR6 signalling requires, in addition, TIRAP which is important for bridging between the cytoplasmic TLR tail and MyD88 (Fitzgerald et al., 2001). Recently, it was shown that infection with Coxsackie virus group B serotype 3 (CVB3) resulted in cardiac remodelling, severe heart failure, and high mortality in TRIF-deficient mice, while wild-type mice showed only mild myocarditis and normal survival postinfection (Riad et al., 2011). Furthermore, virus control was markedly reduced in mice lacking TRIF expression and, interestingly, TRIF-deficient myocytes displayed a TLR4-dependent suppression of interferon- $\beta$ . These findings suggest that TRIF confers cardioprotection against CVB3 infection.

The recruitment of these adaptors triggers a cascade of signalling events, which leads to the activation of the transcription factors NF- $\kappa$ B and interferon-regulatory factors (IRFs). These transcription factors ultimately induce the expression of various inflammatory cytokines, which execute important functions in anti-viral defence. The first step in the synthesis of cytokines leads to the activation of interleukin 1 receptor-associated kinase 4 (IRAK4), which functions as a serine/threonine kinase with an aminoterminal death domain (DD) (Suzuki et al., 2002; Suzuki et al., 2002b). Subsequently, IRAK1 and IRAK2 are phosphorylated by IRAK4 and, after dissociation of MyD88, a complex with TRAF3 and TRAF6 is formed (Kawagoe et al., 2007; Kawagoe et al., 2008; Lin et al., 2010). TRAF6 acts as an E3 ligase in conjugation with the E2 ubiquitin-conjugating enzymes Ubc13 and Uev1A and catalyzes the formation of a lysine63-linked polyubiquitin chain on target proteins, including TRAF6



itself, IRAK, and the NF- $\kappa$ B essential modulator (NEMO) (Deng et al., 2000). Transforming growth factor- $\beta$ -activated kinase 1 (TAK1) is recruited and ubiquitinated by TRAF6 (Wang et al., 2001). Subsequently, the IKK complex composed of IKK $\alpha$ , IKK $\beta$  and NEMO is formed which phosphorylates inhibitor of NF- $\kappa$ B (I $\kappa$ B) kinase- $\beta$  (IKK $\beta$ ). The activated IKK complex then induces phosphorylation and subsequent degradation of I $\kappa$ B by the proteasome. Upon degradation of I $\kappa$ B, the freed NF- $\kappa$ B is no longer sequestered in the cytosol, but translocates into the nucleus, where it drives the expression of cytokine genes. Simultaneously, TAK1 activates the mitogen-activated protein kinase (MAPK) cascade leading to the activation of the transcription factor AP-1, which also targets gene expression of cytokine genes (Wang et al., 2001).

#### 4. Cytosolic sensors for recognizing foreign nucleic acids

Members of the cytosolic RIG-I-like receptor (RLR) family act as cytosolic sensors for genomic RNA of dsRNA viruses and dsRNA intermediates that are generated during replication of ssRNA viruses (Yoneyama et al., 2004; Kato et al., 2005; Bowzard et al., 2009; Ranjan et al., 2009). Retinoic acid-induced protein I is composed of two amino-terminal caspase activation and recruitment domains (CARDs), a central DEAD box helicase/ATPase domain, and a carboxy-terminal regulatory domain (Yoneyama et al., 2004). The latter domain plays a critical role in the specific recognition of dsRNA and 5'-triphosphorylated ssRNA. Other members of the RIG-I family include MDA5 (melanoma differentiation-associated gene 5) and LGP2 (laboratory of genetics and physiology 2). RIG-I and MDA5 distinguish between different RNA viruses and contribute to the host's anti-viral response through recognition of either 5'-triphosphorylated and uncapped ssRNA or dsRNA, species not found among endogenous self-RNA (Kato et al., 2006). Transgenic mice, deficient in RIG-I or MDA5 expression, are highly susceptible to infection with RNA viruses compared to control mice (Kato et al., 2006). The RIG-I homolog LGP2, which lacks the amino-terminal CARDs, potentiates viral RNA recognition by RIG-I and MDA5 through its ATPase domain and has been found to be essential for type I interferon production in response to picornaviridae infection (Satoh et al., 2010). Recently, it has been shown that also DNA-dependent RNA polymerase III is pivotal in sensing viral DNA in the cytoplasm (Ablasser et al., 2009; Chiu et al., 2009). AT-rich dsDNA can serve as a template for RNA polymerase III, which is transcribed enzymatically into dsRNA containing a 5'-triphosphorylated moiety. Activation of RIG-I by dsRNA ultimately induces production of type I interferon and activation of the transcription factor NF- $\kappa$ B.

Recently, it was reported that overexpression of STING (stimulator of interferon genes), a transmembrane protein found in the endoplasmic reticulum of numerous cells such as macrophages, dendritic, endothelial and epithelial cells, induces activation of NF- $\kappa$ B and IRF3 to stimulate type I interferon synthesis (Ishikawa et al., 2009; Barber, 2011). STING-knockout mice were susceptible to lethal infection after exposure to herpes simplex virus 1, suggesting that STING plays an important role in detecting foreign DNA.

Another cytosolic sensor for both bacterial and viral pathogens is AIM2 (absent in melanoma 2), which is essential for inflammasome activation in response to *Fransicella tularensis*, vaccinia virus, and mouse cytomegalovirus (Rathinam et al., 2010). AIM2 regulates caspase-1-dependent maturation of IL-1 $\beta$  and IL-18 and plays a role in natural killer cell-dependent production of interferon- $\gamma$ , as has been shown for AIM2-deficient mice. However, the role of AIM2 in the pathogenesis of myocarditis has not been investigated so far.

| PRRs        | Ligand                    | Localization    | Origin of the ligand | Selected references  |
|-------------|---------------------------|-----------------|----------------------|--|
| TLR2        | Lipoprotein               | Plasma membrane | Bacteria, viruses    | Following coronary artery ligation, <i>tlr2</i> <sup>-/-</sup> mice show reduced mortality and preserved left ventricular function as compared to wild-type mice (Shishido et al., 2003; Riad et al., 2008). Ischemia-reperfusion results in smaller infarct size (Favre et al., 2007). <i>Tlr2</i> <sup>-/-</sup> mice are protected from doxorubicin-induced cardiomyopathy (Nozaki et al., 2004). |
| TLR3        | dsRNA                     | Endolysosome    | Viruses              | <i>Tlr3</i> <sup>-/-</sup> mice are more susceptible to EMCV infection and have a higher viral load, but lesser myocardial inflammation (Hardarson et al., 2007).  |
| TLR4        | Lipopoly-saccharide (LPS) | Plasma membrane | Bacteria, viruses    | <i>Tlr4</i> <sup>-/-</sup> mice are protected from ischemia-reperfusion injury (Chong et al, 2004; Oyama et al., 2004; Kim et al., 2007) and LPS-induced mortality and cardiac dysfunction (Tavener et al., 2004; Nemoto et al, 2009). <i>Tlr4</i> <sup>-/-</sup> mice develop less-severe cardiac hypertrophy following pressure overload by aortic banding than wild-type mice (Ha et al., 2005).  |
| TLR5        | Flagellin                 | Plasma membrane | Bacteria             | Exposure to the TLR5 ligand flagellin triggers cardiac innate immune responses that result in acute contractile dysfunction (Rolli et al., 2010).  |
| TLR6        | Diacyl lipoprotein        | Plasma membrane | Bacteria, viruses    | TLR6 Ser249Pro polymorphism has been associated with lower left ventricular thickness in hypertensive women (Sales et al., 2010).  |
| TLR7 (TLR8) | ssRNA                     | Endolysosome    | Bacteria, viruses    | <i>Tlr7</i> <sup>-/-</sup> mice show markedly reduced myocardial cellular infiltration in experimental autoimmune myocarditis (Pagni et al., 2010). TLR8 expression is higher in DCM patients than in controls (Sato et al., 2007).  |
| TLR9        | CpG-DNA                   | Endolysosome    | Bacteria, viruses    | Upon murine cytomegalovirus-induced myocarditis, <i>tlr9</i> <sup>-/-</sup> mice show higher severity of myocardial infiltration compared to wild-type (Pagni et al., 2010). Myocardial TLR9 expression is reduced in DCM patients (Ruppert et al., 2008).   |
| RIG-I       | Short dsRNA               | Cytoplasm       | Viruses              | RIG-I mRNA is expressed at high levels in normal heart tissue (Ellis et al., 2002). Interferon- $\gamma$ upregulates RIG-I in pericardial mesothelial cells, suggesting that RIG-I may be involved in the pathogenesis of pericarditis (Hatakeyama et al., 2007)   |

Table 1. Pattern recognition receptors (PRR) and their ligands engaged in myocarditis and inflammatory heart disease.

## 5. Concluding remarks

Beside direct effects of replicating viruses, unbalanced autoimmune responses associated with the production of auto-antibodies against cardiac tissue may also contribute to the progression of myocardial injury in inflammatory heart disease (Eriksson et al., 2003). The detection of auto-reactive antibodies directed against a number of different cardiac antigens is a prominent feature of all forms of persistent myocarditis and inflammatory cardiomyopathy, and there are reports demonstrating that the presence of anti-myosin autoantibodies is associated with deterioration of left ventricular function (Liu and Mason, 2001; Shishido et al., 2003; Dörner et al., 2005; Rose, 2009). In addition to the critical role of TLRs in mediating cardiac dysfunction in infectious conditions, emerging evidence suggests that the TLRs are also involved in modulating cardiomyocyte survival and ischemic myocardial injury (Chao, 2009; Riad et al., 2008). Despite significant progress in the identification of receptors triggering innate immune responses, further research is necessary to unravel the cooperative interactions between the innate and acquired immune system active in the protection of the heart against viral or autoimmune damage.

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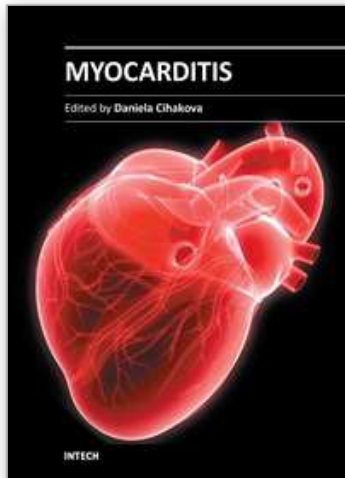
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## **Myocarditis**

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Myocarditis, the inflammation of the heart muscle, could be in some cases serious and potentially fatal disease. This book is a comprehensive compilation of studies from leading international experts on various aspects of myocarditis. The first section of the book provides a clinical perspective on the disease. It contains comprehensive reviews of the causes of myocarditis, its classification, diagnosis, and treatment. It also includes reviews of Perimyocarditis; Chagas's™ chronic myocarditis, and myocarditis in HIV-positive patients. The second section of the book focuses on the pathogenesis of myocarditis, discussing pathways and mechanisms activated during viral infection and host immune response during myocarditis. The third, and final, section discusses new findings in the pathogenesis that may lead to new directions for clinical diagnosis, including use of new biomarkers, and new treatments of myocarditis.

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