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TOPIC HIGHLIGHT

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Innate immune receptors in heart failure: Side effect or potential therapeutic target?

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Abstract

Heart failure (HF) is a leading cause of mortality and morbidity in western countries and occasions major expenses for public health systems. Although optimal medical treatment is widely available according to current guidelines, the prognosis of patients with HF is still poor. Despite the etiology of the disease, increased systemic or cardiac activation of the innate immune system is well documented in several types of HF. In some cases there is evidence of an association between innate immune activation and clinical outcome of patients with this disease. However, the few large trials conducted with the use of anti-inflammatory medication in HF have not revealed its benefits. Thus, greater understanding of the relationship between alteration in the immune system and development and progression of HF is urgently necessary: prior to designing therapeutic interventions that target pathological inflammatory processes in preventing harmful cardiac effects of immune modulatory therapy. In this regard, relatively recently discovered receptors of the innate immune system, *i.e.*, namely toll-like receptors (TLRs) and nod-like receptors (NLRs)-are the focus of intense cardiovascular research. These receptors are main up-stream regulators of cytokine activation. This review will focus on current knowledge of the role of TLRs and NLRs, as well as on downstream cytokine activation, and will discuss potential therapeutic implications.

Key words: Heart failure; Innate immune system; Toll-like receptors; Inflammation

Core tip: Heart failure (HF) is a leading cause of morbidity and mortality despite of current medical and interventional treatment. Activation of the innate immune system leading to or contribute to advanced HF is focus of intense and growing research. This review will focus on the role of innate immune receptors in HF. We will discuss the current knowledge about the correlation of innate immune activation and the clinical course in HF. In addition, we will comment on potential therapeutic implications of modulating the immune system in this syndrome.

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INTRODUCTION

Heart failure (HF) is a one of the leading cause of mortality and morbidity. In developed countries, 1% to 2% of the adult population suffers from this syndrome[1]. In

patients ⩾ 70 years of age, the prevalence increases to more than 10%[2]. Although approximately 50% of HF patients have preserved left ventricular (LV) ejection fraction[1], this review will focus on systolic HF, owing to the lack of data on the influence of the immune system on HF with preserved LV ejection fraction.

The etiology of HF is manifold. Systolic HF arises in more than 60% of cases from coronary artery disease (CAD). Among others, dilated cardiomyopathy, myocarditis, alcohol abuse, and chemotherapy are relevant and often reasons for HF. Current treatment of systolic HF has been documented in a large number of randomized, controlled clinical trials[1]. These studies clearly demonstrate the benefits of drugs such as β-blockers, angiotensin, converting enzyme inhibitors, angiotensin receptor antagonists, mineralocorticoid receptor blockers, and new drugs such as ivabradine. These agents reduce mortality and/or improve clinical symptoms of chronic systolic HF by suppression of the renin-angiotensin, aldosterone system, neurohumoral activation and ion channels. In addition to medical treatment, mechanical interventions such as resynchronization therapy have also proven beneficial in selected patients[3]. However, despite current optimal HF treatment, the prognosis of these patients is still poor and is comparable to neoplastic diseases. This underscores the need for additional therapeutic options. Many different pathophysiological and therapeutic concepts are at the focus of intense current research. Despite various etiologies, there is a growing body of evidence in this context from more than two decades of research for innate immune activation-systemic and/or local-in a significant number of patients and in experimental studies[4]. The innate immune system represents the first line of host defense against pathogens. This system is composed of diverse cellular components including granulocytes (basophils, eosinophils and neutrophils), mast cells, monocytes/macrophages, dendritic cells, and natural killer cells[5]. These cells respond to noxious stimuli and conditions, including infections and tissue injuries that can trigger inflammatory responses[6]. Pro-inflammatory cytokines, which can be excessively produced by immune cells, have been identified over the last decades as "downstream effectors" of the innate immune system[7]. Moreover, several clinical studies that apply pharmacological cytokine inhibition have been carried out for various diseases[4]. However, in HF, suppression of the cytokine tumor necrosis factor (TNF) alpha has failed to show a benefit in patients[8]. One reason for this failure may be a general underestimation of the complexity of the innate immune system. The regulation of cytokines is indeed not well understood[7]. In this regard, the discovery of so-called pattern recognition receptors has substantially enlarged understanding of the innate immune system. Two families of receptors, *i.e.*, toll-like receptors (TLRs) and nod-like receptors (NLRs)-have been relatively recently discovered; they regulate the innate immune response[7,9]. This review will discuss the pathophysiology of TLRs and NLRs and their role as therapeutic targets in systolic HF.

TLRS AND NLRS

TLRs

The family of TLRs represents the best known receptor proteins in the innate immune system. The initially discovered TLR4 has by now been known and researched for nearly two decades[10]. Extensive research has led to discovery of ten functional TLRs in humans, and has enabled detailed decoding of the TLR pathway[11]. Still, the role of TLRs in autoimmune diseases has not yet been fully understood. All TLR share a cytoplasmic Toll/IL-R homology (TIR) domain[12]. They reside in different compartments of the cell, with TLR1, 2 and 4-6 on the plasma membrane and TLR3 and 7-10 on intracellular endosomes and lysosomes. In general, cell surface TLRs recognize microbial membrane lipids, and intracellular TLRs respond to microbial nucleic acids[13]. Furthermore, TLR2 recognizes peptidoglycans, TLR3 dsRNA, TLR4 LPS, TLR7 ssRNA, and TLR9 unmethylated bacterial CpG DNA[14]. Beneath their role in immune reaction against pathogens, TLRs can also respond to damage-associated molecular pattern molecules (DAMPs). DAMPs include cell, derived particles such as heat shock proteins (HSP) and high mobility group box (HMGB), particles from the extracellular matrix such as fibronectin, and other substances like oxidized low density lipoprotein and free fatty acids[15]. HSP60 has been shown to activate TLR2 and TLR4 in macrophages[16]. HSP70 also poses an endogenous stimulus to TLR, which leads to release of nitric oxide and tumor necrosis factor[17]. In dendritic cells, TLR2 is activated by hyaluronic acid derived from the extracellular matrix[18]. Upon activation, all TLRs except TLR3 engage the MyD88 pathway. Activated MyD88 forms a complex with IL-1R-associated protein kinases (IRAK4, IRAK1 and IRAK2) (schematic overview see Figure 1). Phosphorylation of IRAK1 leads to activation of tumor necrosis receptor-associated factor (TRAF) 6, which together with IRAK1 forms a new complex. Transforming growth factor-activated kinase (TAK)1, TAK1-binding proteins (TAB)1, TAB2, and TAB3 are recruited to this complex. Upon activation of TAK1 by ubiquitylated TRAF6 IKK-α, IKK-β, and NF-κB essential modulator (NEMO) form a complex, which degrades IκB. This leads to translocation of NF-κB to the nucleus[19]. NF-κB regulates transcription of proinflammatory genes, upregulation cell-adhesion molecules and chemokines, and increasing nitric oxide (NO)[14]. The MyD88-independent pathway is addressed by TLR3 and by TLR4 as an alternative pathway. TLR4 uses the adaptor protein TRIF-related adaptor molecule (TRAM) to activate TIR-domain, containing adapter-inducing interferon-β (TRIF). TRIF can either activate TRAF6-subsequently leading to NF-κB translocation, or can recruit TRAF3, TBK1, and IKKε. This complex phosphorylates interferon regulatory factor (IRF) 3, which induces its translocation to the nucleus and expression of type I interferone genes[19]. Several mechanisms aid in the function of TLR signaling. sCD14 has been known

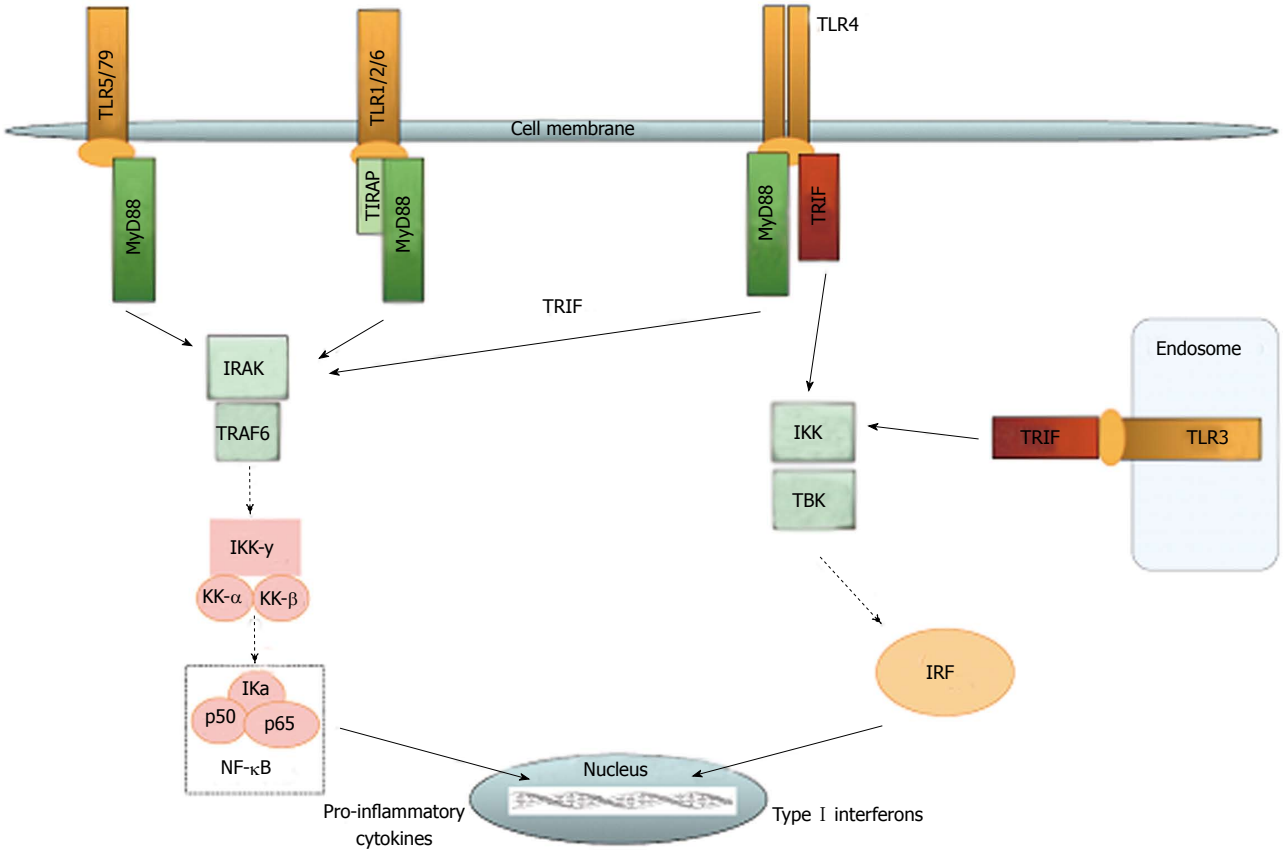

Figure 1 Toll-like receptor signaling. This figure summarizes schematically the complex signalling cascades of the Toll-like receptors. IRF: Interferon regulatory factor; IRAK: Interleukin-1 receptor-associated kinase; TRIF: TIR domain-containing adaptor inducing IFN-β; TLR: Toll-like receptor; IKK: IkB kinase; NF-κB: Nuclear factor κB; TBK: TANK binding kinase.

to chaperone lipopolysaccharide (LPS) from LPS binding protein to the TLR4/MD2 complex and thus support induction of TNF-α and interleukin-6 (IL-6) production. Recent research has shown that sCD14 is also capable of promoting internalization of TLR4 and activation of the TRIF-dependent pathway[20]. MHC class Ⅱ molecules also have the potential of addressing the TLR pathway in a rather unclassical manner. Together with CD40, MHC class Ⅱ can activate tyrosine kinase Btk, which leads to activation of both the MyD88-and the TRIF-pathways[21]. Another example for support of the proinflammatory TLR pathway is miR-155. This micro RNA interacts with Src homology 2 domain-containing inositol 5-phosphatase-1 (SHIP-1) and thereby restrains it from its control function[22]. A potent system such as the TLR proinflammatory pathway requires not only triggering but, perhaps more importantly, control. Recent years have seen establishment of possible control mechanisms for TLR signaling. SHIP-1 is upregulated after LPS stimulation, owing to increased production of transforming growth factor (TGF)-β, and inhibits PI-3 kinase, which consequently blocks TLR-MyD88 and MyD88 independent pathway[23]. IRAK-M functions as a decoy and prevents IRAK-1 from dissociating MyD88. It suppresses TLR-mediated inflammatory response. IRAK-M knock-out mice demonstrate an increase in inflammatory response and IL-1/TLR-signaling[24]. IRAK-M can also interfere with TLR2, although this downregulation is evidently IRAK-1 independent[25]. Other specific inhibitors are SHP2-which has been shown to inhibit only the TLR3 pathway-and sterile-α and armadillo motif-containing protein (SARM), which blocks only the TRIF-pathway without inhibiting MyD88 signaling[26,27]. An alternative splice variant of MyD88 is expressed after LPS stimulation. This variant, MyD88s, inhibits phosphorylation of IRAK1 by IRAK4, and leads to a suppression of the TLR pathway[28]. While microRNA is involved in the promotion of TLR signaling, it also plays an important role in anti-inflammation. miR-146- and miR-21-levels increase after LPS stimulation. miR-146 interacts with TRAF6 and IRAK1, which leads to decreased mRNA levels of both - whereas miR-21 inhibits PDCD4, which is an inhibitor of IL-10[29]. IKKβ, involved in the TLR-pathway, also has anti-inflammatory capacity by virtue of regulating the activation of the prosurvival kinase Akt1[30]. MHC class I also has a rather untypical function. It can be phosphorylated after TLR activation and can then activate Fps tyrosine kinase, which interferes with TLR signaling[31]. While evidence suggests a possible pro-inflammatory role of MHC class Ⅱ, MHC class I evidently supports anti-inflammatory effects.

NLRs

The nucleotide-binding and oligomerization domain

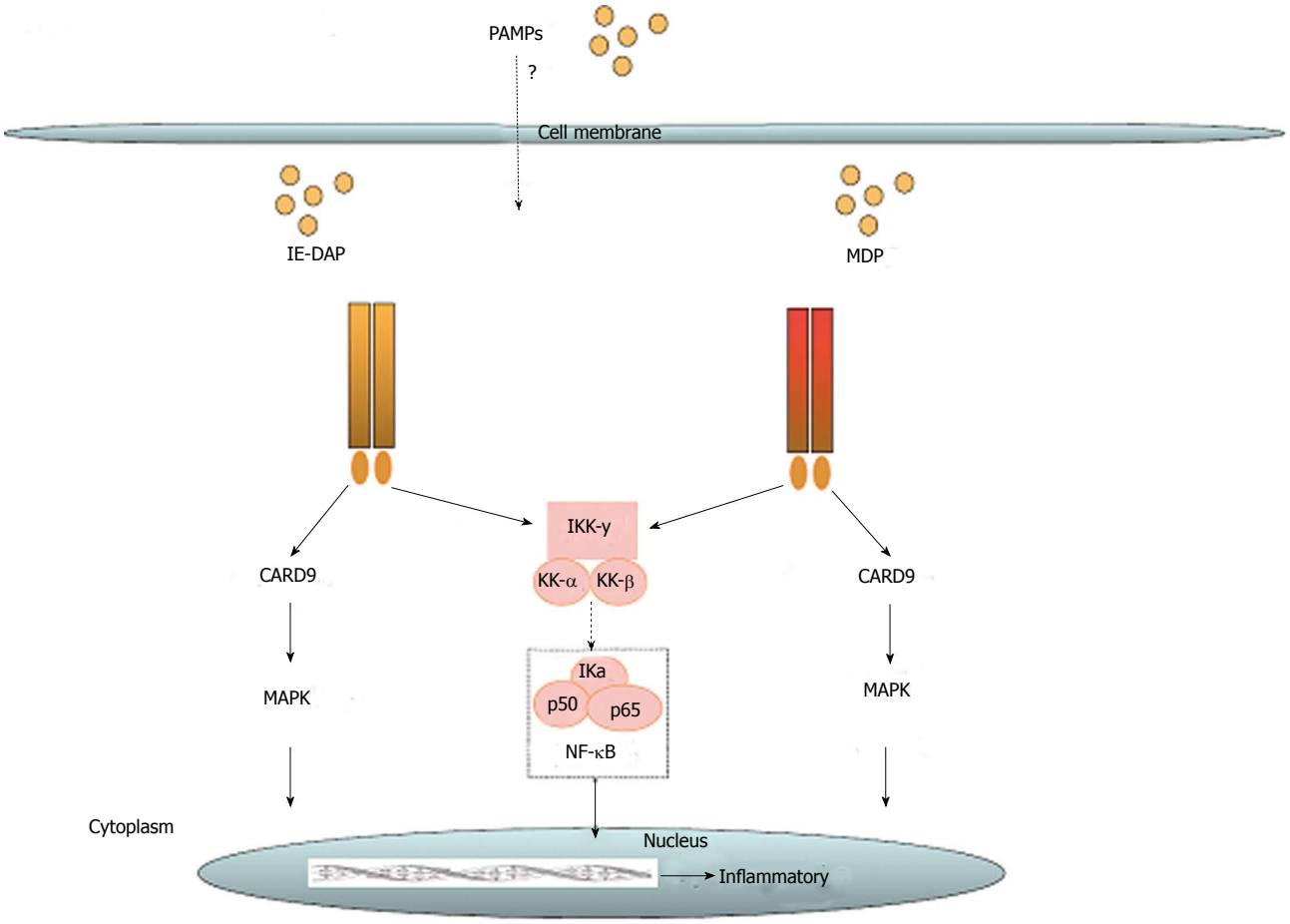

Figure 2 Nod 1 and nod 2 signalling. This figure summarizes schematically the signalling of the nod-like receptors nod 1 and nod 2. PAMP: Pathogen-associated molecular particles; IKK: IkB kinase; MAPK: Mitogen activated kinase; NF-κB: Nuclear factor κB; CARD: Caspase recruitment domain.

NLR family is defined by a common nucleotide binding domain and leucine-rich repeat series. All NLRs have a central ATPase region, which is called the NACHT domain[32]. Until now 22 NLRs have been identified in humans. They differ from each other by heterogeneous N-terminal effector domains and can be divided into four subgroups. Class Ⅱ transactivator (CIITA) is defined by an acidic transactivation domain (AD), and neuronal apoptosis inhibitor proteins (NAIPs) contain a baculovirus inhibitor of apoptosis protein repeat (BIR). The caspase recruitment domain (CARD) is common for NLRCs, including nod 1 and nod 2 (schematic overview see Figure 2). Finally, NLRPs share a pyridine domain (PYD). NLRs are important pattern recognition receptors in the intracellular compartment. Their activation leads to activation of innate immunity through nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), and interferon regulatory factors (IRFs)[33]. NLRPs contribute to innate immunity by formation of the inflammasome. This complex is formed by NLRP1, NLRP2, NLRP3, and NLRC4 upon recognition of physical damage to the plasma membrane or certain pathogen-associated molecular particles (PAMPs). Inflammasome formation can directly lead to caspase 1 activation, or it can recruit the adaptor protein ASC (apoptosis-associated speck-like protein containing a casapase recruitment domain) to activate caspase 1[34]. Serving another means of controlling infection, nod 1 and nod 2 can induce autophagy through activation of LC3-positive speckles[35]. In dendritic cells, nod 2-induced autophagy apparently plays a key role for bacterial elimination and antigen presentation[36]. The role of NLR has been implied for some diseases. In patients with early-onset Crohn's disease, a frameshift mutation of the nod 2 gene has been found, while in early-onset sarcoidosis a gain of function mutation of the NACHT domain has been identified[37]. There also is an indication for activation of NLRP3 in microglia in Alzheimer's disease by peptide amyloid-β[38].

Role of TLRs and NLRs in HF

The role of the innate immune system in HF has been controversially discussed. Inflammation plays an important role in most cardiac diseases, and receptor-mediated innate immunity is primarily investigated with respect to TLRs. The role of innate immune cells and NLRs is also subject to current research. All known human TLRs have been found in the heart. However, until yet, the best-characterized TLR in cardiovascular diseases is TLR4 (Figure 3). Their expression level, however, varies greatly. Expression of TLR4, TLR3, and TLR2 is at least 10 times higher than that of any other TLR in the heart[39]. Although TLRs were first known for their role in innate

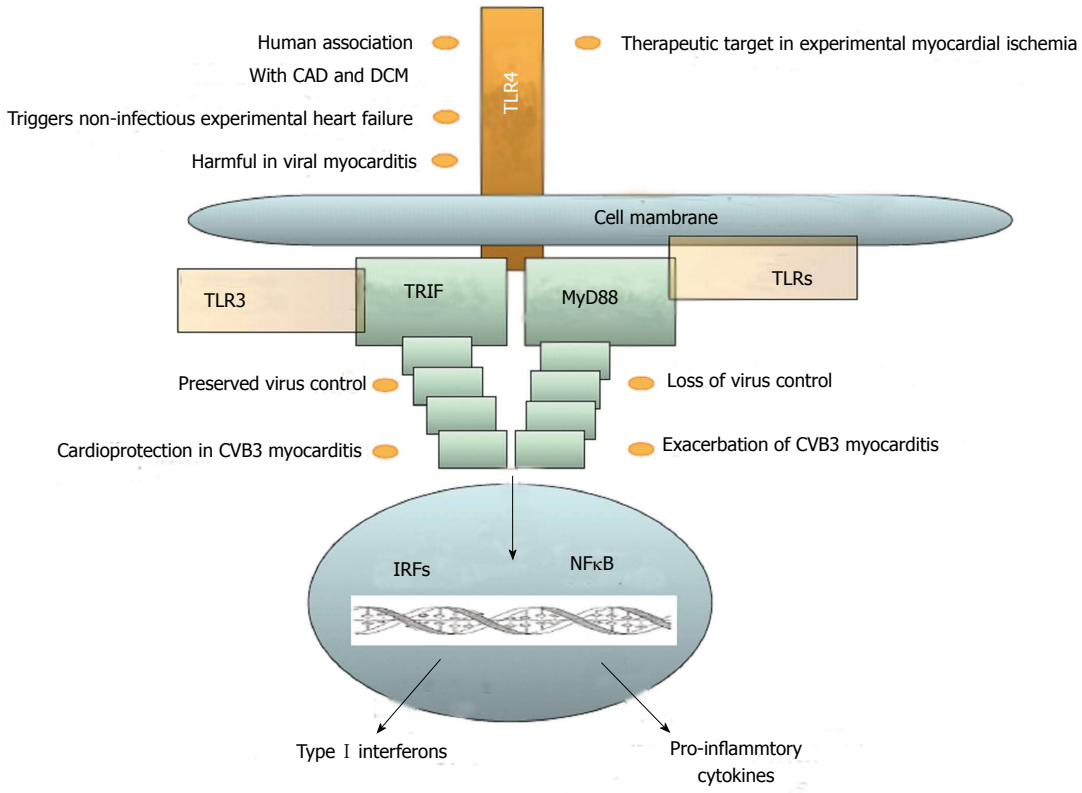

Figure 3 The role of Toll-like receptor 4 in heart failure. This figure summarizes current knowledge of the pathophysiological role of Toll-like receptor 4 (TLR4). CAD: Coronary artery disease; DCM: Dilated cardiomyopathy; TLR3: Toll-like receptor 3; TRIF: TIR domain-containing adaptor inducing interferon-β; MyD88: Myeolid differentiation factor 88; IRF: Interferon regulatory factor; NFkB: Nuclear factor kappa B.

immunity in their action against infection, inflammation in the heart is rarely caused by infectious agents. Other mechanisms lead to an inflammatory response, which often activates TLR pathways. Hemodynamic stress results in inflammation in the myocardium. Myocardial stress increases IL-6 production, which leads to an inflammatory response in the same manner as production of reactive oxygen species (ROS) due to mechanical strain. Macrophage infiltration is triggered by MCP-1 and TGF-β[40]. TNF-α is released by macrophages, mast cells, endothelial cells, and fibroblast. This secretion is triggered not only by infectious agents but also by tissue damage[41]. Necrosis in the myocardium leads to distribution of intracellular particles, which in turn activates the innate immune system. ROS activates innate immune response, but also directly impairs cardiac function. DAMPs activate the complement system and TLRs at the same time[42]. After activation of the TLR pathway, NF-κB induces the expression of pro-inflammatory cytokines and chemokines in endothelial cells, fibroblasts, leukocytes, and vascular cells[43]. Although research has disclosed little for the involvement of NLR in HF, studies have taken place on the effects of the inflammasome in the ischemia-reperfusion model. These results have revealed that mice deficient in caspase-1 or ASC have markedly reduced infarct formation, fibrosis, and cardiac dysfunction. It was further shown that inflammasome activation and IL-1β production occurred primarily in cardiac fibroblasts and leukocytes. This leads to the conclusion that NLRs do play a role in cardiac remodeling and may represent an interesting therapeutic target in the future[34]. Various immune cells evolve to serve functions in primary immune response to tissue damage in the heart, but may also perform a key function in limiting inflammation. Recent investigations have begun to unravel the complex system of macrophage subspecies and functions.

MACROPHAGES

Until now, two different phenotypes have been defined. M1 macrophages are described as first line of defense, with their increased microbicidal capacity as well as production of pro-inflammatory cytokines. M2 macrophages show increased phagocytic activity: they secrete the anti-inflammatory IL-10 and express IL-1 receptor antagonist[44]. The definition of just two subtypes is most likely oversimplified, and a functional perspective could prove more useful in distinguishing pro-inflammatory, regulatory, and reparative macrophages. The phenotype of macrophages is probably defined by a constantly changing variety of cytokines, chemokines, and growth factors, which enable great flexibility in the system[45]. Regulatory T cells (Tregs) have also been reported to possibly influence the macrophage phenotype. These regulatory cells suppress inflammation through IL-10 and TGF-β secretion, or by cell-cell contact. Mice lacking CCR5–which thus reduces Treg infiltration - show increased inflammation and MMP activity[46].

ISCHEMIA/REPERFUSION INJURY

To give some order to these many consequences of cardiac tissue damage, the example of ischemia/reperfusion injury can provide an overview of the immune response. Three phases can be determined that lead to adverse cardiac remodeling. First, neutrophils and pro-inflammatory macrophages migrate to the infarct site, with attraction by chemokines and cytokines secreted upon activation of innate immune pathways. Upon finishing the task of clearing the infarct site of necrotic cells, neutrophils go into apoptosis, which ends the inflammatory phase. Various macrophage subtypes migrate to the infarct in the proliferative phase. They activate endothelial cell growth and myofibroblast formation, with resultant production of a scar. In the final phase, more cells go into apoptosis and collagen cross-links, which possibly leads to ventricle dilation as the infarct matures[47].

During recent decades, intensive research has led to better understanding of ischemia/reperfusion (I/R) injury. I/R injury leads to rapid activation of the immune system, which in turn results in increased expression of TNF, IL-1β, IL-6, NO as well HSP[48,49]. These and other factors lead to infiltration of the infarct with neutrophil granulocytes. In canine and mouse models, infiltration ceased after 3-7 d, and the neutrophils went into apoptosis[50]. Early infiltration of the myocardium can cause more extensive cytotoxic injury to viable cardiomyocytes, which leads in turn to additional damage in the heart[51]. ROS generated by neutrophils may contribute to that adverse effect, as well as interaction with cardiomyocytes through intercellular adhesion molecule-1 (ICAM-1) and integrin[52]. To partially control the immune response, annexin and lactoferrin are transmitted by dying neutrophils to terminate further migration of neutrophils-but at the same time possibly attract macrophages to the site[53]. Furthermore, TNF-α, released at the infarcted area by resident mast cells, also promotes mononuclear cell infiltration[54]. These macrophages begin ingesting the apoptotic cells and, in turn, release cytokines as IL-10, TGF-β pro-resolving lipoxins, and resolvins[55]. Upregulation of IL-10 and TGF-β suppress production of adhesion molecules. Another process for inhibition of leukocyte adhesion is carried out by endogenous integrin ligands of endothelial cells[56]. Some experiments conducted on knock-out mice have provided further insights on the involved immune cells. The attempt to evade the effect of macrophage I/R injury was analyzed in monocyte chemoattractant protein (MCP) 1/CCL2 knock-out mice. MCP1 recruits pro-inflammatory and phagocytic macrophages to the infarct. Compared to wild-type mice, knock-out mice exhibited reduced dilative remodeling with equal infarct size[57]. Similar results were achieved for IL-1-deficient mice. Although infarct size did not vary, the extent of cardiac remodeling was reduced in deficient mice compared to wild type[58]. Those findings support the theory that the initial immune response does not pose the problem, but that long-term activation causes adverse effects. This could partly explain results for ICAM1-deficient mice. Once again compared to wild type, they showed no difference in infarct size, even after 1-3 wk[59]. The same applies to mice with ICAM1 and P-selectin deficiency. Neutrophil migration was decreased, but infarct size did not vary compared to wild type[60]. These results could also suggest that the role of neutrophils has been overestimated. ROS is a mediator among others secreted by neutrophils. It can activate complements, stimulate P-selectin expression promoting cell migration, and upregulate chemokine and cytokine synthesis through the NF-κB pathway[61]. ROS, as well as ATP and potassium abundance, may activate the inflammasome. The inflammasome is expressed by border-zone cardiomyocytes, white blood cells in the granulation tissue, and cardiac firboblasts. Inflammasome formation can be inhibited by P2X7 and cryopyrin, which leads to a decrease in infarct size[62]. Research on TLRs involved in I/R-injury focusses mainly on TLR2 and TLR4. TLR2 seems to play a key role. TLR2 knock-out mice demonstrate better contractile function after I/R injury, and they show similar infarct size, but less ventricular remodeling compared to wild type. Fibrosis is reduced in the non-infarct area, and TGF-β and collagene type 1 expression are lower in knock-out mice. The recovery of LV-developed pressure is also better in TLR2-deficient mice[63,64]. Further research has focused on the transmission of this effect to determine whether it entailed a central effect using TLR2 in the heart, or a peripheral effect involving white blood cells. Infarct size was compared for TLR2-deficient mice and wild-type mice with TLR2-deficient bone marrow. Infarct size did not differ significantly. When TLR2-deficient mice were injected with wild-type bone marrow, infarct size increased compared to purely TLR2-deficient mice. It was possible to inhibit this effect by administering an TLR2 antagonist-which resulted in smaller infarcts, enhanced overall cardiac function, and reduced inflammation and apoptosis[65]. We and others investigated the role of TLR4 in myocardial infarction. TLR4-deficient mice displayed an improved outcome and decreased cardiac inflammation, as also revealed by others[66,67]. Moreover, pharmacological inhibition of TLR4 using the antagonist eritoran led to beneficial effects, which suggests a potential new therapeutic strategy in myocardial ischemia, at least under experimental conditions[68]. Mice deficient in TLR4 also showed smaller infarct size after I/R injury[69]. Pre-treatment with LPS at 24 h before an I/R injury experiment results in better LV function compared to the sham group[70]. TLR2-TIRAP signaling mediates this effect, in which GSK-3β is subsequently inactivated–which prevents it from destabilizing mitochondria and leading to cell death[71].

VIRAL CARDIOMYOPATHY

The role of the innate immune system in viral cardiomyopathy has been primarily established by experiments using mice infected with coxsackievirus B3 (CVB3). In humans it is known that cardiac CVB3 infection needs intact interferon-I signaling[72]. TLR4-deficient mice exhibited higher titers of coxsackievirus B3 (CVB3) two

days after infection, but decreased titers and myocarditis in a 12-d follow up. The cytokines IL-1β and IL-18 were reduced in TLR4-deficient mice[73], Knock-out mice deficient for the TLR downstream adapter protein MyD88 are protected from CVB3 infection[74]. Interestingly, we found in TRIF knock-out mice a much higher susceptibility to CVB3 infection when compared to wild-type mice: to include induction of mortality, loss of virus control, and exacerbation of pro-inflammatory cytokine expression in heart tissue[75]. These data from MyD88 and TRIF knock-out mice suggest not only harmful effects of TLRs, but also cardioprotection in CVB3-induced myocarditis. TLR7 and TLR9 contribute to the susceptibility of MyD88-deficient mice in experimental myocarditis[76]. This is also strengthened by our finding that shows that MyD88 may contribute to the modulation of TLR9 in CVB3-induced myocarditis in mice[77]. In another study, infection of TLR3-deficient mice with encephalomyocarditis virus (EMCV)-a ssRNA virus-interestingly led to earlier death in knock-out mice, combined with increased viral replication and myocardial injury[78]. The mRNA expression of TNF, IL-1β, and IL6 was down-regulated, whereas IFN-β was up-regulated[78]. IRAK-deficient mice and MyD88-deficient mice both exhibit lesser degrees of myocarditis and viral replication after infection, as well as improved survival. Levels of IFN-β were higher in MyD88 knock-out, and IFN-α and IFN-γ were increased in IRAK knock-out. Overall inflammation was reduced[74,79]. Knock-out in cytokines/chemokines led to higher mortality, a greater extent of myocardial injury, higher viral titers for TNF knock-out and EMCV infection, as well as NO knock-out and CVB3 infection[80,81].

DILATED CARDIOMYOPATHY

Activation of the immune system is widely considered a pathophysiological mechanism in DCM[82-87]. For example, we disclosed that the initial white blood cell count upon initial hospital admission in DCM patients predicts long-term mortality in patients with DCM and severe LV dilation[84]. In addition, genetic variants of TLR4 are significantly associated with cardiac recovery in DCM patients, which suggests a potential role of receptor-mediated innate immunity in this disease[88]. Since TLRs are evidently involved in HF, and although viral or bacterial agents are much less frequently the cause than is ischemia, for example, it is interesting to examine a number of known DAMPs and their link to HF. For HSP60 and HSP70, a possible connection to HF has been evidenced. Both are increased in advanced HF. HSP60 trafficking through the plasma membrane is linked to apoptosis, and serum levels of HSP70 correlate with the severity of cardiac dysfunction[89]. Decreased levels of TLR2 and TLR4 have been defined in all subgroups of cardiomyopathy, ischemic cardiomyopathy (ICM), dilated cardiomyopathy (DCM), and viral cardiomyopathy (VCM), whereas TIRAP and IRAK4 are up-regulated[7]. A much wider overview of genetic alternations in cardiac disease allows fundamental compound analysis of innate immune signaling genes. It has showed that the failing heart shows a different expression plot when compared to non-failing heart tissue. Further gene expression in viral cardiomyopathy and idiopathic dilated cardiomyopathy is similar and is distinguished from ischemic cardiomyopathy. This phenomenon suggests different immunological involvement of VCM and DCM compared to ICM, and supports the theory that DCM may evolve from VCM.

THERAPEUTIC IMPLICATIONS

Early studies on the influence of the inflammatory response in HF confirmed the harmful effects of methylprednisolone administration in patients with myocardial infarction[90]. Since that time, many new options have evolved. Nevertheless, it is apparently no less difficult to achieve a positive result, even though current knowledge of innate immunity in HF is much more detailed. These difficulties are obvious in two studies on anti-TNF alpha therapy, with etanercept eventually proving not beneficial and even deleterious[91,92]. Another problem may lie in the limited comparability of humans and animal models. Whereas, in a canine model, antibody-inhibiting leukocyte adhesion acted in a protective manner to limit infarct size by 40% to 50%, there was no effect on infarct size in humans with STEMI administration of CD11b/CD18 integrin receptor inhibition[93,94]. There are, on the other hand, a number of promising substances. TLR4 antagonist eritoran significantly reduces infarct size[68]. New variations of lipid A have been found. They bind to TLR4 but demonstrate reduced agonistic activity (CRX-527, lipad-Iva). TAK-242 also inhibits TLR4 signaling, yet until now its target remains unknown. Ibudilast (AV411) is another TLR 4 antagonist, one that suppresses pro-inflammatory cytokines such as TNF and IL-6. It may induce IL-10 and is currently under trial for opioid dependence. OPN-401, a viral protein-derived peptide, inhibits TLR4 signaling but is still in development. OPN-305 is a promising monoclonal antibody-inhibiting TLR2 and is currently in orphan status for prevention of I/R injury after organ transplantation. AP177-DNA aptamer binds to TLR and antagonizes TLR2 ligand binding[95]. Anakinra, a IL1 receptor antagonist, suppresses post-infarct inflammation and has showed lower incidence of HF[96]. In summary, although knowledge of the pathophysiology of the innate immune system in HF has substantially increased and new therapeutic targets have been addressed under experimental conditions, future investigations, especially clinical trials and experimental research in human tissue–are needed to develop effective innate immune system modulating treatment in HF.

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