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A REVIEW ON THERAPEUTIC POTENTIAL OF TOLL-LIKE RECEPTORS IN CARDIOVASCULAR DISEASES

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ABSTRACT

Toll-like receptors are the surface molecule and they are most responsile for the recognition of the exogenous infectious ligand and endogenous molecule, which are released during host tissue injury and there by downstream signelling pathway are activated by the interaction of TLRs with their ligand. That induces an immune responses by producing cytokines, type 1 interferones and other inflammatory diseases including atherosclerosis, septic cardiomyopathy, viral myocarditis, ischemia and cardic remodeling after myocardial infraction. Individual TLRs are also initiate and integrate homeostasis response within heart. Blockade of these TLRs may be beneficial in both preventing and decreasing the complications in cardiovascular system. The proposed review on role of toll like receptors in cardiovascular diseases reveals that endogeneous molecule which trigger innate immunity via TLRs in cardiovascular diseases.

KEYWORDS: Atherosclerosis; Receptors; Infection/Inflammation; Arteries; Immunology.

INTRODUCTION

For decades, the morbidity and mortality of aging population due to cardiovascular disease has been a burden on the health care system and unfortunately, we are witnessing no revolution at the beginning of the 21st century. The origination and development of cardiovascular disease is heterogeneous; infection, inflammation[1,2] and even autoimmunity are involved. The role of the immune mechanism in cardiovascular disease is confirmed by studies in genetically modified mice. Experimental research has shown that interference with the immune response caused by endogenously or exogenously derived triggers or immunization can alter the progression of cardiovascular diseases.[3] Pattern recognition receptors (PRRs) are important component of the innate immune system responsible for recognizing hazards and damage. PRRs present on the immune and non-immune cells, including the tissues of cardiovascular system.[4] PRRs have the ability to recognize unique patterns reserved during evolution. As a result, distinct molecular patterns ranging from molecular patterns associated with pathogens to damage associated with molecular patterns can activate PRRs with unique and exclusive pro inflammatory cascades.[5] Toll like receptors (TLRs), receptors for the finish product of glycation and receptors such as the nucleotide binding oligomerisation domain like receptors (NLRs) are all examples of PRR of the innate immune system. In particular, TLRs have provided important new information regarding our understanding of the role of inflammation in health and disease.[6]

The Toll like receptors were discovered in Drosophila melanogaster when research revealed that a mutation in the toll gene lead to abnormal development. Toll like receptors are responsible for recognizing and initiating an inflammatory responses to microbial components expressed by bacteria, fungi, protozoa a viruses as well as endogenous molecules released by dying cells or generated as a result of tissue damage and oxidation.[7] The toll like receptors identifies the exogenous and endogenous ligands. The inflammatory genes expressed as a result of TLR activation cytokines cause expression pattern guides the adaptive immune responses, chemokine that guide the migration of immune cells to target tissues, cell adhesion molecule, that promote turnover, and the infiltration of immune cells In to the vascular wall and translocation to end organs.[8] TLRs respond to host derives circulating molecules released by dying and damaged cell after hypoxia, trauma and cell death. Prolonged or excessive activation of TLRs on immune and vascular cells has been suggested to induce low grade chronic inflammation, leading to endothelial dysfunction subsequent cardiovascular diseases. Toll like receptors appears in the atherosclerotic lesions.[9]

ABBREVIATIONS

ApoE, apolipoprotein E; CD, cluster of differentiation; CaMKII, Ca2+/calmodulin- dependent protein kinase; DAMPs, damageassociated molecular patterns; HSP, heat shock protein; IFN, interferon; IKK, I kB kinase; IL, interleukin; IRAK, interleukin 1 receptor-associated kinase; IRF, interferonregulatoryfactor; LDL, lowdensitylipoprotein; LPS, lipopolysaccharide; MAL, MyD88-adapter- like; MAPK, mitogenactivatedprotein kinase; MyD88, myedifferentiation primary response gene 88; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PAMPs, pathogen-associated molecular patterns; PI3K, phosphatidyl inositol 4,5bisphosphate 3-kinase; PRRs, pattern recognition receptors; RIP-1, receptor-interacting serine/threonine-protein 1; SARM, sterile a- and armadillo-motif-containing protein; SHR, spontaneously hypertensive rats; TAK1, transforming-growth-factor-b-activated kinase 1; TIR, Toll/interleukin-1 receptor; TIRAP, TIR domain containing adapter protein; TLR, Toll like receptors; TNF-a, tumor necrosis factor a; TRAF6, tumor necrosis factor-receptor-associated factor 6; TRAM, TIR-domain-containing adapterinducing interferon-b related adapter molecule; TRIF, TIR-domain-containing adapter-inducing interferon-b; UNC93B1, Unc-93 homologue B1.

Toll like receptors

The toll gene was first discovered as coding for a receptor responsible for the dorsal ventral pattern in drosophila embryos. TLRs expression is very ubiquitous in all species such as mammals, fruit flies, nematodes, chicken and plants.[10] The human drosophila protein analogue is capable of initiating an adaptive immune response.[11] Most of the ligands can be classified as PAMPs. However TLR4 also respond to endogenous factors produced by stress or cell damaging, like heat shock proteins, extracellular components of fibronectin and hyaluronan.[12] TLRs recognize viral and bacterial products (i.e., PAMP) as well as host- derived fungi and endogenous molecules (DAMP). This TLR capacity gives both protective against microbial infections and a homeostatic role in response to endogenous materials. So far it has been shown that there are 10 TLR genes in humans (TLR1 - TLR10) and 12 (TLR1– TLR9, TLR11 - TLR13) in mice13. Generally, TLRs can be divided into two groups based on their cell location when detecting their respective ligands. TLR 1, 2, 4–6 and 11 are located on the cell surface (cell surface TLR) and TLR 3, 7–9 and[13] reside at the endosomal compartments (intracellular TLR).[14] TLR4 is the receptor for Gram negative bacterial lipopolysaccharide product (LPS). TLR2 responds to bacterial lipopeptides, but can also meaning non- lipopeptide PAMPs.[15] TLR10 recognizes listeria ligands in collaboration with TLR2. Mouse TLR11 detects TLR13 detects bacterial ribosomal RNA and the components of vesicular stomatitis Virus.[16] TLR3 recognizes double marking RNA, which is a component of many viruses but also detects small interference RNA and auto-RNA derived from damage. TLR7 and TLR8 have been found to detect single modes Viral RNA.[17]

Assembly proteins and accessories

The ligand, TLRs occur as dimers in a low affinity complex. Causes of ligand binding conformational changes that encourage engagement of the two TIR domains of each cytosolic site receiver. As the TIR areas are nearby, a new signaling platform is created.[18] Differentiation group (CD) 14 is a co-receptor for TLR4 and MD2 (lymphocyte antigen 96) and plays a role in the recognition of LPS.[19] Class B trapping receptor, has a role in amyloid-beta and recognition of oxidized low density lipoproteins (LDL). Recognition of these ligands triggers the formation of a trimeric complex composed of CD36 and TLR4 / TLR6 heterodimer.[20]

Adapter molecule and kinase

Recruitment of adapter proteins represents the early phase of TLR signal transduction and therefore the first step in activating the innate immune system.

1. Myeloid Differentiation Primary Response Gene 88-dependent Pathway:

Mouse deficient in MyD88 revealed that MyD88 was necessary for signaling by various TLR, such as TLR2, TLR4, TLR7 / 8 and TLR9.[21] In addition to its TIR domain, MyD88 has a death domain at the N terminus which interacts with a family of four deaths containing a domain kinases associated with IL-1R. IRAK4 is the most important proximal receptor kinase[22] and is would be the first kinase to interact with MyD88. Support the vital importance of IRAK4, studies in humans deficient in IRAK4 and mouse cells showed a deep reduction in TLR responses.[23] This event leads to the activation of TRAF6 and its exit into the cytosol, where it forms a transforming growth complex factor b activated kinase 1 (TAK1), binding to TAK1 protein 1 and protein 2/3 binding to TAK1.[24] IKK activation promotes phosphorylation and proteosomal degradation IkB, allowing NF-kB to move around the nucleus to promote transcription of cytokine genes.[25]

TAK1 induces activation of the MAPK family, such as regulation of the extracellular signal kinase 1/2, p38 and Jun kinase amino-terminal, mediator activation of activator protein 1 and cyclic adenosine monophosphate response element binding protein, which also play a role in the expression of the cytokine gene. So the net result of MyD88 signaling pathway is the production of cytokines. However, within immune cells such as plasmacytoid dendritic cells, MyD88 signaling also leads to type I IFN expression.[26] The assembly of the myddosome is believed to occur in a hierarchically sequential like this ligand binding triggers conformational changes in TLR-TIR areas that allow the recruitment of large propellers oligomers containing the death domains of MyD88, which then recruits IRAK4 and leads to its interaction with IRAK1 or IRAK2.[27] Another adapter protein containing TIR, known as MAL

or TIRAP helps stabilization of the MyD88 oligomerisation at the level receptor. Initially it was suggested that MAL could represent an independent MyD88 signally but it is now recognized that MAL is a bridging adaptor that connect MyD88 to TLRs and in particular to TLR4 and TLR2.[28]

2. Toll/Interleukin-1 Receptor Domain-Containing Adapter-Inducing Interferon-b- dependent Pathway.
TRIF is an adapter containing TIR used by TLR3 and TLR4. TRIF recruitment by these receptors allow the interaction of TRAF6 and TRAF3 with the receptor complex. TRAF6 recruits serine interacting with receptors / threonine protein 1 (RIP-1) kinase, which leads to activation of the TAK1 complex, which subsequently activates NF-kB and MAPK, leading to induction of pro inflammatory genes. TRAF3, on the other hand, recruits TRAF Family NF-kB activator binding kinase 1 associated with the members, inhibitor of the kappa light polypeptide gene activator in B cells, epsilon kinase and essential modulator NF- kB, leading to activation of the interferon regulatory factor (IRF) 3 and translocation to the nucleus, to induce the expression of IFN type I genes. Unlike TLR3, TLR4 does not interact directly with TRIF, but instead it requires a a bridging adapter protein, TRAM, to transduce its signal.[29] TRAM is considered the most restricted adapters because it seems to work only in the TLR4 pathway. In in addition to the activation of NF-kB and IRF3, TRIF is involved in apoptosis mediated by TLR3.[30] This route involves RIP-1, Fas associated protein with death domain and caspase-8. SARM is an adapter protein containing TIR which, in unlike MyD88, TRIF, MAL and TRAF, does not induce activation of NF-κB.[31] SARMs an adapter protein containing TIR which, in unlike MyD88, TRIF, MAL and TRAF, does not induce activation of NF-kB. Its importance in TLR signaling is due to its inhibition effects on TRIF.[32]

Toll-like Receptor Signaling Regulators
Soluble decoy receptors have been described for some TLRs. Six sTLR2 isoforms have been reported be naturally present in human plasma. In vitro studies have shown that recombination TLR4 inhibited LPS-induced activation of NF-kB and TNF-a production in macrophages.[33] sTLR4 is thought to reduce the TLR4 function by interrupting the interaction of the receiver with its MD2 and CD14 co-receptors. sTLR2 abolished the production induced by bacterial lipopeptides of IL-18 and TNF-a in monocytes. MyD88s inhibits recruitment of IRAK4 to MyD88 and therefore it prevents activation of NF-kB.[34] It can however inhibit the dissociation of IRAKS and TRAF6 from TLR complex. Suppressor of cytokine 1 signaling is a non-redundant negative regulator TLR signaling.[35] Although the exact mechanism by which PI3K inhibits TLRs is not clear, it has PI3K has been reported to trigger inhibition of IL-12 synthesis and prevents over expression of a Th1 answer.[36] The tumorigenicity suppressor 2 interacts with MyD88 and MAL and NF-kB escrow induced by MyD88. Single immunoglobulin interleukin-1 receptor interacts with TLR4 and IRAQ, inhibiting the transduction of their signal.[37] Reducing TLR expression is another mechanism that can negatively regulate TLR signaling. This can be accomplished by degrading TLRs or inhibition of TLR expression via the action of anti-inflammatory drugs cytokines.[38]

THE ROLE OF TOLL RECEPTOR SIGNELLING IN CARDIOVASCULAR DYSFUNCTION

A. Atherosclerosis

Atherosclerosis was considered to be simple lipid storage disease. Now however, atherosclerosis is recognized as a chronic and progressive inflammatory condition, and this inflammation occurs hand in hand with an incipient accumulation of lipids arterial wall. As a result, LRTs have been involved as important contributors to the pathogenesis of atherosclerosis.[39] TLRs contribute to the progression of atherosclerosis, especially expressed in atherosclerotic lesions and contributing to the degradation of the matrix and the destabilization of plaque.[40] Activation of TLR2 causes a macrophage lipid accumulation induces a dedifferentiated, migratory and proliferative phenotype in vascular smooth muscle cells and triggers an inflammatory reaction in endothelial cells. Likewise, TLR4 deficiency improved indices of atherosclerosis ApoE and LDL receptor deficient mouse.[41] Although TLR5 is expressed in the vascular system and macrophages, the contribution of TLR5 to atherogenesis is limited at this stage.[42] Activation of TLR7 limits inflammation activation of macrophages and production of cytokines on Toll receptors and the vascular system.[43]

Finally, the genetic suppression of TLR9 exacerbated atherosclerosis in ApoE-deficient mice a high-fat diet and a TLR9 agonist reduced the severity of the lesions, collectively indicating that TLR9 constrains the atherogen process. Overall, the data suggest that TLRs participate in pathogenesis of atherosclerosis. Inappropriate or excessive inflammation in response to PAMPs and DAMPs initiate and advance pathogenesis of atherosclerosis.[44] The other However, a few surveys have observed a effect of TLR in atherosclerosis. which more closely matches their function that is evolutionarily conserved.[45]

A. Hypertension

Uncontrolled immune system activation and inflammation have been suggested as a unifying mechanism between these three organs systems. Thus, LRTs represent potential candidates involved in this aberrant inflammation. TLR4 is the best defined TLR involved in the etiology of hypertension. This can come from the known association between TLR4 and angiotensin II, which some have classified as DAMP.[46] Renal denervation can significantly decrease myocardial TLR4 expression in SHR, and angiotensin II positively regulates the expression of TLR4 on mesangial cells.[47]

In renal tubular epithelial cells it has been observed that TLR2 upregulated NACHT, leucine rich repeats and PYD domains containing the protein 3 inflammasome and its substrate IL-1b and TLR2-NF-kB signaling contributed significantly to renal perfusion Injury.[48] TLR3, TLR7 and TLR8 have all been linked with maternal hypertension in rodent models with preeclampsia-like symptom. In addition TLR7 / 8, as well as TLR9, from SHR splenocytes evoked the largest pro-inflammatory responses to angiotensin II when primed with their respective exogenous ligands.[49] Activation of TLR9 increased blood pressure and induced vascular dysfunction in normotensive men rat and induced mothers hypertension in pregnant rats. In addition, TLR9 has been observed as a negative regulator of cardiac vagal tone and baroreflex.[50]

B. Stroke/Cerebrovascular Injury

Cerebral ischemia triggers acute inflammation, which can worsen brain damage caused by a stroke. Regulation of inflammation after stroke is multifaceted and includes vascular effects, distinct cellular responses, cell death and chemotaxis. There is a lot of the types of cells that are affected, including neurons, astrocytes, microglia and endothelial cells, all responding to resulting neuroinflammation in different ways.[51]

The roles of TLRs in stroke and cerebrovascular lesions can be classified in two categories:

1) TLR activation postischemia which mediates neuroinflammation and neurodegeneration and
2) TLR stimulation before neuroprotective ischemia and the brain prerequisites for tolerating hypoxia and nutrient deprivation.[52]

TLR2-deficient mice are protected from the brain Ischemia-induced cell damage and death and leukocyte and microglial infiltration in the brain. In addition, ischemia causes increased expression of TLR2 in neurons and microglia associated with lesions.[53] Although acute ischemic lesions (24 at 72 hours) were observed to be smaller in TLR2- deficient mice, subsequent innate immune response would have been more pronounced at later times (day 7) and resulted in an exacerbation of ischemia lesion.[54] The anti-inflammatory, luteolin protects the brain ischemic damage by downregulation of TLR5 (and TLR4).[55] A TLR8 agonist has increased neuronal cell death during oxygen and glucose starvation, and in vivo administration increased mortality, neurological deficit and infiltration of T cells after stroke.[56] The neuroprotection induced by the activation of TLR9 against ischemic damage by increasing serum TNF-α and the activation of PI3K / protein kinase B dependent signaling.[57]

TOLL LIKE RECEPTOR LIGANDS IN CARDIOVASCULAR DISEASE

A. Infections, Pathogens, and Cardiovascular Disease

Epidemiological studies have reported positive associations between the risk of cardiovascular disease morbidity and mortality and markers of infection. In one clinical study, 75% of patients with coronary artery the disease had been exposed to at least three of the five pathogens tested and the increasing risk of coronary arterial disease was associated with increased total number of pathogens.[58] Oral infections and study of epidemiology of vascular diseases (INVEST) investigated if periodontal bacteria were associated with prevalent hypertension and continuous elevation blood pressure measurements.[59] Recent studies have shown who do not support the use of preventive antibiotics in adults with acute stroke.[60]

B. Molecular models associated with damage are new Mediators of sterile inflammation

Chronic inflammation due to uncontrolled control activation of the immune system contributes to cardiovascular health, but as discussed previously, the association between these events could not be fully attributed to bacterial and viral infections. Recognition of the innate immune system and response to DAMPs are becoming an increasingly accepted mechanism. DAMPs are endogenous molecules that are normally compartmentalized in cell membranes and protected against exposure to the components of immune system. The the immune system detects these molecules as a danger and elicits a response.[61] Mitochondria were once prokaryotic organisms that entered eukaryotic cells to become organelles essential for the synthesis of ATP (endosymbiosis). This ρancestry of mitochondria means that they express evolutionarily conserved similarities with bacteria, including the translation of their peptides starting with an N-formyl methionine residue and their DNA being mainly unmethylated CpG dinucleotides.[62]

C. Mechanisms of molecule associated with damage presentation of the model in cardiovascular diseases

In most cases, the participation of DAMPs as an inflammatory mediators in presumed cardiovascular disease that cell death is an instigating mechanism for their release. Prolonged or excessive activation of TLRs on these cells provide a pro-inflammatory state leading to the endothelium dysfunction and subsequent cardiovascular disease.[63] Cell death is not an absolute precursor to the participation of DAMPs in pathophysiology of cardiovascular disease. We refer to reader to the following journals for more information on cell death in cardiovascular disease[64] and the emerging DAMP classifications.

The Therapeutic Potential of Toll-like Receptors in Cardiovascular Disease

TLRs and signaling molecules are associated been exploited as potential targets for drug development.

There are different validation criteria for determining whether TLR is good therapy targets for certain diseases are:

1) the expression of the receptor in the study condition.
2) evidence showing that activation of the receptor leads to an exacerbation the phenotype of the disease in experimental models.
3) data demonstrating that mice deficient in one TLRs are protected against disease.
4) the evidence that certain TLR polymorphisms are associated with predisposition to the specific disease.

A. Toll-like Receptor Signaling Inhibition

Cardiovascular disease such as hypertension, stroke and atherosclerosis are chronic inflammations conditions. The Eritrean does not directly inhibit TLR4, but instead it competitively binds to a large internal pocket of MD-2 and terminates signaling mediated by TLR4 / MD2.[65] Eritrean protected mice myocardial ischemia and reduced size of the infarction, attenuated cardiac enlargement in a murine model of aortic constriction, attenuated ischemia / reperfusion-related inflammation and improved the course of renal ischemia / reperfusion injury, and reduced expression of inflammatory genes in a myocardial rat model ischemia / reperfusion.[66] T2.5 has been shown to antagonize the TLR2-induced activation of mice and human macrophages in vitro and in vivo. In a transient brain mouse model ischemia, treatment with T2.5 reduces inflammation and neural death.[67] OPN305 is able to block both TLR2 / 1- and Signaling mediated by TLR2 / 6, reducing mediation by TLR2 production of pro-inflammatory cytokines. In 2009, OPN305 obtained orphan status for the prevention of ischemia / reperfusion injury associated with solid organ transplantation.[68] Synthetic compounds such as imidazoquinoline and propidium iodide inhibits intracellular signaling TLR.[69]

A mechanism of action of antimalarial compounds and imidazoquinolines involve the ability of these compounds to mask the Nucleic acid TLR binding epitope. In a mouse model of lupus, chronic treatment with hydroxychloroquine has not alter the activity of lupus disease but reduce hypertension and aortic endothelial dysfunction. In addition, chloroquine and hydroxychloroquine had beneficial effects on experimental pulmonary hypertension via inhibition of autophagy and type II lysosomal bone morphogenetic protein degradation of receptors.[70] Preclinical and clinical studies show that in addition to their hypotensive actions, blockers of angiotensin II receptors have anti-inflammatory and anti-atherosclerotic effects regardless of reductions in blood pressure, mRNA levels of TLR.71 In rodent ischemia / reperfusion models injury, Valsartan reduction in the size of the infarction and the production of inflammation cytokines due to its effects on TLR4-NF-ĶB mediated activation.[72]

Investigate the effects of anti-inflammatory effects of atorvastatin on murine pro-B cell lines, previous studies have shown atorvastatin did not exert its inhibitory effect via TLR4 receptor-ligand binding mechanism, but instead, it altered the recruitment of TLR4 in the lipid raft.[73] In addition, atorvastatin inhibited activation of NF-kB by stabilizing IkBa and inactivate ERK phosphorylation and reduce LPS expression of TLR4 mRNA in a human umbilical venous endothelial cells.[74] These effects were similar to those accomplished by the TLR gene silence.

B. Toll-like Receptor Signaling Activation

The most widely explored application of LRT agonists is their use as vaccine adjuvants. Specific TLR agonists with low toxicity and high potency are preferred to other adjuvants for the development of prophylaxis vaccines. In addition, preclinical data supports the use of TLR3, TLR4, TLR7, and TLR7/8 agonists to improve cancer vaccines and viral diseases.[75] Nevertheless, TLR activation proved to be beneficial before ischemic insults. peptidoglycan before ischemia / myocardial reperfusion the injuries reduced the size of the infarction, heart function and sensitivity of the myocardium to damage.[76] Stimulation of peptidoglycans increased phosphorylation of tyrosine TLR2 and increased association of the phosphoinositide p85 subunit 3-kinase with TLR2.[77] Reprogramming of TLR signaling activity is the proposed mechanism of beneficial effects of TLR agonism before ischemic events. LPS-induced TLR4 activation before myocardial ischemia also demonstrated cardioprotective effects.[78]

C. New Approaches for Targeting Toll-like Receptor Signaling

The Cytosolic TIR domain mediates TLR signaling and is the common structural characteristic between TLR and TLR adapter proteins.79. In the beginning stages of TLR signaling, there are multiple interactions TIR domains of TLRs and their adapters which mediate recruitment, assembly and stabilization of adapters TLR signaling complex Interruption of these interactions has been accomplished using lures derived from TIR domains, TIRAP / MAL and TRAM and resulted in inhibition of TLR signaling in vitro and in vivo.[80] Intense interest in the BB loop of The TIR domain has guided research efforts in development inhibitory peptide.[81] The inhibitory peptides and peptidomimetics have relatively low power for LRTs, and therefore high concentrations should be used for effective blocking. AT against this problem protein inhibitors with greater inhibitory power was used. Mutated forms of TLR adapters have been shown to inhibit TLR signaling as dominant negative mutants. A dominant negative form of MyD88 has been used in cell cultures isolated from atherosclerotic plaques and reduces the production of cytokines and inflammatory mediators.[82]

D. Challenges with toll-like receptors Drug development

Cell penetration fractions, including short cationic peptides and fatty acids have been successfully added to the inhibitory peptides to cross cell membrane and target TLR signaling.83 TLR activation on smooth muscle cells increases formation of reactive oxygen species and reduces calcium sequestration in the sarcoplasmic reticulum. Adventitial fibroblasts and fibrocytes are newly identified components of the vascular wall that may contribute to proinflammatory events via activation of TLRs.

CONCLUSION

The recent and intense interest in PRRs, and especially LRT, revealed that the innate immune system makes an important contribution to development cardiovascular diseases, now recognized as chronic inflammatory conditions. Many remains to be learned, however, about the mechanisms thanks to which LRTs and the innate immune system contribute to the genesis and maintenance of the cardiovascular system sickness. Currently there is a growing interest in the adventitious compartment of blood vessels and in particular the adventitious fibroblast, which play an important role in regulating the structure and function of the vascular wall (Stenmark et al., 2013; El Kasmi et al., 2014). TLR activation changes intracellular signaling induced by the second messenger in vascular cells. Accumulate evidence indicates that TLR activation modulates calcium homeostasis. Calcium is a second messenger in intracellular vascular signaling that plays a vital role in contractile and dilatory responses of the smooth vascular muscle cells and endothelial cell function. Depreciated calcium signaling is a common feature of hypertension and other vascular diseases; however, it is unclear how Activation of TLR changes calcium signaling and calcium sensitization mechanisms in the vascular system.

TLRs become promising therapeutics targets for atherosclerosis and cardiac ischemia due to their involvement in the pathogenesis of the disease. TLRs are triggered by conventional bacterial and viral particles (such as C. pneumoniae and PGN), but recent data suggest that molecules (like HSP, HMGB-1, EDA and MRP) released from damaged cells can also bind and stimulate these receptors. Although the molecular mechanism by which TLRs influence atherosclerotic development has been partly revealed in recent years, further research is need to come to a better understanding of TLR involvement in this inflammatory disease. TLR-related research has gained much attention and continues to be a dynamic field since TLR discovery in humans. In the near future, studies will reveal new potential endogenous ligands and provide more mechanistic insight into their biological functions. Especially endogenous activators are appealing for both researchers and clinicians, since they are yielded only during pathological conditions and therefore might represent useful diagnostic tools and therapeutic targets. In addition, pharmacological interventions antagonizing these endogenous molecules will likely cause fewer side effects.

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