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Review

TLR signalling and association of TLR polymorphism with cardiovascular diseases

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ABSTRACT

Toll-Like receptors (TLRs) are the primary receptors of innate immunity. Considerable evidences have shown that innate immune defence interaction with pro-inflammatory pathways could be through TLRs that in turn leads to development of inflammatory diseases. These TLRs are present on various tissues and cells of cardiovascular system. Previous studies involving SNPs analysis of TLRs demonstrated that TLRs are involved in development and progression of diseases like atherosclerosis, cardiac dysfunction in sepsis and congestive heart failure. In this review, we aimed to bring together the studies which have been conducted previously to establish a link between TLR polymorphism in context to development of cardiovascular diseases (CVD).

Contents

1. Cardiovascular diseases: an overview

Cardiovascular disease encompasses wide spectrum of diseases affecting heart, blood vessels or entire cardiac system. Major CVDs include atherosclerosis, coronary artery disease, angiogenesis, septic cardiomyopathy, ischemia, cardiac hypertrophy, valvular disease, congestive heart failure, thrombosis etc.

A vast majority of cardiovascular diseases occur due to atherosclerosis. Atherosclerosis is a complex multigenic disease which leads to chronic inflammation of arterial vasculature resulting in plaque initiation and progression. This situation is a result of accumulation of lipids and foam cells derived from macrophages in the sub-endothelial space [1]. Atherosclerosis is the major cause of death globally and disability

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as compared to any other pathology except infection and infectious diseases [2]. Thus, in view of the severity of the cardiovascular diseases and the deaths caused by them, it becomes extremely important to understand the pathophysiological mechanism behind them.

Most of the cardiovascular diseases lead to chronic local or systemic inflammation. Inflammation caused by manifestation of cardiovascular diseases, is mediated by the release of pro-inflammatory molecules like cytokines and chemokines. These molecules are released from cells upon activation by receiving various signals via receptors present on their surface. TLRs are one of the well characterised receptors which play a key role in inflammation mediated by the various infectious agents [3]. With the advent of science and technology in the last decade, their role in noninfectious immune mechanism is also emerging. The role of TLR signalling in the progression of non-infectious diseases like rheumatoid arthritis, lupus, inflammatory bowel disease and cardiovascular diseases is also under investigation [4]. Most of the cells of cardiovascular system express TLRs; cardiomyocytes express TLR 2, 3, 4 and 6, smooth muscle cells and endothelial cells of the vasculature express TLR 1 and 6 [4] so, the possibility of a putative role of TLRs in development of CVDs cannot be ruled out. Thus, studies have been done regarding the involvement of innate immunity and TLRs in development of cardiovascular diseases like atherosclerosis, myocardial remodelling, valvular disease and thrombosis [5]. Therefore, it can be proposed that interweaving of immune defence system with the pathologic determinants of CVD is dependent on TLR signalling. As TLRs play a key role of receiving signals, it is speculated that polymorphisms in TLRs can alter and modify the cellular response and production of cytokines which can further be associated with susceptibility towards wide spectrum of infectious and non-infectious diseases [6]. In order to understand how TLR polymorphism affects disease occurrence, it is important to know about TLRs and their signalling.

2. Innate host defence and TLRs

Humans need a protective mechanism which can act from birth onwards as they are exposed to plethora of infectious microbes since the time of birth. These infectious agents are capable of causing multitude of diseases which can limit survival and healthy living system. Our body is endowed with the in-born mechanism called innate immunity for protection against range of infectious diseases. Innate immunity is pre-programmed and thereby forms the first line of defence of the body against invading foreign pathogen. The pathogens attacking body have certain conserved and constitutive patterns expressed on their surfaces. These patterns are called Pathogen Associated Molecular Patterns (PAMPs) and are recognized by the components of innate immunity such as TLRs. In addition to molecular patterns of pathogens, TLRs can also recognise the altered self-molecules released during damage or disease in the body called Damage Associated Molecular Patterns (DAMPs) [7–10]. Thus, they recognise the so called “danger signals” produced by microbes as well as endogenous tissue. TLRs receive signal by binding to PAMPs and DAMPs and play a key role in signal transduction pathway which is manifested in the form of response such as inflammation or a disease [11]. Recognition of PAMPs by TLRs represents one of the most ancient defence system exhibited in plants, insects and mammals. This provides an evidence for phylogenetic conservation of innate immune response in all multicellular organisms.

Toll receptors were first discovered in *Drosophila melanogaster* in 1996 for its protective role in flies against the fungus *Aspergillus fumigates* [12]. TLR4 the homologue of toll receptor of Drosophila was the first TLR to be identified in humans [13]. The various type of TLRs have been cloned which differ on the basis of distinct function in recognition of pathogen in innate immunity. Together they are known as TLR family. A total of 13 TLRs have been cloned till date, 11 in humans [14] and 13 in mice [15]. The TLR family constitute of receptors residing both at the cell surface and inside the cell, showing the specialization of receptor subsets for particular ligand and task [16]. Based on subcellular localisation, TLRs have been divided into two groups; the ones which are expressed on plasma membrane, which includes TLR1, TLR2, TLR4–6 and the ones residing in endosomal compartment including TLR3 and TLR7–9 [17]. The membrane associated TLRs respond to the PAMPs of bacterial surfaces, whereas TLRs of endosomes respond to nucleic acid based PAMPs of bacteria and viruses [11]. Interestingly, all TLRs in humans have same basic molecular structure. They belong to class of type I transmembrane glycoproteins having an extracellular leucine rich repeat (LRR) motif, a transmembrane and an intracellular signalling domain [11]. The cytosolic or intracellular domain is called TIR (Toll-IL-1R (Interleukin-1-Receptor)) homology domain. Different TLRs recognise different PAMPs thus have different ligand specificities.

3. Ligand specificity of TLR

The TLRs serve as pathogen recognition receptor (PRR) for broad range of ligands that involves the bacterial cell wall components, viral DNA or dsRNA, small anti-viral or immunomodulatory molecules etc. The summary of the TLR and their cognate ligand is given in Table 1.

4. TLR signalling

Signalling through TLRs induces a chain of events which involve production of pro-inflammatory molecules such as chemokines and cytokines, activation of complement system, recruitment of phagocytic cells and antigen presenting cells (APCs) at the site of pathogen invasion.

The signal transduction pathway originates from the Cytoplasmic TIR domain of TLR after the ligand binding. The TIR domain of TLRs further recruits the downstream adaptor molecules like MyD88 (myeloid differentiation primary response gene 88), TIRAP/Mal (TIR-domain-containing adapter/MyD88 adaptor-like), TICAM1/TRIF (TIR-domain-containing adaptor molecule 1/TIR-domain-containing adaptor inducing interferon β) and TRAM (TRIF-related adaptor molecule). Amongst these downstream adapters, MyD88 plays the most critical role in TLR signalling pathway (Fig. 1 however presence of MyD88 independent pathway is also known [31].

5. MyD88 dependent signalling

MyD88 is the most critical adaptor molecule involved TLR signalling pathway. TLR2, TLR5, TLR7/8, TLR9, and TLR11 signalling occurs through MyD88 dependent pathway [32,33,34,35]. Upon pathogen invasion, the PAMPs binds to TLRs brining about change in their cytosolic domain which then recruits MyD88 to TLR by the complementary interaction between their TIR domains. Further, downstream signal transduction is carried out by the recruitment of the serine/threonine IL-1 receptor–associated kinase-4 (IRAK-4) to MyD88. After binding to MyD88, IRAK-4 recruits IRAK-1 and causes its phosphorylation. After phosphorylation IRAK-1 shows kinase activity and gets auto-phosphorylated, to generate new docking sites. These docking sites enable tumor necrosis factor receptor–associated factor-6 (TRAF6) to bind to MyD88/IRAK-4/IRAK-1 complex. After activation, IRAK-1 and TRAF6 dissociate from the MyD88/IRAK-4/IRAK-1 complex and activate c-Jun. N-terminal kinase (JNK) and inhibitor of NF-κB kinase (IKK) by interaction with another complex that consists of TAK1 [TGF (transforming growth factor)-β-activated kinase 1] and TAB1, 2 and 3 (TAK-1-binding proteins 1, 2 and 3). The active JNK and IKK induce activation of AP-1 (activator protein-1) and NF-κB. NF-κB move to nucleus and act as the transcription factor for the genes encoding pro-inflammatory chemokines and cytokines. Thus, the transcription of genes coding for TNFα, IL-6, IL-8, and IL-1β occurs [36,37,38].