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Review article

Toll like receptor 4 and hepatocellular carcinoma; A systematic review

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ABSTRACT

Introduction: Toll like receptor 4 (TLR4) is an extracellular pathogen recognition receptor (PRR) which recognizes a wide range of pathogens and damage associated molecular patterns (PAMPs and DAMPs). It can activate intracellular signaling and consequently transcription factors which participate in transcription from either immune related or malignancy genes. Thus, it has been hypothesized that TLR4 may be a cause of hepatocellular carcinoma (HCC). This article has reviewed the roles of TLR4 in the pathogenesis of HCC.
Method: "TLR4", "hepatocellular carcinoma", "liver tumor" and "liver cancer" were used as key words for searching in Scopus, Google Scholar and MEDLINE scientific databases.
Results: Most of the investigations documented the roles of TLR4 in induction of HCC via several mechanisms including increased number of T regulatory lymphocytes and liver resident follicular helper like cells, increased production of pro-inflammatory and malignancy related molecules including cytokines, NANOG, Caspase-1, Ephrin-A1, NO and BCL6. TLR4 participates in the proliferation of the cells and also production of the molecules in both chronic infectious and non-infectious inflammatory diseases.
Discussion: TLR4 is an innate immunity receptor which plays a pathogenic role during chronic inflammation and can induce HCC in human.

Contents

1. Introduction

Hepatocellular carcinoma (HCC) is a prevalent malignancy worldwide [1]. It is more prevalent in Asia, and less common in Europe,

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America and Middle East countries [2]. Several factors and mechanisms are responsible for inducing HCC in human. It has been reported that liver cirrhosis, primary biliary cirrhosis, hepatitis viral infections, co-infection of hepatitis viruses and human immunodeficiency virus (HIV), nonalcoholic fatty liver disease, silent chronic liver disease, alcoholic liver disease, nonalcoholic steatohepatitis, hypersensitivities including autoimmune hepatitis, toxins such as aflatoxin B1 and hereditary hemochromatosis are the most important risk factors for HCC [3,4]. HCC has been classified to 8 categories based on the histomorphologic features including well vascularized tumors with wide trabeculae (>3 cells), small cell changes, prominent acinar pattern, absence of Kupffer cells, mitotic activity, cytologic atypia, vascular invasion and the loss of the reticulin network [5]. HCC surveillance is variable and significantly dependent on early detection, curative therapy administration, and existence of cirrhosis [6]. It has been hypothesized that the viral factors and host immune system can be considered as the main risk factors for induction of HCC in the population [7]. It appears that pathogen recognition receptors (PRRs), as the molecules involved in the pathogen/damage associated molecular patterns (PAMPs/DAMPs) recognition, can be considered as candidates to induce or stimulate HCC. The main mechanisms used by the PRRs in the pathogenesis of HCC have been evaluated previously. Among PRRs, toll like receptors (TLRs) are the important PRRs which have been evaluated regarding their roles in the pathogenesis of HCC. TLRs can recognize PAMPs/DAMPs and induction of related intracellular signaling. There are 10 TLRs in/on the human immune and non-immune cells which use myeloid differentiation primary response (MYD88) alone (TLR1, TLR2, TLR5, TLR6, TLR7, TLR8 and TLR9), TIR-domain-containing adapter-inducing interferon-β (TRIF) alone (TLR3) and both TRIF and MYD88 (TLR4), as adaptor proteins [8,9]. Accordingly, it appears that TLR4 has a wider range of functions than other TLRs [8], which corroborates its role as an important molecule involved in the pathogenesis of HCC. The aim of this article is to review the main mechanisms used by TLR4 in the induction of HCC.

2. TLR4 recognizes several ligands and induces both TRIF and MYD88 dependent pathways

TLR4 is a known highly conserved member of PRRs and has been recognized as age-related macular degeneration 10 (ARMD10) and cluster of differentiation 282 (CD284) [10]. Its gene location is far from other TLRs and is located on 9q33.1 [11,12]. TLR4 consists of three main domains including extracellular leucine-rich repeats (LRRs), hydrophobic intramembrane domain, and intracytoplasmic toll-IL-1 receptor (TIR) domain. Its extracellular LRRs domain recognizes several ligands including Lipopolysaccharide (LPS), free fatty acids, microbial lipids, monophosphoryl lipid A (MPLA), hyaluronan, high-mobility group box-1, allergenic nickel and heat shock protein 60 and 70 [13,14]. Interaction between TLR4 and their ligands leads to activation of two distinct pathways which are dependent on the location of TLR4/ligands interactions [15]. TLR4/ligands interactions on the cell membrane lead to activation of MYD88 dependent pathway. Accordingly, TIR domain-containing adaptor protein (TIRAP), which is also known as MyD88 adapter-like (Mal), interacts with TIR domain of TLR and consequently activates MYD88 molecule [15]. Activated MYD88 mediates phosphorylation of Interleukin-1 receptor associated kinase (IRAK)-4 and IRAK-1 [16]. Activation of IRAK-1 leads to phosphorylation and activation of TNF receptor associated factor (TRAF)-6 molecule [17]. Activated TRAF-6 is a key stage of TLRs intracellular signaling pathways which can activate important transcription factors including nuclear factor-kappaB (NF-κB), activator protein 1 (AP-1) and interferon regulatory factor 3 (IRF3) [17]. The transcription factors translocate to the nucleus and, hence, transcripts from pro-inflammatory cytokines as well as type interferons [15]. TLR4/ligands interaction in the endosomes leads to recruitment of TRIF-related adaptor molecule (TRAM) which contains TIR domain and consequently activation of TRIF molecule [18]. TRIF, as an adaptor protein, mediates phosphorylation of Iκκ, as inhibitor of NF-κB, and consequently translocation of the transcription factor to the nucleus [18]. TRIF also mediates activation of mitogen-activated protein kinase (MAPK) pathway which leads to activation of AP-1 [18]. TRAF3 is another target of TRIF which mediates activation of IRF5 transcription factor [18]. Intracellular signaling pathways of anti-inflammatory cytokine receptors, including Janus kinase (JAK)/Signal transducer and activator of transcription 3 (STAT3) pathway are the main inhibitory pathways for TLR4 signaling. Fig. 1 shows the intrasignaling pathways of TLR4.

3. Hepatocellular carcinoma

HCC is the sixth most common cancer worldwide and is associated with increasing mortality [19,20]. It is the most serious chronic hepatitis B/C complication [21]. Multiple risk factors can influence HCC and, hence, HCC has a complex pathogenesis [21]. Based on the HCC heterogeneity, developing effective therapies against this dangerous cancer is challenging. Despite the advances in our knowledge regarding the etiology and mechanisms responsible for development of HCC, the molecular pathogenesis of this lethal cancer is yet to be completely understood. HCC has clinical and histopathological heterogeneity and its cellular differentiation has a wide range from very well to poorly differentiated tumors. Additionally, HCC has various morphologic features such as cirrhotomimetic, clear cell, myxoid, sarcomatoid, fibrolamellar, neutrophilic-rich, lymphocyte-rich, cirrhous, biphenotypic (a combination of hepatocellular and cholangiocarcinoma) and steatohepatitic HCCs [22]. Although there is a wide histological diversity of HCC, there is limited information regarding the molecular or genetic mechanisms for development of HCC. Therefore, it is worthy to expand our knowledge regarding the main risk factors and the mechanisms which lead to development of HCC.

Several agents have been introduced as risk factors for development of HCC which can be categorized into three classes including viral, liver and host factors [23,24]. Viral factors consist of the hepatitis B virus (HBV) and hepatitis C virus (HCV) related molecules which may participate in induction of HCC. These risk factors include high HBV-DNA/HCV-RNA copy numbers, HBV/HCV mutants, hepatitis B virus e antigen (HBeAg), HBV/HCV genotype and chronic raised liver enzymes [24–26]. Liver factors include advanced liver cirrhosis and fibrosis, impaired liver function and active viral/non-viral hepatitis [24,27,28]. Interestingly, host and environmental factors including gender, diabetes mellitus, obesity, some genetic variations, older age, cirrhosis, family history of HCC, opium addiction, smoking, alcohol and immune status are the most prevalent risk factors for HCC. The roles played by immune system and its related molecules in the pathogenicity of HCC have yet to be clearly elucidated. Accordingly, the roles of TLR4 as a plausible risk factor for development of HCC and participation in its pathogenesis are discussed in this review article.

4. Methods

Medical Literature Analysis and Retrieval System Online (MEDLINE), Google Scholar and Scopus, as the main three databases, were searched regarding "TLR4, liver tumor, liver cancer and hepatocellular carcinoma" as key words. The research studies which evaluated the TLR4 expression and functions in other liver diseases rather than HCC and the publications in a language other than English have been excluded from the current review article as well. The articles published from 1990 to 2017 have been enrolled in this project. Accordingly, after initial searching, 90 papers were included in the investigation and after excluding the papers according to the exclusion criteria, 63 papers were presented in the current review article.