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### interrelationship between Toll-like receptors and infection after orthotopic liver transplantation

### El-Bendary M *et al*. TLRs and post liver transplantation infection

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**Abstract**

Early microbial recognition by the innate immune system is accomplished by Toll-like receptors (TLRs), with resultant initiation of a pro-inflammatory response against infecting organisms. In spite of presence of an abundance of Toll-like receptors on the surface of the liver, gut bacteria does not elicit an inflammatory reaction in healthy individuals due to tolerance to these TLRs, suggesting that the inflammatory responses seen in the liver are the result of breakdown of this tolerance. While orthotopic liver transplantation is often life saving in many instances, death following this procedure is most commonly due to infection that occurs in up to 80% of transplant recipients, most commonly due to microbial causes in up to 70% of cases and viral infections in 20%, while fungal infections affect only 8% of cases. The probability of acquiring infection following hepatic transplantation is heightened due to affection of the innate immune defense mechanisms of the host following this procedure. Single nucleotide polymorphisms of TLRs have been associated with increased likelihood of either development of post-transplant infection or eradication of infecting organism. However, conflicting reports from other studies reveal that prevalence of this single nucleotide polymorphism is not increased in infected patients.

**Key words:** Toll like receptors; infection; liver transplantation; cirrhosis; immunity; orthotopic

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**Core tip:** microbial recognition by the innate immunity is accomplished by Toll-like receptors (TLRs). In spite of presence of an abundance of TLRs on the surface of the liver, gut bacteria does not elicit an inflammatory reaction in healthy individuals due to tolerance to these TLRs suggesting that the inflammatory responses seen in the liver are the result of breakdown of this tolerance. The probability of acquiring infection following hepatic transplantation is heightened due to affection of the innate immunity of the host. There is controversy about the association between genetic polymorphism of TLRs with the development of post-transplant infection.

**Introduction**

Host protection against invading pathogens is dependent on the coordinated reactions of both innate and adaptive immune systems beginning with the early detection and subsequent initiation of a pro-inflammatory response against infecting organisms[1], while the adaptive immune system is responsible for pathogen removal in the later stages of infection and creation of immunological memory[2]. Early microbial recognition by the innate immune system is done by use of germ-line encoded pattern recognition receptors (PRRs) capable of identifying molecular arrangements particular to the invading microbe known as pathogen-associated molecular patterns (PAMPs) as well as those arising from direct injury to host cells termed damage-associated molecule patterns (DAMPs)[3,4].

Recognition of PAMPs and DAMPs is carried out by a subgroup of PRRs called Toll-like receptors (TLRs) of which there are ten identified human types. These receptors consist of a membrane-spanning glycoprotein and a 200 amino acid region in their highly conserved C-terminal known as the Toll/IL-1R (TIR) domain**[4]**. While TLR4 was the first TLR to be identified mainly for its recognition of lipopolysaccharide (LPS) such as that present in the outer membranes of Gram-negative bacteria, every TLR subsequently identified has the ability to recognize specific sequences of PAMPs. Furthermore, on the basis of subcellular localization, TLRs can be classified into two main groups. TLRs 1, 2, 4, 5, and 6 are receptors situated on the cell surface and are primarily responsible for recognition of bacterial PAMPs, while TLRs 3, 7, 8, 8, and 11 are intracellular receptors for detection of viral PAMPs and DNA. TLR 11 also has the added ability to recognize uropathogenic bacteria**[5]**.

Joining of the Toll-receptor with its respective ligand, by way of its leucine-rich repeat (LRR) domain, initiates a downstream cascade resulting in upregulation of pro-inflammatory cytokines and chemokines and signaling of interferon secretion. While TLRs are primarily a part of host innate immunity, they connect the innate with the adaptive immune systems by playing a role in dendritic cell maturation, antigen presentation, and T and B-cell recruitment and activation[6], immune reactions that are important in host infection with viral agents, including hepatitis C virus (HCV) infection. Initiation of the afore mentioned signaling cascade occurs by joining of the TIR domain to any of four primary adaptor molecules, namely myeloid differentiation factor 88 (MyD88), TIR-domain containing adaptor-inducing interferon-beta (TRIF), TIR-associated protein (TIRAP), and TRIF-related adaptor molecule (TRAM)[7].

All TLRs utilize MyD88 except TLR3 that employs TRIF. TLRs 2 and 4 signaling requires TIRAP in conjunction with MyD88, while induction of antiviral interferon response and stimulation of nuclear factor kappa B (NFκB) by TLR 3 and 4 is dependent on TRIF, the TLR4-TRIF signaling pathway further utilizing TRAM[6]. Both MyD88-dependent and -independent pathways are vital signal transduction pathways that enable host TLRs to initiate immune reactions in response to recognition of pathogenic microorganisms including hepatitis viruses B and C[8,9].

**TLRs and liver**

The liver is the first defensive structure against bacteria and their derivatives persistently received from the gut by way of the portal circulation[10].In spite of presence of an abundance of TLRs on the surface of parenchymal, as well as non-parenchymal, hepatic cells[8], the continuous exposure of hepatic cells to gut bacteria does not elicit a inflammatory reaction in healthy individuals, demonstrating the development of a type of tolerance to TLR ligands and giving rise to the suggestion that the inflammatory responses seen in the liver are the result of breakdown of this tolerance[11].

***Kupffer cells***

Stimulation of TLRs 2, 3, 4, and 9 expressed on hepatic Kupffer cells faced with gut pathogen associated molecular patterns (PAMPs) leads to generation of a number of cytokines including tumour necrosis factor α (TNF-α), interleukin (IL)-1b, IL-6, IL-12 and IL-10[12]. In addition, these cells partake in the fibrogenetic process by inducing the secretion of transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), matrix metalloproteinases, and reactive oxygen species (ROS)[8].

***Hepatocytes***

TLRs 2, 3, 4, and 5 are expressed in low amounts, in contrast to Kupffer cells, on hepatocytes where they function to capture and remove endotoxins introduced into the liver from portal, as well as hepatic, circulation. In addition, stimulation of TLRs by their ligands results in induction of a pro-inflammatory cytokine response, albeit much less defined than that observed with Kupffer cells[12].

***Hepatic stellate cells***

TLRs 4 and 9 are expressed on hepatic stellate cells where they cause chemokine and adhesion molecule upregulation. In addition, stimulation of TLR4 also promotes signaling of transforming growth factor-β (TGF-β) and induction of fibrogenesis while participating in cell defense through the TLR4-MyD88-mediated inflammatory response upon exposure to LPS[6,9,12,13]. As a result, single nucleotide polymorphisms (SNPs) of TLR4 are associated with enhanced risk of fibrosis progression in patients with chronic HCV infection[13], and offer an approach to recognize fibrosis risk genes[14-16].

***Biliary epithelial cells***

These cells express TLRs 2, 3, 4, and 5, of which TLR 2 and 4 stimulation leads to upregulation of interleukin-1 receptor-associated kinase (IRAK) with resultant tolerance to LPS, a particularly important host protection mechanism against uncontrolled TLR signaling brought about by the activation of biliary epithelial cells specific pathogen-related molecular arrangement located in the intestinal lumen[17].

***Other hepatic cells***

Stimulation of TLR4 expressed on liver sinusoidal endothelial cells activates a nuclear factor kappa β (NFκB) dependent pathway resulting in secretion of TNF-α and reactive oxygen species[18], while hepatic dendritic cells (DCs), the primary antigen presenting cells (APCs) of the liver, primary sources of interferon α (IFN-α) released in response to ligand-induced stimulation of TLRs 4, 7, and 9[19].

**Post orthotopic Liver Transplantation infections**

While orthotopic liver transplantation is often lifesaving in many instances, death following this procedure is most commonly due to infection that occurs in up to 80% of transplant recipients, most commonly due to microbial causes in up to 70% of cases with viral infections coming second at 20% and fungal infections affecting only a minority of cases at 8% (table 1)[20]. Risk of infection to recipients of liver transplantation is reliant on strength of the infectious agent in conjunction with host immune state[21], as evidenced by the increased likelihood of patients with patients with end-stage liver disease (ESLD) acquiring infections due to associated conditions of defective immunity, including neutropenia, weakness of the mucocutaneous wall, occurrence of necrotic tissue, ischemia, and diabetes mellitus[22].

Post-transplant infection occurs from a number of different sources including de novo infection or recurrence of infection in the recipient patient, transplantation of infected graft, and nosocomial infection during hospital stay. Cause of the infection may be ascertained from the period directly following the transplant. The immunosuppressive state of these patients is dependent on the amount, type, and duration of the immunosuppressive agent used[21].

Risk Factors for Infection Following Liver Transplantation

Recipients of orthotopic liver transplantation become more susceptible to infective agents in situations of present underlying causative, immunosuppressive state of the recipient with regards to type of immunosuppressive drug administered and the extent of the disease, technical complications during the transplant procedure, and exposure to pathogens within the hospital and public environment[23].

## **TLRs and infection after liver transplantation**

## ***TLRs and infectious liver diseases***

Pathophysiology of a number of infectious diseases, including *Listeria, Salmonella,* and the *Plasmodium* species, is affected by TLRs. Following the invasion of hepatic tissue, *Listeria monocytogenes* replicates in hepatocytes and Kupffer cells, prompting the infected Kupffer cells to subsequently initiate a counterattack through a TLR2/MyD88-dependent pathway to secrete of the pro-inflammatory cytokines tumour necrosis factor-α (TNF-α) and interleukin-12. While this extensive pro-inflammatory release of cytokines in response to *L. monocytogenes* infection is defective in MyD88-deficient rats, giving rise to a higher rate of mortality[12], TLR2-deficient mice show normal clearance of the infection in spite of a diminished cytokine response. This suggests that although TLR2 does participate in the cytokine cascade, clearance of *L. monocytogenes* is dependent on a number of collaborating TLRs[24].

Infection with *Salmonella typhimurium* is typically cleared by Kupffer cells in the liver through an antimicrobial response involving TLR4 and nitric oxide, consequently leading to granuloma formation[25], while infection with *Salmonella choleraesuis* results in liver injury by induction of TLR2-mediated upregulation of Fas-ligand on natural killer cells[26]*.* In spite of these TLRs playing a major role in the pathogenesis of *Salmonella*, elimination of *S. choleraesuis* does not depend on the actions of TLR2 and TLR4, as intracellular growth of this pathogen had diminished on activation of TLR9, suggesting that eradication of *Salmonella* is also dependent on several TLRs[27].

Malaria causes liver injury in humans by infection with *Plasmodium falciparum* and in mice by *Plasmodium berghei* through a TLR/MyDD88-mediated pathway leading to lymphocytic infiltration and subsequent death of hepatocytes[28]. Variants of TLRs 1 and 6 were found to be associated with milder forms of malaria, while TLR9 (1486 C/T) variant was more likely related to higher levels of malarial parasitemia[29].

Other SNPs of TLRs have also been associated with increased likelihood of infection. SNP of TLR2 (R753Q), resulting in impaired TLR2 signaling, has been associated with increased susceptibility to tuberculosis infection in a Turkish study[30], while a Tunisian study reported that tuberculosis patients demonstrated higher frequency of TLR2 (Arg677Trp)polymorphism than healthy control subjects, suggesting that presence of this polymorphism was a risk factor for pulmonary tuberculosis[31]. This finding was contradicted, however, in another study showing that TLR2 (Arg677Trp)polymorphism did not convey risk to tuberculosis in a population of Iranian and Indian subjects[32].

***TLR signaling and HCV recurrence following liver transplantation***

The probability of acquiring infection following hepatic transplantation is heightened due to affection of the innate immune defense mechanisms of the host following this procedure. That said, recurrence of HCV infection after liver transplantation (LT) is a universal occurrence, with the course of infection being greatly accelerated when compared to infection outside of the transplant setting[33].

TLR2 signaling pathway plays a major role in recurrence of HCV following liver transplantation. Homozygosity of TLR2 (Arg753Gln) polymorphism has been associated with higher mean fibrosis levels as well as higher graft cirrhosis and loss, leading to higher mortality of HCV cases post-transplantation. On the other hand, SNPs of TLR4 (Asp299Gly) and (Thr399Ile) showed no association with any serious complications following liver transplantation[34]. However, TLR2 (R753Q) SNP has been reported to hinder immune recognition of HCV core and NS3 proteins that is reliant on TLR2, possibly explaining why allograft failure develops in patients with chronic hepatitis C who undergo liver transplantation[35].

Abnormal blood mononuclear cell secretion of interferon-α and NK CD56dim cell secretion of interferon-γ due to impaired TLR7/8-mediated pathway are associated with more aggressive post-transplantation recurrence of HCV infection in comparison to slower course HCV infections following liver transplantation[36]. Furthermore, patients demonstrating rapid progression of fibrosis show impaired blood mononuclear cell secretion of tumour necrosis factor-α (TNF-α) and interleukin-6 both at baseline and with TLR3 receptor stimulation. TLR3 receptors are functional receptors expressed on monocytes where they are dominant initiators of host antiviral responses[37-39].Therefore, it is reasonable to assume that hindered secretion of TLR3-mediated monocyte-derived TNF-α and interleukin-6 results in impaired NK and dendritic cell stimulation leading to increased fibrosis[36].

Natural killer CD56 dim cells secrete IFN-γ that stimulates dendritic cells and T cells, thereby aiding Th1 anti-viral cytokine responses. Impairment of this secretory release promotes Th2 rather than Th1 cytokine response[40,41], leading to impaired HCV-directed T cell response, particularly with regards to CD4+T cell protection against progression of liver disease[42]. Rapid progression of fibrosis in HCV patients is attributed to inadequate viral control by the immune system[43,44], leading to heightened production of pro-inflammatory cytokines with increased stimulation of pro-fibrogenic pathways[15,45,46].

Secretion of interferon-α and interferon-γ has been shown to be extremely important in host viral defense mechanisms, with emphasis on the fundamental role of TLR7/8 signaling pathways in recurrence of HCV infection post-LT. This consideration becomes even more eminent when coupled with data demonstrating the negative effect of calcineurin inhibitors on TLR7/8-mediated human NK CD56dim cell secretion of interferon-γ in patients having undergone liver transplantation[36,47].

***Polymorphism of TLR2 and infections with Gram-positive bacteria after liver transplantation***

It is generally accepted that cell wall components of Gram-positive bacteria, particularly peptidoglycan and lipoteichoic acid, are recognized by TLR2[48]. SNPs in certain *TLR* genes have been reported to negatively impact responses of these receptors to their corresponding ligands[35]. TLR2 (R753Q) SNP, caused by substitution of arginine for glutamine at position 753, was shown to result in defective intracellular signaling resulting in modification of cytokine secretion in response to stimulation by peptidoglycan, lipopeptides, and other bacterial components leading to increased susceptibility to bacterial infections[35]. In addition, this SNP showed high association with Gram-positive septic shock infections and staphylococcal infections[49].

Similarly, cell membrane constituents of *S. aureus* did not elicit TNF-α response from TLR2-deficient macrophages[50]. Compared with wild-type rats, those with TLR2-deficiency showed increased susceptibility to infection with *S. aureus.* These TLR2-deficient rats demonstrated increased mortality rates of 80% on day 8 and 90% on day 14 after being subjected to experimentally high infectious doses *S. aureus*, compared to rates of 0% and 40%, respectively, in wild-type rats***.*** Moreover, cirrhotic patients have been shown to demonstrate increased susceptibility to spontaneous bacterial peritonitis with presence of the variant SNP TLR2 (R753Q)[50,51].

Nevertheless, post-transplantation susceptibility to infection in patients with TLR2 (Arg753Gln)polymorphism remains inconclusive, with one study showing no association of this SNP with infections of viral or fungal nature following transplantation of allogeneic stem cells, although there has been an association between TLR2 (Arg753Gln) SNP and CMV infection and replication post-LT[52]. However, other reports provide conflicting results, revealing that prevalence of this SNP was not increased in patients with Gram-positive bacteremia[53], a difference that may be attributed to the variation in patient sample as this study included cases of HIV infection, Gram-positive bacterial infections, and septic shock[53,54]. Another study evaluating *S. aureus* infection of prosthetic joints demonstrated that frequency of TLR2 (R753Q) SNP was relatively similar between infected patients and controls, with the likelihood of developing complications of *S. aureus* infection was basically similar between patients with wild-type TLR2 gene and those with polymorphism[55].Furthermore, no association could be ascertained between aggressive *S. aureus* infection and presence of mutant TLR2 (R753Q) SNP[56]. A lack of difference in TLR2 (R753Q) SNP between patients with and without Gram-positive infections has also been reported, these infections found in transplant patients with TLR2 (R753Q) SNP in similar frequencies as in those with wild-type gene[57].

While these results appear to propose a lack of significant impact of TLR2 in human infection, other data has suggested the contrary. The same study by Lee *et al*[57]also reported that TLR2 (R753Q) SNP showed marked association with increased risk of septic shock, in addition to a relatively insignificant tendency towards risk of recurring infection. However, no significant relationship could be determined between TLR2 (R753Q) SNP and 90-d all-cause death. This can be partly attributed to presence of other receptors playing a role in pathogen recognition, such as identification of Gram-positive infections through the nucleotide oligodimerization domain[58]. Similarly, infection with *S. aureus* in an animal model is recognized by several types of TLRs, including TLR2[50]. Another explanation for the apparent clinical irrelevance between TLR2 and infection may the dose of infectious pathogen, as TLR2 and survival form *S. aureus* infection were found to be correlated only in cases of infections with large dose of pathogen[50].

***Relationship between polymorphism of TLR2 and infection with cytomegalovirus following liver transplantation***

The report of TLR2 (R753Q) SNP inhibiting TLR2 signaling on exposure to cytomegalovirus glycoprotein B may provide the basis for association of this polymorphism with human cytomegalovirus disease[59]. Homozygosity of TLR2 (Arg753Gln) SNP has been reported to be associated with high incidence of CMV infection post-transplantation of liver and the kidney[60,61], in addition to indicating risk for CMV infection, especially tissue-invasive type, following liver

transplantation[62].

TLRs have been reported to take part in the innate defense mechanisms against infection with CMV, with CMV-induced activation of TLR2 resulting in production of cytokines via a nuclear factor kappa B (NFκB)-mediated pathway[63]. TLR2 (Arg753Gln) SNP requires presence of only a single functional wild-type allele to control CMV infection, as cells with heterozygosity for this polymorphism function similarly as those with wild-type gene, having the capability to respond on activation with TLR2 agonist[64]. Conversely, cases with homozygosity for TLR2 (Arg753Gln) SNP show replication of cytomegalovirus and manifest clinical disease. However, it should be noted that CMV disease is less manifest in cases with heterozygosity for this SNP, in spite of the fact that viral replication is more pronounced[60].

***Effects of Cyclosporine and Tacrolimus on TLR signaling after liver transplantation***

The deficient peripheral blood mononuclear cell (PBMC) pro-inflammatory cytokine secretion observed on stimulation of TLRs 2, 4, and 7/8 on administration of tacrolimus and cyclosporine therapy in patients when compared to healthy control subjects suggests a class effect for calcineurin inhibitors on function of these TLRs. However, examination by flowcytometry demonstrated that no specific individual cell subtype could be identified as accountable for the functional modification of these receptors, suggesting that the suppressive effect of calcineurin inhibitors on TLRs 2, 4, and 7/8 is apparent in PBMCs but variable in individual cell subtype**s**[65].

Similarly, calcineurin inhibitors have also been shown to down-regulate TLR4 stimulated by lipopolysaccharides, although pre-treatment of cells with tacrolimus resulted in diminished inflammatory response to lipopolysaccharides, suggesting initiation of lipopolysaccharide intolerance (73). Impaired secretion of tumor necrosis factor-α (TNF-α) and interleukin-6 mediated through TLRs 2, 4, and 7/8 pathways has been demonstrated from PBMCs cultured with both TLR agonist and calcineurin inhibitors when compared with controls[65].

**CONCLUSION**

The liver is the first host defensive structure against the bacteria and bacterial products that are persistently received from the gut by way of the portal circulation. However, this massive influx of gut bacteria does not elicit an inflammatory reaction in healthy individuals due to tolerance of the abundantly present TLRs on the surface of hepatic cells. While orthotopic liver transplantation is often lifesaving in many instances, death following this procedure is most commonly due to infection that occurs in up to 80% of transplant recipients. SNPs in certain *TLR* genes have been associated with increased susceptibility to infections (table 2). SNPs of TLR2 have been associated with both Gram-positive and Gram-negative bacteria (*e.g.*, *Listeria, Salmonella)*, *mycobacteria tuberculosis*and the*Plasmodium*species, in addition to CMV infection and the universal recurrence of HCV following liver transplantation. Similarly, impaired TLR7/8-mediated pathway has been associated with more aggressive post-transplantation recurrence of HCV infection, while reports on TLR3 polymorphism have demonstrated comparable results.

Our hypothesis is that *TLR* genes and their proteins have influence in the outcome of post liver transplantation infection. This risk factor are responsible for mortality rate of liver transplant. Understanding the genetic variation of *TLR* gene in liver transplant may clarify the underling mechanisms behind the post-transplant infection.   It may also enables the development of early diagnostic tests for predication of either the persistence or clearance of infection.  Genetic study may be also open some windows for new treatments, or interventions to prevent disease onset or minimize disease severity.

Association between TLRs genotypes and post transplant infection have traditionally been studied by determining the genotype of known markers. However. these associations studies of single gene typically explain less than 25% of the heritable risk estimated for each of those diseases. Furthermore, the heterogeneity, ethnic variation and complex relationship between genotype and phenotype may also difficult, to predict which genes are most likely to be implicated as a candidate gene for a particular outcome. We recommended several approaches to investigate the association of *TLR* (1-10) genes with the outcome of post-transplant infection. These approaches include: (1) Genome wide association study (GWAS) using next-generation sequencing techniques (NGS) for the whole genome to identify the entire underlying genetic variation and its disease relevance. Applying NGS to GWAS will help for better identification of candidate genes in a short time, and in an efficient way. (2) Gene expression epigenetic analyses of *TLR* gene may also provide more information about the underlying mechanism of these factors for the disease outcome. (3) furthermore, correlation study of different genotype with serum levels of cytokine net levels are also required. And (4) Multicentric well-designed studies of large sample size are needed to avoid false negative results that may arise from under-evaluation of interactions involving gene-to-gene relations or gene environment among different ethnic populations.

***Limitations of the study***

The major limitation of this article is the study design, as it is a narrative review article. It is well known that narrative review articles are more susceptible to selection bias and this may affect its conclusion. Systematic review articles adhere to strict methodology, thus are, potentially, more reliable scientifically.

**References**

1 **Medzhitov R**, Janeway C Jr. The Toll receptor family and microbial recognition. *Trends Microbiol* 2000; **8**: 452-456 [PMID: 11044679 DOI: 10.1016/s0966-842x(00)01845]

2 **Iwasaki A**, Medzhitov R. Toll-like receptor control of the adaptive immune responses. *Nat Immunol* 2004; **5**: 987-995 [PMID: 15454922 DOI: 10.1038/ni1112]

3 **Janeway CA Jr**, Medzhitov R. Innate immune recognition. *Annu Rev Immunol* 2002; **20**: 197-216 [PMID: 11861602 DOI: 10.1146/annurev.immunol.20.083001.084359]

4 **Kawai T**, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol* 2010; **11**: 373-384 [PMID: 20404851 DOI: 10.1038/ni.1863]

5 **Broz P**, Monack DM. Newly described pattern recognition receptors team up against intracellular pathogens. *Nat Rev Immunol* 2013; **13**: 551-565 [PMID: 23846113 DOI: 10.1038/nri3479]

6 **Schwabe RF**, Seki E, Brenner DA. Toll-like receptor signaling in the liver. *Gastroenterology* 2006; **130**: 1886-1900 [PMID: 16697751 DOI: 10.1053/j.gastro.2006.01.038]

7 **Mencin A**, Kluwe J, Schwabe RF. Toll-like receptors as targets in chronic liver diseases. *Gut* 2009; **58**: 704-720 [PMID: 19359436 DOI: 10.1136/gut.2008.156307]

8 **Sun L**, Dai JJ, Hu WF, Wang J. Expression of toll-like receptors in hepatic cirrhosis and hepatocellular carcinoma. *Genet Mol Res* 2016; **15**: [PMID: 27420991 DOI: 10.4238/gmr.15027419]

9 **El-Bendary M**, Neamatallah M, Elalfy H, Besheer T, Elkholi A, El-Diasty M, Elsareef M, Zahran M, El-Aarag B, Gomaa A, Elhammady D, El-Setouhy M, Hegazy A, Esmat G. The association of single nucleotide polymorphisms of Toll-like receptor 3, Toll-like receptor 7 and Toll-like receptor 8 genes with the susceptibility to HCV infection. *Br J Biomed Sci* 2018; **75**: 175-181 [PMID: 29947302 DOI: 10.1080/09674845.2018.1492186]

10 **Mehal WZ**, Azzaroli F, Crispe IN. Immunology of the healthy liver: old questions and new insights. *Gastroenterology* 2001; **120**: 250-260 [PMID: 11208734 DOI: 10.1053/gast.2001.20947]

11 **Seki E**, Brenner DA. Toll-like receptors and adaptor molecules in liver disease: update. *Hepatology* 2008; **48**: 322-335 [PMID: 18506843 DOI: 10.1002/hep.22306]

12 **Seki E**, De Minicis S, Osterreicher CH, Kluwe J, Osawa Y, Brenner DA, Schwabe RF. TLR4 enhances TGF-beta signaling and hepatic fibrosis. *Nat Med* 2007; **13**: 1324-1332 [PMID: 17952090 DOI: 10.1038/nm1663]

13 **Neamatallah M**, El-Bendary M, Elalfy H, Besheer T, El-Maksoud MA, Elhammady D, Abed S, Elegezy M, Kandeel L, Eldeib D, Mousa N, Abd El-Hafeez M, El-Gilany AH, Esmat G. Impact of Toll-like Receptors 2(TLR2) and TLR 4 Gene Variations on HCV Susceptibility, Response to Treatment and Development of Hepatocellular Carcinoma in Cirrhotic HCV Patients. *Immunol Invest* 2020; **49**: 462-476 [PMID: 31615295 DOI: 10.1080/08820139.2019.1673772]

14 **Abdel-Azziz MY**, Zalata KR, El-Bendary MM. Insulin resistance and liver fibrosis progression in patients with chronic hepatitis C virus infection. *Arab J Gastroenterol* 2010; **11**: 30-34 [DOI: 10.1016/j.ajg.2010.01.004]

15 **Besheer T**, El-Bendary M, Elalfy H, Abd El-Maksoud M, Salah M, Zalata K, Elkashef W, Elshahawy H, Raafat D, Elemshaty W, Almashad N, Zaghloul H, El-Gilany AH, Abdel Razek AA, Abd Elwahab M. Prediction of Fibrosis Progression Rate in Patients with Chronic Hepatitis C Genotype 4: Role of Cirrhosis Risk Score and Host Factors. *J Interferon Cytokine Res* 2017; **37**: 97-102 [PMID: 28068153 DOI: 10.1089/jir.2016.0111]

16 **Guo J**, Loke J, Zheng F, Hong F, Yea S, Fukata M, Tarocchi M, Abar OT, Huang H, Sninsky JJ, Friedman SL. Functional linkage of cirrhosis-predictive single nucleotide polymorphisms of Toll-like receptor 4 to hepatic stellate cell responses. *Hepatology* 2009; **49**: 960-968 [PMID: 19085953 DOI: 10.1002/hep.22697]

17 **Harada K**, Isse K, Sato Y, Ozaki S, Nakanuma Y. Endotoxin tolerance in human intrahepatic biliary epithelial cells is induced by upregulation of IRAK-M. *Liver Int* 2006; **26**: 935-942 [PMID: 16953833 DOI: 10.1111/j.1478-3231.2006.01325]

18 **Uhrig A**, Banafsche R, Kremer M, Hegenbarth S, Hamann A, Neurath M, Gerken G, Limmer A, Knolle PA. Development and functional consequences of LPS tolerance in sinusoidal endothelial cells of the liver. *J Leukoc Biol* 2005; **77**: 626-633 [PMID: 15860798 DOI: 10.1189/jlb.0604332]

19 **Shu SA**, Lian ZX, Chuang YH, Yang GX, Moritoki Y, Comstock SS, Zhong RQ, Ansari AA, Liu YJ, Gershwin ME. The role of CD11c(+) hepatic dendritic cells in the induction of innate immune responses. *Clin Exp Immunol* 2007; **149**: 335-343 [PMID: 17521321 DOI: 10.1111/j.1365-2249.2007.03419]

20 **Pedersen M**, Seetharam A. Infections after orthotopic liver transplantation. *J Clin Exp Hepatol* 2014; **4**: 347-360 [PMID: 25755581 DOI: 10.1016/j.jceh.2014.07.004]

21 **Fishman JA**, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. *Infect Dis Clin North Am* 2010; **24**: 273-283 [PMID: 20466270 DOI: 10.1016/j.idc.2010.01.005]

22 **Blair JE**, Kusne S. Bacterial, mycobacterial, and protozoal infections after liver transplantation--part I. *Liver Transpl* 2005; **11**: 1452-1459 [PMID: 16315310 DOI: 10.1002/lt.20624]

23 **Romero FA**, Razonable RR. Infections in liver transplant recipients. *World J Hepatol* 2011; **3**: 83-92 [PMID: 21603030 DOI: 10.4254/wjh.v3.i4.83]

24 **Edelson BT**, Unanue ER. MyD88-dependent but Toll-like receptor 2-independent innate immunity to Listeria: no role for either in macrophage listericidal activity. *J Immunol* 2002; **169**: 3869-3875 [PMID: 12244184 DOI: 10.4049/jimmunol.169.7.3869]

25 **Tötemeyer S**, Foster N, Kaiser P, Maskell DJ, Bryant CE. Toll-like receptor expression in C3H/HeN and C3H/HeJ mice during Salmonella enterica serovar Typhimurium infection. *Infect Immun* 2003; **71**: 6653-6657 [PMID: 14573691 DOI: 10.1128/iai.71.11.6653-6657.2003]

26 **Shimizu H**, Matsuguchi T, Fukuda Y, Nakano I, Hayakawa T, Takeuchi O, Akira S, Umemura M, Suda T, Yoshikai Y. Toll-like receptor 2 contributes to liver injury by Salmonella infection through Fas ligand expression on NKT cells in mice. *Gastroenterology* 2002; **123**: 1265-1277 [PMID: 12360487 DOI: 10.1053/gast.2002.36006]

27 **Sanchez-Campillo M**, Chicano A, Torío A, Martín-Orozco E, Gámiz P, Hernández-Caselles T, García-Peñarrubia P. Implication of CpG-ODN and reactive oxygen species in the inhibition of intracellular growth of Salmonella typhimurium in hepatocytes. *Microbes Infect* 2004; **6**: 813-820 [PMID: 15374003 DOI: 10.1016/j.micinf.2004.04.010]

28 **Adachi K**, Tsutsui H, Kashiwamura S, Seki E, Nakano H, Takeuchi O, Takeda K, Okumura K, Van Kaer L, Okamura H, Akira S, Nakanishi K. Plasmodium berghei infection in mice induces liver injury by an IL-12- and toll-like receptor/myeloid differentiation factor 88-dependent mechanism. *J Immunol* 2001; **167**: 5928-5934 [PMID: 11698470 DOI: 10.4049/jimmunol.167.10.5928]

29 **Leoratti FM**, Farias L, Alves FP, Suarez-Mútis MC, Coura JR, Kalil J, Camargo EP, Moraes SL, Ramasawmy R. Variants in the toll-like receptor signaling pathway and clinical outcomes of malaria. *J Infect Dis* 2008; **198**: 772-780 [PMID: 18662133 DOI: 10.1086/590440]

30 **Ogus AC**, Yoldas B, Ozdemir T, Uguz A, Olcen S, Keser I, Coskun M, Cilli A, Yegin O. The Arg753GLn polymorphism of the human toll-like receptor 2 gene in tuberculosis disease. *Eur Respir J* 2004; **23**: 219-223 [PMID: 14979495 DOI: 10.1183/09031936.03.00061703]

31 **Ben-Ali M**, Barbouche MR, Bousnina S, Chabbou A, Dellagi K. Toll-like receptor 2 Arg677Trp polymorphism is associated with susceptibility to tuberculosis in Tunisian patients. *Clin Diagn Lab Immunol* 2004; **11**: 625-626 [PMID: 15138193 DOI: 10.1128/CDLI.11.3.625-626.2004]

32 **Naderi M**, Hashemi M, Hazire-Yazdi L, Taheri M, Moazeni-Roodi A, Eskandari-Nasab E, Bahari G. Association between toll-like receptor2 Arg677Trp and 597T/C gene polymorphisms and pulmonary tuberculosis in Zahedan, Southeast Iran. *Braz J Infect Dis* 2013; **17**: 516-520 [PMID: 23830055 DOI: 10.1016/j.bjid.2012.12.009]

33 **Yoshida O**, Kimura S, Jackson EK, Robson SC, Geller DA, Murase N, Thomson AW. CD39 expression by hepatic myeloid dendritic cells attenuates inflammation in liver transplant ischemia-reperfusion injury in mice. *Hepatology* 2013; **58**: 2163-2175 [PMID: 23813862 DOI: 10.1002/hep.26593]

34 **Eid AJ**, Brown RA, Paya CV, Razonable RR. Association between toll-like receptor polymorphisms and the outcome of liver transplantation for chronic hepatitis C virus. *Transplantation* 2007; **84**: 511-516 [PMID: 17713436 DOI: 10.1097/01.tp.0000276960.35313.bf]

35 **Brown RA**, Gralewski JH, Eid AJ, Knoll BM, Finberg RW, Razonable RR. R753Q single-nucleotide polymorphism impairs toll-like receptor 2 recognition of hepatitis C virus core and nonstructural 3 proteins. *Transplantation* 2010; **89**: 811-815 [PMID: 20090572 DOI: 10.1097/TP.0b013e3181cbac18]

36 **Howell J**, Sawhney R, Skinner N, Gow P, Angus P, Ratnam D, Visvanathan K. Toll-like receptor 3 and 7/8 function is impaired in hepatitis C rapid fibrosis progression post-liver transplantation. *Am J Transplant* 2013; **13**: 943-953 [PMID: 23425350 DOI: 10.1111/ajt.12165]

37 **Rehermann B**. Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence. *J Clin Invest* 2009; **119**: 1745-1754 [PMID: 19587449 DOI: 10.1172/JCI39133]

38 **Hart OM**, Athie-Morales V, O'Connor GM, Gardiner CM. TLR7/8-mediated activation of human NK cells results in accessory cell-dependent IFN-gamma production. *J Immunol* 2005; **175**: 1636-1642 [PMID: 16034103 DOI: 10.4049/jimmunol.175.3.1636]

39 **El-Bendary M**, Neamatallah M, Elalfy H, Besheer T, El-Setouhy M, Youssef MM, Zein M, Elhammady D, Hegazy A, Esmat G. Association of genetic polymorphisms of chemokines and their receptors with clearance or persistence of hepatitis C virus infection. *Br J Biomed Sci* 2019; **76**: 11-16 [PMID: 30175654 DOI: 10.1080/09674845.2018.1518299]

40 **Guo H**, Qiao Z, Zhu L, Wang H, Su L, Lu Y, Cui Y, Jiang B, Zhu Q, Xu L. Th1/Th2 cytokine profiles and their relationship to clinical features in patients following nonmyeloablative allogeneic stem cell transplantation. *Am J Hematol* 2004; **75**: 78-83 [PMID: 14755372 DOI: 10.1002/ajh.10443]

41 **El-Bendary M**, Neamatallah M, Esmat G, Kamel E, Elalfy H, Besheer T, Eldeib D, Eladl AH, El-Setouhy M, El-Gilany AH, El-Waseef A. Associations of human leucocyte antigen class II-DQB1 alleles with hepatitis C virus infection in Egyptian population: a multicentre family-based study. *J Viral Hepat* 2016; **23**: 961-970 [PMID: 27599887 DOI: 10.1111/jvh.12573]

42 **El-Bendary M**, Neamatallah M, Elalfy H, Besheer T, Kamel E, Mousa H, Eladl AH, El-Setouhy M, El-Gilany AH, El-Waseef A, Esmat G. HLA Class II-DRB1 Alleles with Hepatitis C Virus Infection Outcome in Egypt: A Multicentre Family-based Study. *Ann Hepatol* 2019; **18**: 68-77 [PMID: 31113612 DOI: 10.5604/01.3001.0012.7864]

43 **Papatheodoridis GV**, Barton SG, Andrew D, Clewley G, Davies S, Dhillon AP, Dusheiko G, Davidson B, Rolles K, Burroughs AK. Longitudinal variation in hepatitis C virus (HCV) viraemia and early course of HCV infection after liver transplantation for HCV cirrhosis: the role of different immunosuppressive regimens. *Gut* 1999; **45**: 427-434 [PMID: 10446114 DOI: 10.1136/gut.45.3.427]

44 **Attallah AM**, Omran MM, Farid K, El-Bendary M, Emran TM, Albannan MS, El-Dosoky I. Development of a novel score for liver fibrosis staging and comparison with eight simple laboratory scores in large numbers of HCV-monoinfected patients. *Clin Chim Acta* 2012; **413**: 1725-1730 [PMID: 22759976 DOI: 10.1016/j.cca.2012.06.031]

45 **Bataller R**, Paik YH, Lindquist JN, Lemasters JJ, Brenner DA. Hepatitis C virus core and nonstructural proteins induce fibrogenic effects in hepatic stellate cells. *Gastroenterology* 2004; **126**: 529-540 [PMID: 14762790 DOI: 10.1053/j.gastro.2003.11.018]

46 **El-Bendary M**, Nour D, Arafa M, Neamatallah M. Methylation of tumour suppressor genes *RUNX3, RASSF1A* and *E-Cadherin* in HCV-related liver cirrhosis and hepatocellular carcinoma. *Br J Biomed Sci* 2020; **77**: 35-40 [PMID: 31790342 DOI: 10.1080/09674845.2019.1694123]

47 **El-Bendary M**, Neamatallah M, Elalfy H, Besheer T, El-Setouhy M, Kasim N, Abou El-Khier NT, Kamel E, Eladl AH, El-Waseef A, Abdel-Aziz AF, Esmat G. Association of interferon gamma gene polymorphism and susceptibility to hepatitis C virus infection in Egyptian patients: A multicenter, family-based study. *JGH Open* 2017; **1**: 140-147 [PMID: 30483551 DOI: 10.1002/jgh3.12024]

48 **Van Amersfoort ES**, Van Berkel TJ, Kuiper J. Receptors, mediators, and mechanisms involved in bacterial sepsis and septic shock. *Clin Microbiol Rev* 2003; **16**: 379-414 [PMID: 12857774 DOI: 10.1128/cmr.16.3.379-414.2003]

49 **Lorenz E**, Mira JP, Cornish KL, Arbour NC, Schwartz DA. A novel polymorphism in the toll-like receptor 2 gene and its potential association with staphylococcal infection. *Infect Immun* 2000; **68**: 6398-6401 [PMID: 11035751 DOI: 10.1128/iai.68.11.6398-6401.2000]

50 **Takeuchi O**, Hoshino K, Akira S. Cutting edge: TLR2-deficient and MyD88-deficient mice are highly susceptible to Staphylococcus aureus infection. *J Immunol* 2000; **165**: 5392-5396 [PMID: 11067888 DOI: 10.4049/jimmunol.165.10.5392]

51 **Nischalke HD**, Berger C, Aldenhoff K, Thyssen L, Gentemann M, Grünhage F, Lammert F, Nattermann J, Sauerbruch T, Spengler U, Appenrodt B. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. *J Hepatol* 2011; **55**: 1010-1016 [PMID: 21356257 DOI: 10.1016/j.jhep.2011.02.022]

52 **Carvalho A**, Cunha C, Carotti A, Aloisi T, Guarrera O, Di Ianni M, Falzetti F, Bistoni F, Aversa F, Pitzurra L, Rodrigues F, Romani L. Polymorphisms in Toll-like receptor genes and susceptibility to infections in allogeneic stem cell transplantation. *Exp Hematol* 2009; **37**: 1022-1029 [PMID: 19539691 DOI: 10.1016/j.exphem.2009.06.004]

53 **Yoon HJ**, Choi JY, Kim CO, Park YS, Kim MS, Kim YK, Shin SY, Kim JM, Song YG. Lack of Toll-like receptor 4 and 2 polymorphisms in Korean patients with bacteremia. *J Korean Med Sci* 2006; **21**: 979-982 [PMID: 17179672 DOI: 10.3346/jkms.2006.21.6.979]

54 **Horcajada JP**, Lozano F, Muñoz A, Suarez B, Fariñas-Alvarez C, Almela M, Smithson A, Martínez E, Mallolas J, Mensa J, Gatell JM. Polymorphic receptors of the innate immune system (MBL/MASP-2 and TLR2/4) and susceptibility to pneumococcal bacteremia in HIV-infected patients: a case-control study. *Curr HIV Res* 2009; **7**: 218-223 [PMID: 19275590 DOI: 10.2174/157016209787581382]

55 **El-Helou O**, Berbari EF, Brown RA, Gralewski JH, Osmon DR, Razonable RR. Functional assessment of Toll-like receptor 2 and its relevance in patients with Staphylococcus aureus infection of joint prosthesis. *Hum Immunol* 2011; **72**: 47-53 [PMID: 20937339 DOI: 10.1016/j.humimm.2010.10.001]

56 **Moore CE**, Segal S, Berendt AR, Hill AV, Day NP. Lack of association between Toll-like receptor 2 polymorphisms and susceptibility to severe disease caused by Staphylococcus aureus. *Clin Diagn Lab Immunol* 2004; **11**: 1194-1197 [PMID: 15539529 DOI: 10.1128/CDLI.11.6.1194-1197.2004]

57 **Lee SO**, Brown RA, Kang SH, Abdel-Massih RC, Razonable RR. Toll-like receptor 2 polymorphism and Gram-positive bacterial infections after liver transplantation. *Liver Transpl* 2011; **17**: 1081-1088 [PMID: 21563293 DOI: 10.1002/lt.22327]

58 **Kapetanovic R**, Nahori MA, Balloy V, Fitting C, Philpott DJ, Cavaillon JM, Adib-Conquy M. Contribution of phagocytosis and intracellular sensing for cytokine production by Staphylococcus aureus-activated macrophages. *Infect Immun* 2007; **75**: 830-837 [PMID: 17118979 DOI: 10.1128/IAI.01199-06]

59 **Brown RA**, Gralewski JH, Razonable RR. The R753Q polymorphism abrogates toll-like receptor 2 signaling in response to human cytomegalovirus. *Clin Infect Dis* 2009; **49**: e96-e99 [PMID: 19814623 DOI: 10.1086/644501]

60 **Kijpittayarit S**, Eid AJ, Brown RA, Paya CV, Razonable RR. Relationship between Toll-like receptor 2 polymorphism and cytomegalovirus disease after liver transplantation. *Clin Infect Dis* 2007; **44**: 1315-1320 [PMID: 17443468 DOI: 10.1086/514339]

61 **Cervera C**, Lozano F, Saval N, Gimferrer I, Ibañez A, Suárez B, Linares L, Cofán F, Ricart MJ, Esforzado N, Marcos MA, Pumarola T, Oppenheimer F, Campistol JM, Moreno A. The influence of innate immunity gene receptors polymorphisms in renal transplant infections. *Transplantation* 2007; **83**: 1493-1500 [PMID: 17565323 DOI: 10.1097/01.tp.0000264999.71318.2b]

62 **Kang SH**, Abdel-Massih RC, Brown RA, Dierkhising RA, Kremers WK, Razonable RR. Homozygosity for the toll-like receptor 2 R753Q single-nucleotide polymorphism is a risk factor for cytomegalovirus disease after liver transplantation. *J Infect Dis* 2012; **205**: 639-646 [PMID: 22219347 DOI: 10.1093/infdis/jir819]

63 **Razonable RR**, Rivero A, Brown RA, Hart GD, Espy MJ, van Cruijsen H, Wilson J, Groettum C, Kremers W, Smith TF, Paya CV. Detection of simultaneous beta-herpesvirus infections in clinical syndromes due to defined cytomegalovirus infection. *Clin Transplant* 2003; **17**: 114-120 [PMID: 12709076 DOI: 10.1034/j.1399-0012.2003.02104]

64 **von Aulock S**, Schröder NW, Traub S, Gueinzius K, Lorenz E, Hartung T, Schumann RR, Hermann C. Heterozygous toll-like receptor 2 polymorphism does not affect lipoteichoic acid-induced chemokine and inflammatory responses. *Infect Immun* 2004; **72**: 1828-1831 [PMID: 14977997 DOI: 10.1128/iai.72.3.1828-1831.2004]

65 **Howell J**, Sawhney R, Testro A, Skinner N, Gow P, Angus P, Ratnam D, Visvanathan K. Cyclosporine and tacrolimus have inhibitory effects on toll-like receptor signaling after liver transplantation. *Liver Transpl* 2013; **19**: 1099-1107 [PMID: 23894100 DOI: 10.1002/lt.23712]

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**Table 1 Types of infections after orthotopic liver transplantation**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **First month post transplant** | **1-6 mo post transplant** | **> 6 mo post transplant** |
| Bacterial infections | *Staph aurus*, *Strptoccoi enterococci*, *Salmonella pseudomonas,* MRSA, VRE, *Anerobes, Clostridium difficile* | Multidrug resistant bacteria*Listeria spp* | Multidrug resistant bacteria |
| Viral | Human herpes virus 6 | CMV, HCV, EBV, VZV | HHV8, HEV, EBV, Parvovirus B19 |
| Fungal | *Candida*, *Asprgillus* | MucormucosisPneumocystitis jerovicii (PJP) | *Nocardia*, *Rhodococcus*, *Legionella**Cryptococcus*Blastomycosis, histoplasmosis |
| Mycobacterial |  | TB | TBNon tuberculous *Mycobacteria* (Mycobacterial avium complex, Myco. triplex) |
| Protozoal |  |  | Strongyloiodosis, toxoplasmosisEchinococcosisChagas disease |
| Types of infections | Wound infections, Abdominal infections, catheter related infections, pneumonia, UTI, abscess, cholangitis, peritonitis | Community acquired infectionsInvasive fungal infection | Community acquired pathogens,Opportunistic infections |

CMV: Cytomegalovirus; EBV: Epstein–Barr virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HEV: Hepatitis E virus; HHV: Human herpes virus; HIV: Human immune deficiency virus; HSV: Herpes simplex virus; MRSA: Methicillin-resistant *staphylococcus aureus*; VRE: Vancomycin-resistant *enterococcus*; VZV: Varicella zoster virus.

**Table 2 Association of Toll-like receptors alleles with infections post liver transplantation and their clinical significance**

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of Infection** | **Type of organism** | **TLR alleles**  |  **Clinical significance** |
| Bacterial infections | Staph aurus | TLR2 (Arg753Gln) | Inconclusive association with septic shock |
| TLR2 (R753Q) | May correlated only in cases of infections with large dose of pathogen |
| *Listeria monocytogenes* | TLR2/MyD88-dependent pathway | participate in cytokine cascadeNo role in clearance |
| *Salmonella typhimurium* | TLR4 | Granuloma formation |
| *Salmonella choleraesuis* | TLR2, TLR4 | Have role in pathogenesis No role in clearance |
| TLR9 | Has role in clearance |
| Protozoal | *Plasmodium falciparum* | TLR1, TLR6 | Mild form of malaria |
| TLR9 (1486 C/T) | severe form of malaria |
| Mycobacterium | Mycobaterial tuberculosis | TLR2 (R753Q) | increased susceptibility to T.B in Turkish |
| TLR2 (Arg677Trp) | increased susceptibility to T.B in Tunisian but not to Iranian and Indian populations. |
| Viral | Hepatitis C virus (HCV) | TLR2 (Arg753Gln) | Recurrence of HCV post transplant (PT) with higher graft cirrhosis and graft failure |
| TLR2 (R753Q) | higher rate of *graft* failure |
| TLR3 | increased liver fibrosis |
| TLR4 (Asp299Gly) and (Thr399Ile) | No associated PT complications  |
| TLR7/8-mediated pathway | Aggressive PT recurrence of HCV  |
| Cytomegalovirus (CMV) | TLR2 (R753Q)TLR2 (Arg753Gln) | Increased incidence of CMV PT |

TLR: Toll-like receptor.