Reply to the reviewers' comments

Reviewer #1:

Comment: The article deals with a long and detailed description of how the immune system responds following post-transplant aggression of infectious agents. This description sounds more like a chapter of a book or a summary of knowledge in literature than as a review. In fact, the article does not produce new knowledge nor does it express merit assessments on the subject matter. Nothing is said about the methodology used to search for articles: the search criteria are not indicated (keywords, search engines and repositories or databases, type and value of scientific journals, etc.), nor the criteria for choosing and exclusion of the articles that emerged from this research. In this way the description of the relationship between TLRs and the infecting agent is detailed but arbitrary.

Reply

The authors thank the reviewer for this valuable comment. The major limitation of this article was the design, being a narrative review article not a systematic review or meta-analysis, simply providing updates regarding the association between liver transplantation and TLRs, while focusing on the interrelationship between SNPs of TLRs and infections that may occur following liver transplantations. To our knowledge, this is the first review highlighting this topic, referencing all previously published studies regarding this point. It is common knowledge that narrative review articles are more susceptible to selection bias which may possibly affect its conclusion, while systematic review articles adhere to strict methodology and are, therefore, potentially more scientifically reliable.

Comment

In this way the description of the relationship between TLRs and the infecting agent is detailed but arbitrary. The article also contains numerous repetitions of concepts about the genesis of infections and the role of TRL in their determinism. The underlining of the role of the SNPs considered also follows the same fate. In this regard, a table with an indication of the individual SNP, its effect (positive or negative) and its real or prospective translation in the clinical setting would have been useful.

Reply

Thank you for this important comment, and the following modifications have been made

- **Table (2) describing the association of Toll-like receptor (TLR) alleles with post-liver transplantation infections and their clinical significance has been constructed and cited in the text.**
- **Some repetitive phrases have been deleted.**

Comment:

The conclusion does not offer considerations on what emerged from the treatment of the topic, but is limited to an uncritical ratification of what is present in the literature without indicating any research lines or possible future clinical effects and to the statement about the need for further studies but without indicating objectives or hypotheses of work on it.

Reply

Our hypothesis is that Toll like receptor 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- wide gene association study GWAS using next-generation sequencing techniques for the whole genome to identify the entire underlying genetic variation and its disease relevance. Applying NGS to WGAS 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.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.

Reviewer #2:

Comment

1. The major limitation of this article is the study design, 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. In spite of this limitation, the document seems well balanced and carefully prepared. 2. A paragraph in the discussion acknowledging the study design limitation—discussed above—must be included to alert readers.

Reply

Thank you for this valuable insight. Limitations of the study have already been added at the end of the manuscript as advised.

Comment:

The manuscript would benefit from careful proofreading because there are few typos. For example, in the hepatic stellate cells section the phrase `In [6, 9, 12, 13], while participating in cell defense… upon the exposure to LPS…´ seems unfinished. Other minor typos occur throughout the manuscript, such as the reference ´Blair and Kusne, 2005´ differing from the reference format employed.

Reply

- This has been corrected as follows:
    - 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]*
- **All references have been revised according to the style of the journal** and all the PubMed numbers and DOI citation numbers to the reference list have been provided

Scientific editor

Comment Language editing certificate was not properly provided. Please upload language certificate of language editing company

Reply

Dr. Dina Elhammady, one of the authors of the article, is a native English speaker and a copy of her United States passport was uploaded with the original submission.

Comment:

(1)PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references

Reply:

All the PubMed numbers and DOI citation numbers to the reference list have been provided

Comment

The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Reply:

The authors do not need to provide an “Article Highlights” section in a review article.