Review of: "Role of sphingosine kinase and sphingosine-1-phosphate receptor in the liver pathology of mice infected with Plasmodium berghei ANKA"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

This is an in vivo study in mice that investigated the effect of malaria infection on the expression of sphingosine kinases (SphKs) and S1P receptors in the liver of mice. For the first time, the investigators observed increased expression of SphK1 mRNA and decreased expression levels of S1PR1, S1PR2 and S1PR3 in the liver of mice infected with Plasmodium berghei (PbA). This report found that S1P-related enzymes and receptors have important effects on liver injury during malaria infection, and targeting the S1P signaling pathway may become an important direction for the treatment of malaria.

There are still some areas of concern, including the following:

1. There are high rates of mortality and morbidity associated with malaria infection throughout the world (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6683112/). However, in this study, the authors did not state the mortality rate of PbA-infected mice.
2. S1P is an important mediator for the role of SphKs and S1P receptors (https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.13348), and this study did not assay S1P levels in blood and liver tissues of control mice and PbA-infected mice.
3. In contrast to the immunohistochemical staining results, the real-time PCR results showed no significant difference in the mRNA levels of SphK2, S1PR1, and S1PR2 between control mice and PbA-infected mice, and the authors did not seem to explain the reason for this phenomenon.
4. It is known that S1P mediates different biological effects through S1PR1, S1PR2 and S1PR3, respectively. This study did not investigate the effect of changes in the respective levels of S1PR1, S1PR2 and S1PR3 on liver damage during malaria infection.
5. It is interesting and curious that intervention in animal experiments is relatively easy to implement, why not use FTY720 treatment to observe whether the impact on Plasmodium infection?
6. Circulating S1P is mainly derived from red blood cells and endothelial cells. Does Plasmodium-infected erythrocytes affect S1P production and plasma levels?
7. Among the five S1P receptors, S1P4 and S1P5 are more related to infection and immune regulation, so why not detect the changes in the expression levels of S1P4 and S1P5?
8. In this paper, the protein detection of S1PR1 / 2 / 3 and SphK1 / 2 was conducted by immunohistochemistry, so how to determine the expression levels of hepatocytes, endothelial cells, and Kupffer cells, respectively?
9. Page 8 inverted lines 7 and page 9 line 3, the authors state that S1P is a protein and, in fact, sphingosine-1-phosphate

is a small molecule signal lipid molecule, not a protein.

10. Since this paper does not study the role of S1P in malaria and its mechanism, the illustration 4 (Fig 4) has no practical interpretation of this paper, but a simple literature review, which is completely unnecessary.