

## Peer Review File

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### **Reviewer A**

A new finding in this paper is the involvement of GAS5/miR-222 in liver fibrosis in BA.

**Reply:** We greatly appreciate the reviewer's positive feedback.

Comment 1: They have shown that elevated GAS5 decreases IGF1/AKT signaling, but it would be shown those things in BA liver tissue and HSCs.

**Reply:** We have added the expressions of IGF1 and AKT1 in BA liver tissues and HSCs in Figure 5A-B, and compared the expressions of IGF1 and AKT1 in BA patients with different stages of fibrosis.

**Changes in the text:** Line 233-235 (Revised Main Document)

Comment 2: It has been shown previously that GAS5 binds directly to miR-222, and it is nice to show the same here.

**Reply:** Figure 4D illustrates the interaction of GAS5 and miR-222 by a luciferase gene report assay.

**Changes in the text:** Line 220-221 (Revised Main Document)

Comment 3: If liver fibrosis is associated with GAS5/miR-222 expression, it should be shown that the degree of liver fibrosis is also associated with GAS5/miR-222 expression in BA liver specimens.

**Reply:** We have added the expressions of GAS5 and miR-222 in BA patients with

different stages of fibrosis in Figure 1D and Figure 4C.

**Changes in the text:** Line 205-206 for Figure 1D, and line 218-219 (Revised Main Document)

With respect to the BA model caused by RRV infection, it would have been worthwhile to examine the expression level of GAS5/miR-222 in different liver fibrosis as well as in clinical specimens.

**Reply:** We truly appreciate the reviewer's valuable suggestions. We have added the expressions of GAS5 and miR-222 in experimental BA model (Figure 7A), and compared their levels in BA mice with different stages of fibrosis (Figure 7B). Furthermore, we also evaluated the change of liver fibrosis after GAS administration by Masson staining (Figure 7D).

**Changes in the text:** Line 248-252 (Revised Main Document)

## **Reviewer B**

1. Please introduce the abbreviation 'siRNA' in line 62 in its first appearance, and use this abbreviation in line 110 without defining it again.

**Reply:** We have revised it according to the editor's suggestions.

**Changes in the text:** Line 63, line 111 (Revised Main Document)

2. It suggests indicating where the patients and healthy control subjects are from (which hospital).

**Reply:** We have added this information in the manuscript.

**Changes in the text:** Line 92-93 (Revised Main Document)

3. Line 150, please introduce the abbreviation 'PBS' in its first use in the text, and check the whole text to ensure all abbreviations in their first use are properly defined.

**Reply:** We have added the full name of "PBS" in the manuscript.

**Changes in the text:** Line 151 (Revised Main Document)

4. For research involving human experiments, the article must include a statement that ethical approval was obtained (or a statement that it was not required and why), including the name of the ethics committee(s) or institutional review board(s), the number/ID of the approval(s), and a statement that the participants (or their parent or legal guardian in the case of children under 18) gave informed consent before taking part (or a statement that it was not required and why).

**Reply:** We have added the ethical statement of human studies in the manuscript.

**Changes in the text:** Line 96-99 (the "Method" section of Main Text) and Line 318-325 (the "Ethical Statement" section of Footnote)

5. For any experiments involving animals, the authors must indicate the nature of the ethical review permissions, relevant licenses (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals by which the research was conducted.

**Reply:** We have added the ethical statement of animal studies in the manuscript.

**Changes in the text:** Line 183-186 (the “Method” section of Main Text) and Line 318-325 (the “Ethical Statement” section of Footnote)

6. Figures & Tables

1) Figure 6A, 6B, 6C and main text, should it be ‘AKT1’ or ‘AKT’?

**Reply:** AKT1 is the gene symbol of AKT, we have added this gene annotation (AKT1) in the descriptions of AKT siRNAs and Figure 6A-C.

**Changes in the text:** Line 111, 239, and 437 (Revised Main Document)

2) Figures, cell map should describe magnification in the corresponding Figure Legends.

**Reply:** we have added the scale bars in Figure 7C and described the magnification times in the figure legend 7.

**Changes in the text:** Line 449-451 (Revised Main Document)

3) Any abbreviations used in figures and tables or their description should be defined in a footnote beneath each corresponding table/figure. Even if they were explained in the main text, full terms must be presented again in the corresponding figures and tables, so that figures and tables can be read on their own.

**Reply:** We have added the full name of “qPCR” in all figure legends.

**Changes in the text:** Line 408-409, 415, 424-425, 429-430 (Revised Main Document)

10. References 15 and 33 are duplicate, please adjust it.

**Reply:** We have deleted the duplicated reference.

**Changes in the text:** Line 353-355 (Revised Main Document)