

Review Form 1.7

Journal Name:	Annual Research & Review in Biology
Manuscript Number:	Ms_ARRB_98385
Title of the Manuscript:	Lactic acid inhibits the cytotoxicity of NK-92 cells via activating the lactate receptor GPR81
Type of the Article	Original Research Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<https://www.journalarrb.com/index.php/ARRB/editorial-policy>)

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<p>Compulsory REVISION comments</p> <p>1. Is the manuscript important for scientific community? (Please write few sentences on this manuscript)</p> <p>2. Is the title of the article suitable? (If not please suggest an alternative title)</p> <p>3. Is the abstract of the article comprehensive?</p> <p>4. Are subsections and structure of the manuscript appropriate?</p> <p>5. Do you think the manuscript is scientifically correct?</p> <p>6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form. (Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)</p>	<p>The authors evaluated how lactic acid impacts NK-92 cell viability and cytotoxicity functions. Using a selective agonist of GRP81 (3,5-DHBA) and 3-hydroxybutyric acid (3-OBA). The pharmacological approaches suggest that lactic acid inhibits NK-92 cell viability and cytotoxic functions by targeting the lactate receptor GPR81.</p> <p>General: Overall, the research question is addressed superficially, and the pharmacological approach is insufficient to provide reliable conclusions. A complementary approach would strengthen (validate or invalidate) conclusions. The use of 3-OBA as a selective antagonist of GRP81 is misleading as there is still a lack of proof that 3-OBA is a <i>bona fide</i> GRP81 antagonist.</p> <p>Questions / suggestions:</p> <p>How 3,5-DHBA affects cell NK-92 cell viability and cytotoxic functions? Does 3-OBA reverse those effects? To strengthen the conclusions, authors should silence GPR81 in NK-92.</p> <p>There is room to improve the discussion and highlight the weaknesses of this study (Please see general comments).</p>	
<p>Minor REVISION comments</p> <p>1. Is language/English quality of the article suitable for scholarly communications?</p>	<ul style="list-style-type: none"> - What are the sources of 3,5-DHBA and 3-OBA? - Paragraph 3.4, last sentence: It is likely a mistake. The data do not suggest that lactic acid induces cytotoxic activity in NK-92. Lactic acid reduces cell NK-92 viability and cytotoxic functions. - Discussion, fourth paragraph, second sentence: against (not against). - Discussion, last paragraph: To clarify the text, please define MCT1 and MCT2 as monocarboxylate transporters. 	
<p>Optional/General comments</p>	<p>There are a few points that the authors should address or discuss. The most important is the use of 3-OBA (3-hydroxy-butyrate acid) as a selective antagonist of GPR81. I refer the authors to the following paper (<i>doi: 10.3389/fphar.2021.803907</i>) claiming that 3-OBA is not proven a GRP81 antagonist but rather a GPR109A (HCAR2) agonist. Is GPR109A expressed by NK-92 cells?</p> <p>The weaknesses of the approach are not discussed. To validate the conclusions, the authors should silence GRP81 in NK-92 cells should be attempted.</p> <p>The silencing of GRP81 will help understand if the effects of lactic acid are through GRP81 signaling or regulation of cellular energy metabolism. In fact, 3-hydroxybutyrate is known to inhibit lactate and glucose utilization.</p>	

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<p>Are there ethical issues in this manuscript?</p>	<p><i>(If yes, Kindly please write down the ethical issues here in details)</i></p>	

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