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PONE-D-23-00791
"Reassessing the adrenomedullin scavenging function of ACKR3 in lymphatic endothelial cells"
Original Submission

[redacted] **(Reviewer 2)**

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5. Review Comments to the Author Please use the space provided to explain your answers to the questions above. You may also include additional comments for the author, including concerns about dual publication, research ethics, or publication ethics. (Please upload your review as an attachment if it exceeds 20,000 characters)	In the study by Halin et Al., "Reassessing the adrenomedullin scavenging function of ACKR3 in lymphatic endothelial cells" the role of ACKR3 as scavenger of the vascular peptide hormone adrenomedullin (AM) was clarified. In this work, in vitro experiments were performed to evaluate the uptake of AM in primary human Lymphatic Endothelial Cells (LECs) and in ACKR3-overexpressing Human Epithelial Kidney (HEK) cells. The aim of this work was to verify a competition between the normal ACKR3-ligand CXCL11/12 and AM, to evaluate if this receptor can influence/reduce the AM proliferative effects on LECs. The Authors conclude that the AM does not compete with CXCL11/12 for ACKR3 binding, but it binds their canonical receptor (CALCRL and PAMP2/3. In my opinion this finding may have a relevance in this field, but major revisions are required. The background should be improved, experimental procedures should be better described and rearranged. For example, first cell culture (including HEK cells), second the treatments and silencing on LECs, then the plasmid construction and transfection, finally the assay. A few questions: Why three type of LECs were used? Why the coating was different between adLECs and nd- and jd-LECs? The abbreviations should be uniformed and the same name should be used for the same protein, for example: ACKR3 was used throughout manuscript, but to indicate the antibody against this protein the CXCR/RDC-1 APC was used. The terms CXCL11/12-AF647 should be clarified as extended terms of CXCL; AF647 should be described as alexa flour 647; Atto 565 should be explained. In the introduction, CCX771 should be described as an antagonist of ACKR3. The description of the plasmids in the section "construction of expression plasmids for HEK293 cell transfection" should match with the description in the section "HEK293 cell transfection…" In Figure1D, the error bars should be indicated in the graphic, which could be expanded to avoid the overlap between 37 °C ° and 37 °C + CCX771. Please check and harmonize all the figures. For example, in fig 2D CXCL11/12 is reported as CXCl11/12; cell types are indicated in fig 3A, but not in fig 2.
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