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Structure of the manuscript

- Title
- Abstract
- Introduction
- Materials and Methods
- Results
- Discussion
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Surfactant Dysfunction and Lung Inflammation in the Female Mouse Model of Lymphangioleiomyomatosis (LAM)

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Aquaporin 11 insufficiency modulates kidney susceptibility to oxidative stress

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Atochina-Vasserman EN, Biktasova A, Abramova E, Cheng DS, Polosukhin VV, Tanjore H, Takahashi S, Sonoda H, Foye L, Venkov C, Ryzhov SV, Novitskiy S, Shlonimskaya N, Ikeda M, Blackwell TS, Lawson WE, Gow AJ, Harris RC, Dikov MM, Tchekneva EE. Aquaporin 11 insufficiency modulates kidney susceptibility to oxidative stress. *Am J Physiol Renal Physiol* 304: F1295–F1307, 2013. First published March 13, 2013; doi:10.1152/ajprenal.00344.2012.—Aquaporin 11 (AQP11) is a newly described member of the protein family of transport channels. AQP11 associates with the endoplasmic reticulum (ER) and is highly expressed in proximal tubular epithelial cells in the kidney. Previously, we identified and characterized a recessive mutation of the highly conserved Cys227 to Ser227 in mouse AQP11 that caused proximal tubule (PT) injury and kidney failure in mutant mice. The current study revealed induction of ER stress, unfolded protein response, and apoptosis as molecular mechanisms of this PT injury. Cys227Ser mutation interfered with maintenance of AQP11 oligomeric structure. AQP11 is abundantly expressed in the S1 PT segment, a site of major renal glucose flux, and *Aqp11* mutant mice developed PT-specific mitochondrial injury. Glucose increased AQP11 protein expression in wild-type kidney and upregulation of AQP11 expression by glucose in vitro was prevented by phlorizin, an inhibitor of sodium-dependent glucose transport across PT. Total AQP11 levels in heterozygotes were higher than in wild-type mice but were not further increased in response to glucose. In *Aqp11* insufficient PT cells, glucose potentiated increases in reactive oxygen species (ROS) production. ROS production was also elevated in *Aqp11* mutation carriers. Phenotypically normal mice heterozygous for the *Aqp11* mutation repeatedly treated with glucose showed increased blood urea nitrogen levels that were prevented by the antioxidant sulforaphane or by phlorizin. Our results indicate an important role for AQP11 to prevent glucose-induced oxidative stress in proximal tubules.

proximal tubules; acute kidney injury; protein oligomerization.

CONVENTIONAL AQUAPORINS (AQPs) are oligomeric transport protein characterized by the presence of two highly conserved Asn-Pro-Ala (NPA) signature motifs (18, 19). AQP11 is a member of a new aquaporin subgroup AQP11/AQP12, characterized by a poorly conserved NH_2-terminal signature motif (17). Previous publications have indicated that AQP11 is a membrane-bound protein of the endoplasmic reticulum (ER), suggesting an important role for AQP11 in ER homeostasis and a role in water translocation to subcellular membranous formations to maintain cytosolic and/or vesicle osmoregulation (10, 17, 20, 38). In the kidney, AQP11 is abundantly expressed in proximal tubule (PT; Refs. 17, 28, 30). We recently identified and characterized a sudden juvenile death syndrome (*sjds*) mutation of Cys227 to Ser227 in $Aqp11^{sjds/sjds}$ mice. Using genetic complementation analysis, we showed that loss-of-function Cys227Ser mutation caused severe PT damage and kidney injury in $Aqp11^{sjds/sjds}$ mice that die due to kidney failure by the age of 20 days old (28, 29). Cysteine is an important constituent of protein oligomeric formation, and it is plausible that the oligomeric state of cysteine-rich AQP11 determines its function. At present, it remains unclear whether Cys227 is essential in the formation of AQP11 oligomers.

$Aqp11^{sjds/sjds}$ mutants and *Aqp11* null mice develop a similar lethal phenotype with vacuole formation in proximal tubular cells (PTC; Refs. 28, 30). The mechanisms of tubular injury in *Aqp11*-deficient mice remains unclear (10, 17, 20, 38). Recent data indicate that ER disturbance and stress lead to kidney tubular atrophy and injury (11). Our studies provide evidence that the Cys227Ser deactivating mutation causes the alteration of protein oligomerization and induces kidney injury via induction of ER stress and unfolded protein response (UPR). The PT, a major site of glucose transport in the kidney, has emerged as a target for novel therapeutic strategies in the treatment of diabetes and its complications that emphasize the importance of PT in glucose regulation in kidney (3, 12, 33). Hyperglycemia-induced reactive oxygen species (ROS) play a major role in the tubular injury. Genetic factors predisposing PTC to hyperglycemia-induced injury remain uncertain. Our studies provide strong evidence that AQP11 expression is regulated by glucose and that this response is lost in *Aqp11* insufficient kidney. The *Aqp11* insufficiency in PT predisposed kidney to glucose-induced renal dysfunction that was prevented by antioxidant therapy as well as by inhibition of glucose transport in PT.

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Abstract

- Pre statement of the problem
- 2-3 sentences of known literature
- Hypothesis to be tested
- 3-4 sentences of the methods used
- 3-4 sentences of the results and discussion
- 1 sentences of conclusion

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Introduction

Should consist of three main sections:

- First section should explain what is the problem that the paper will address, where and why there is a need for this work in the context of the present literature

- Second section should describe what is already known concerning the field in the present literature (this section provides the bests of why the statements are made in the first section

- Third section should briefly explain how the question will be addressed within the paper and what will be shown

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Materials and Methods

- There should be an introductory section that describes the materials to be used in the study
- For each method used there should be a separate section with its own heading that describes *in detail* how the method was performed.
- It is acceptable to refer to prior research but it should be easy for any other competent researcher to repeat the study (you want people to use your methods)

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Results

- The length of the results section varies with the journal to which you are submitting (in fact some journals encourage results and discussion in one section)
- For a pure results section describe the experiment and the result precisely but without prejudice or judgments
- Each separate piece of data (table, chart, or image) should have its own section and precise description
- It's important that significant differences are noted (consider the difference between statistical significance and actual significant)

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Discussion

- Opening paragraph should summarize the research reflecting the question developed in the introduction and how the present work has addressed that question

- In general only have four discursive paragraphs that examine the results and where they have been surprising or interesting and in particular how they relate to the known literature

- Final section should state the major conclusion and how it can be generalized to the scientific community at large

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Final Notes

- For high impact research it is important that the main research question is well presented and is of interest to people outside of your immediate field.
- Quality of the actual experiments and data presented is critical
- Placement of the work in the context of the known literature is also key
- The watch word is generalizability

Tips for Publishing in Scientific Journals

Then make sure that the questions you investigate are important and of interest to others in the field.
the most successful papers are those that present innovative research. But the best papers also present their story in a clear and logical way.
The thinking behind the paper is clear, so the writing is clear.
Writing research papers with all these qualities can require a bit of strategic thinking, practice, and know-how.

Choose an appropriate journal

- Aiming your paper at the most appropriate journal can save much effort and reveal your results to the world sooner.
- Survey the various journals and see where your work would fit best.
- Get advice from colleagues and others in the field who have experience as authors, reviewers, and journal editors.
- It may be tempting to send your paper to a top journal even if your results are not of the highest novelty or broadest interest.
- But you can save time and reduce your frustration if you send it to the appropriate journal first instead of waiting until it's rejected by a top journal.

The reviewing process (I)

- Journals run by professional editorial staff (such as *Science*, which receives about 12,000 submissions per year)
- The editor send papers out to peer reviewers--working scientists who evaluate your paper for accuracy, logic, and scientific interest.
- Reviewers are chosen by the editor on the basis of their expertise in the field, often utilizing extensive databases assembled by the journal and the editor's knowledge of the area.
- Some scientists are better reviewers than others--they are more critical and thorough, a fact that quickly becomes known to editors.
- The review process can take anywhere from a few days to several weeks. After review, the editor makes a decision about publication, taking into account all of the feedback he or she has received.

The reviewing process (II)

• You can help the review process go smoothly by providing a **cover letter** that includes, in very clear language, a concise version of the whole logic of the paper that makes clear its importance and context.

• These might include information about your own availability, related work being reviewed at other journals (from your lab or other labs), or the names of other scientists who are working on the same problem and so would have a conflict of interest in reviewing your paper. Keep the list short; otherwise, the editor will be forced to ignore your list or get an uninformed review.

• If it is necessary to ask that a few individuals be excluded from review, explain why.

Respond to reviewers' comments positively and constructively

You increase the chances of your paper being accepted if you make the assumption that the reviewers are offering their suggestions as constructive criticism