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RESEARCH NEWS

Piezo1 helps bile on the pressure

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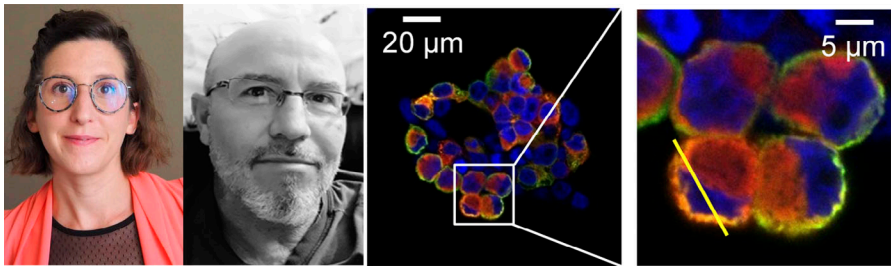
***JGP* study shows that a mechanosensitive complex containing Piezo1 and Pannexin1 couples osmotic pressure to ATP secretion in bile duct cholangiocytes.**

Cholangiocytes are epithelial cells that line the bile ducts within the liver and modify the composition of hepatocyte-derived bile. In this issue of *JGP*, Desplat et al. identify a mechanosensory complex that may help cholangiocytes respond to changes in osmotic pressure (1).

The activity of cholangiocytes can be regulated not only by chemical signals, such as hormones and bile acids, but also by mechanical cues arising from changes in bile composition and flow. "Abnormal mechanical tension is also an aggravating factor in many biliary diseases, including primary sclerosing cholangitis," explains Patrick Delmas, a Research Director at Centre National de la Recherche Scientifique/Aix-Marseille-Université. "So, identifying the molecular players in cholangiocyte force sensing could provide a step forward for better management of biliary diseases."

Current models suggest that mechanical cues trigger an influx of calcium into cholangiocytes, leading to the release of ATP, which, by stimulating purinergic receptors at the cell surface, promotes further calcium influx and induces the secretion of anions, water, and HCO_3^- to modify the tonicity and pH of hepatic bile (2, 3). To identify mechanosensitive proteins that might regulate this pathway, Delmas and colleagues, including first author Angélique Desplat, purified mouse cholangiocytes from intrahepatic bile ducts and subjected them to hypotonic stress (1). The subsequent cell swelling activates calcium influx and ATP release.

Desplat et al. found that depleting or inhibiting the stretch-activated ion channel Piezo1 significantly reduced this response to hypotonic stress. This mechanosensitive channel mediates the initial calcium influx into cholangiocytes when activated by cell swelling.



Angélique Desplat (left), Patrick Delmas (center), and colleagues identify a mechanosensitive pathway that couples hypotonic stress to calcium influx and ATP release in cholangiocytes. Cell swelling induces calcium influx through the stretch-activated ion channel Piezo, triggering ATP release by Pannexin1 channels. This leads to the activation of P2X4 receptors and further calcium influx. Piezo1 (red) and Pannexin1 (green) colocalize in cells and may interact to form a mechanosensory complex that facilitates the hypotonic stress response.

The subsequent release of ATP is mediated by a different channel, however. Desplat et al. found that cholangiocytes express high levels of the gap junction family protein Pannexin1, and that pharmacologically inhibiting Pannexin1 channels reduced the amount of ATP released in response to hypotonic stress and Piezo1 activation.

Delmas and colleagues suspect that the increase in intracellular calcium mediated by Piezo1 may activate Pannexin1 channels to release ATP, and this activation may be facilitated by a physical association between the two proteins: the researchers found that recombinant versions of the two channel proteins colocalize within the plasma membrane of cholangiocytes and can be coimmunoprecipitated.

Finally, the researchers determined that the ATP released through Pannexin1 channels amplifies the signal initiated by hypotonic stress by activating purinergic P2X4 receptors, leading to further increases in intracellular calcium levels. Transfecting Piezo1-deficient HEK293 cells, which usually don't respond to hypotonic stress, with cDNAs encoding Piezo1, Pannexin1, and P2X4R was sufficient to reconstitute the entire pathway of calcium influx and ATP release.

Cholangiocytes express other mechanosensitive channels, including TRPV4, which has previously been implicated in the cells' response to hypotonic stress (4). The functions of TRPV4 and Piezo1 may therefore be partially redundant, providing some robustness to cholangiocytes mechanical signaling pathways. However, it is also possible that, in vivo, the two channels respond to different stimuli and elicit distinct downstream effects. "Further investigation is warranted to better understand the respective roles of these two molecular players," says Delmas. "To continue our work, we would like to challenge our model in vivo by testing whether Piezo1 agonists are able to regulate bile acid secretion."

References

1. Desplat, A., et al. 2021. *J. Gen. Physiol.* 153:e202113050. https://doi.org/10.1085/jgp.202113050
2. Feranchak, A.P., and J.G. Fitz. 2002. *Semin. Liver Dis.* 22:251–263. https://doi.org/10.1055/s-2002-34503
3. Tabibian, J.H., et al. 2013. *Compr. Physiol.* 3: 541–565. https://doi.org/10.1002/cphy.c120019
4. Gradilone, S.A., et al. 2007. *Proc. Natl. Acad. Sci. USA.* 104: 19138–19143. https://doi.org/10.1073/pnas.0705964104

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