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COMMENTARY

Take a big sip and shrink it with ASOR

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Chloride is the most abundant anion in animal cells, and chloride channels allowing its diffusion across cell membranes have fundamental roles in physiology and diseases. Various types of chloride channels and transporters have been identified and implicated in a variety of biological functions (e.g., trans-epithelial fluid secretion, cell volume regulation, electrical excitability, cellular signaling, vesicular trafficking, and acidification) and human diseases (e.g., cystic fibrosis, macular degeneration, myotonia, kidney stones, renal salt wasting, epilepsy, leukodystrophy, and hyperekplexia) [3, 7]. A recent paper by Zeziulia and colleagues, published in Nature Cell Biology, sheds light on the physio-pathological importance of a lately identified and still poor known chloride channel, TMEM206 (also named PACC1) [12].

In 2019, TMEM206 entered the scene as the molecular identity of the proton-activated chloride channel, a type of channel which mediates outwardly rectifying plasma membrane chloride currents that are elicited only upon a marked extracellular acidification [9, 11]. Although such activity was previously described in a wide range of cell types [1], and TMEM206 displayed a wide pattern of expression (near ubiquitous) in human tissues (The Human Protein Atlas, www.proteinatlas.org), its physiological importance remained undervalued. Indeed, very few types of mammalian cells are normally exposed to such an acidic extracellular pH (the activation threshold is near pH 6 at body temperature), inferring that this channel may be active only under pathological conditions characterized by severe tissue acidosis, a feature associated with various diseases, including cancer, infection, and ischemia [10]. In this respect, the TMEM206-mediated proton-activated chloride channel was soon implicated in acid-induced neuronal cell death [5, 9, 11], and Tmem206 gene ablation in mice was shown to attenuate the pathogenesis of ischemic brain injury [11].

More recently, housekeeping functions are emerging for this channel. Indeed, TMEM206 was shown to traffic from the plasma membrane to acidic intracellular compartments, which provide a perfect environment for its activation also under physiological conditions [6, 12]. In endosomes, TMEM206 takes part in the regulatory mechanisms controlling vesicular acidification, a process pivotal to receptor and ligand endocytosis, trafficking, recycling, and degradation [6]. Once activated by lumenal acidification, TMEM206 allows the efflux of chloride into the cytosol, and thus serves as "brake" to prevent excessive acidification [6]. Accordingly, Osei-Owusu and colleagues found that TMEM206 deletion increased, whereas TMEM206 overexpression reduced, the endosome lumenal chloride levels and acidification, and, consequently, transferrin-receptor-mediated endocytosis [6]. In their recent paper, Zeziulia and colleagues uncovered novel and complex mechanisms governing the change in size of macropinosomes, intracellular vacuoles generated by the evolutionary ancient process called macropinocytosis, which cells use to take up large amounts of extracellular fluid together with macromolecules [4]. In order to avoid a steady increase of cell volume, and to allow downstream vesicular sorting and recycling, macropinosomes must shrink, a process that had been known to involve TPC sodium channels, proton transporters, and a so far enigmatic chloride channel [8]. Now, Zezulia et al. provide compelling evidence that TMEM206 channels, activated by TPC mediated voltage-changes and by lumenal acidification, are necessary for macropinosome shrinkage [12].

Importantly, macropinocytosis is central for immune cell activation and migration, and for nutrient supply in many cancer cells, particularly those carrying RAS mutations [2]. In these regards, Zeziulia and colleagues found that

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TMEM206 ablation impaired the C5a-dependent migration of macrophages, possibly by reducing the recycling of endocytic vesicles and thus lowering the abundance of surface chemokine receptors [12]. In pancreatic duct cancer MIA PaCa-2 cells devoid of TMEM206, the resulting slow resolution of macropinosomes, by providing more time and substrates for lysosomal degradation, increased the nutrient supply and, thus, the survival of cancer cells [12].

In conclusion, the findings by Zeziulia and colleagues open new perspectives on the importance of TMEM206 in cellular physiology, and possibly highlight TMEM206 as a potential novel target for human diseases.

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