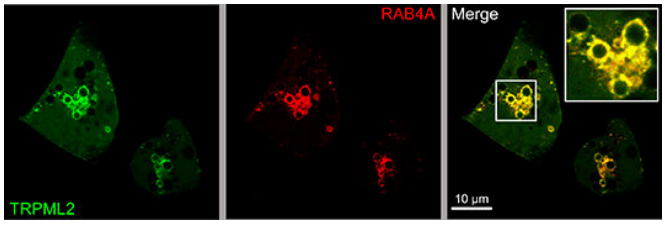
An unconventional ion channel

13 November 2020



TRPML2 channels (green) on vacuolin-enlarged fast recycling vesicles (positive for the fast-recycling marker RAB4A (red)), permitting to microdissect these vesicles from the cell, and subsequently electrophysiologically characterize them. Credit: C. Grimm

Scientists at Ludwig-Maximilians-Universitaet (LMU) in Munich have identified the first mechanosensitive ion channel to be found in an intracellular vesicle system. It responds to concentration changes within the vesicle, and probably controls the initiation of immune reactions.

Small membrane vesicles, known as endosomes or lysosomes play a key role in the uptake, secretion and intracellular transport of proteins and ions. Various types of endosomes are involved in the transport of cargoes into and out of cells, while lysosomes degrade their contents in a controlled manner. Trafficking of substances between the various classes of vesicles is largely controlled by the ion channels located in their membranes. In cooperation with Martin Biel (Chair of Pharmacology at LMU) and Christian Wahl-Schott (Medical University Hannover), pharmacologist Christian Grimm at LMU's Walther Straub Institute of Pharmacology and Toxicology has now characterized an unusual ion channel in the endolysosomal system of cells called macrophages. This particular ion channel responds specifically to mechanical stimuli that are associated with deformation of the vesicle membrane and changes in the concentration of substances present within the vesicle. As the team reports in the online journal *Science Advances*, this mechanosensitive channel is probably involved in the secretion of signaling molecules that regulate the immune system, and may help to determine the system's reaction time.

The endolysosomal system comprises diverse types of vesicles, which interact with factors that are attached to the inner face of the cell's outer membrane (the plasma membrane). These interactions regulate the uptake of cargo by the vesicle, and determine its transport to, and processing by other vesicle types. Ultimately, these cargos are either recycled to the plasma membrane or delivered to vesicles known as lysosomes for degradation. These processes may also include morphological changes, such as the pinching-off of vesicles or their incorporation into the endoplasmic reticulum, which consists of a network of membrane tubules that controls membrane trafficking within the cell. Two types of vesicles are responsible for the recycling of cargoes to the plasma membrane. What are called 'fast' recycling endosomes secrete their contents across the plasma membrane within a matter of minutes. The mechanisms responsible for rapid recycling in macrophages have remained unclear.

Christian Grimm is a master of the endolysosomal patch-clamp technique, which can be used to determine the functional characteristics of the ion channels in the endolysosomal system. Thanks to recent refinements of this method, he was able to measure the biophysical properties of the TRPML2 channels, which are found in the membranes of fast recycling endosomes in macrophages. Macrophages form part of the innate immune system, which detects invasive bacteria and viruses, and triggers a rapid immune response designed to eliminate them.

The TRPML2 channel participates in the secretion of messenger molecules that regulate immune responses, as Grimm and his colleagues had shown in a previous study. "TRPML2 is particularly active in recycling endosomes," says Cheng-Chang

Chen, lead author of the new paper. "We have now shown, for the first time, that the channel is activated by mechanical stimuli and alterations in osmolarity—a parameter that reflects the concentration of the dissolved substances in the vesicle." These stimuli come into play when, for example, vesicles are budded off from the tubular components of the endolysosomal system, owing to the accompanying alterations in the surface-to-volume ratio. "TRPML2 is the first ion channel found in intracellular membranes that has been shown to react to these stimuli. This property distinguishes it from all other endolysosomal channels," Grimm adds. He and his colleagues are convinced that this feature enables TRPML2-containing vesicles to promptly secrete their contents upon detection of invasive pathogens. The channel thus contributes to the rapid response of the innate immune system.

Unlike many other cell types, macrophages have no dedicated secretory organelles, apart from those derived from the endolysosomal system. The unconventional character of the stimulus to which TRPML2 responds could serve as a means of optimizing the function of specific transport pathways in macrophages. "In the case of an acute infection, the innate immune system cannot afford to wait 24 hours before synthesizing and secreting immunomodulators. They must be able to mount a quick response," says Grimm. In addition, the results suggest that changes in the surface-to-volume ratios of membrane tubules and vesiculation of endosomes are a prerequisite for the maintenance of the physiological functions of immune cells.

More information: Cheng-Chang Chen et al. TRPML2 is an osmo/mechanosensitive cation channel in endolysosomal organelles, *Science Advances* (2020). DOI: 10.1126/sciadv.abb5064

Provided by Ludwig Maximilian University of Munich