How immune cells kill bacteria with acid

Crucial protein for acidification of macrophage phagosome discovered

The first line of immune defense against invading pathogens like bacteria are macrophages, immune cells that engulf every foreign object that crosses their way. After enclosing it in intracellular membrane vesicles, a process called phagocytosis, macrophages kill their prey with acid. However, it is not yet entirely understood how the acidification process is established. In their quest to systematically study proteins that transport chemicals across cellular membranes, researchers at CeMM characterized the critical role for transporter SLC4A7 in this process, providing valuable new insights for many pathologic conditions from inflammation to cancer. Their results were published in *Cell Host & Microbe*.

(Vienna the 17.05.2018) Among the many different kinds of immune cells that patrol the body, macrophages are the first when it comes to fight against a foreign threat. With their flexible and versatile surface, they engulf every microorganism or particle that could be harmful for the health of the organism, and enclose it in an intracellular membrane vesicle called phagosome. To eliminate the threat and break it down to its constituents, the interior of the phagosome needs to be effectively and progressively acidified. For this crucial part of phagocytosis, the macrophages must undergo multiple metabolic changes, which are not yet entirely understood.

The team of Giulio Superti-Furga, Scientific Director of the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, discovered in their latest study that a membrane protein belonging to the family of "solute carriers" (SLCs) plays an essential role in phagocytosis and phagosome acidification. Their work was published in the journal *Cell Host & Microbe* (DOI 10.1016/j.chom.2018.04.013).

SLCs represent the largest group of transporter proteins responsible for the movement of chemical molecules across cellular membranes. As phagocytosis and the acidification of phagosomes require the exchange of ions and nutrients, the scientists in Superti-Furga´s laboratory hypothesized that SLCs might be essential for macrophages to undergo those processes. To test their hypothesis, the researchers developed an essay with special cells in which they impaired the 391 human SLC genes individually using CRISPR/Cas9 gene editing technology.

Those cells, each of them carrying a single defective SLC gene, were subsequently tested on how they performed during phagocytosis. Strikingly, among all SLCs, SLC4A7, a sodium bicarbonate transporter, was the only one who turned out to be essential for macrophages to undergo

phagocytosis and acidification. Cells with impaired SLC4A7 were unable to acidify their phagosomes and by consequence decreased their capacity to kill bacteria.

Having identified their prime candidate SLC4A7, the scientists, in collaboration with the laboratory of Nicolas Demaurex of the University of Geneva, investigated further and unveiled the mechanism causing the impaired phagosome acidification. "SLC4A7 is located on the surface of macrophages and necessary for bicarbonate import from the environment into the cell cytoplasm" Giulio Superti-Furga, senior author of the study explains. "The SLC4A7-driven bicarbonate import is essential for buffering the cellular pH during phagocytosis. If SLC4A7 was lost, the activation of macrophages led to accumulation of protons in their cytoplasm, which further inhibited the acidification of phagosomes."

The results of this study do not only provide new fundamental insights into the molecular functioning of one of the most important cells of the immune system. As phagocytosis plays a significant role in various pathologic conditions from inflammation to cancer, these new insights are likely of relevance beyond the context of infectious diseases. The effort to understand the role of the different cellular transporters, supported by a grant of the European Research Council (ERC), has added a small new piece to the large and fascinating puzzle coupling trafficking of chemical matter to metabolism and cellular function.

The study "The Bicarbonate Transporter SLC4A7 Plays a Key Role in Macrophage Phagosome Acidification" was published in *Cell Host & Microbe* on 17.05.2018. DOI: 10.1016/j.chom.2018.04.013

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As Scientific Director of CeMM, Giulio Superti-Furga has been fostering the precise and preventive medicine of the future by integrating basic research and clinical expertise to pursue pioneering

diagnostic and therapeutic approaches. Among his major achievements to date are the elucidation of basic regulatory mechanisms of tyrosine kinases in human cancers, the determination of the precise mechanism of action of several drugs and the discovery of fundamental organization principles of the proteome and lipidome. In recent years, he has been focusing on membrane transporters, advocating the more systematic study of their function in the scientific community, He is a member of the Austrian Academy of Sciences, the German Academy of Sciences Leopoldina, the European Molecular Biology Organization (EMBO), the European Academy of Cancer Sciences, and the Academia Europaea.
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