First breath shapes the lung's immune system

Before birth, lungs are filled with a germ-free liquid, and it is only with the first breath that they abruptly expand in order to take over the oxygenation of blood. This sudden exposure to the outside environment includes incoming airborne microbes and pollutants, which requires the lungs to develop appropriate defense mechanisms, while maintaining the gas exchange. The postnatal immunological development of the lungs remained largely unknown until a group of scientists at CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and the Medical University of Vienna shed light at a complex immune program that starts right after birth: the study published in Cell Reports reveals how first breath-induced interleukin-33 signaling shapes the performance of pulmonary immune cells and influences anti-bacterial defenses.

(Vienna, February 21, 2017) The lung is an important interface between the body and the outside environment: with each breath, a surface of roughly 100 square meters exchanges oxygen for carbon dioxide. More than 10,000 liters of air pass adult lungs every day and with this come numerous viruses, bacteria and pollutants, which need to be prevented from entering the body.

To defend the organism from these intruders, the lungs harbor their own arsenal of highly specialized immune cells that are equipped to maintain the balance between host defense and tissue quiescence. However, how this balanced immune homeostasis in lungs emerged after birth, was largely unexplored. Now, for the first time, the group of Sylvia Knapp, Director of Medical Affairs at CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and Professor of Infection Biology at the Medical University of Vienna showed with the help of mouse models that the very first breath of a newborn releases crucial signals that shape the lifelong immunological milieu of lungs.

The study, published in *Cell Reports* (DOI:10.1016/j.celrep.2017.01.071), reveals that the mechanical forces of spontaneous ventilation at birth lead to the release of interleukin (IL)-33, a cytokine with a wide-range of effects: So-called "type 2 innate lymphoid cells" (ILC2s) follow the IL-33 signal and migrate into the lung tissue, where they release IL-13, another cytokine. This second signal determines the faith of alveolar macrophages by inducing the anti-inflammatory M2 phenotype.

"ILC2-cells are crucial in defending the lungs against parasites or influenza viruses, but little was known about their role in lung homeostasis", first author Simona Saluzzo, PhD Student funded by the CCHD Program at CeMM and the Medical University of Vienna, explains. "Now we understand that right after birth, ILC2 are responsible for the differentiation of alveolar macrophages into specialized cells that keep the immune system in check and ensure that the lungs stay calm and healthy to ensure proper gas exchange."

These ILC2-induced effects protect the lungs from excessive inflammation to daily encountered environmental triggers – but there is a catch, senior author Sylvia Knapp emphasizes: "We could show in our study that the described mechanisms are crucial in achieving lung quiescence after the first contact with the outside world. However, these processes at the same time increase the susceptibility to bacterial infections, such as caused by pneumococci. In other words: The mechanism that maintains the lung function of gas exchange at the same time explains why bacterial pneumonia is the primary cause of death by an infectious disease in Western countries."

Attached pictures: 1. Fluorescent staining of IL-33 in a newborn mouse lung © Simona Saluzzo/CeMM; 2. Graphical abstract of the study © Simona Saluzzo/CeMM; 3. Senior author Sylvia Knapp (right) and first author Simona Saluzzo (left) © Wolfgang Däuble/CeMM

The study "First-breath induced type-2 pathways shape the lung immune environment" was published in *Cell Reports* on February 21, 2017. DOI:10.1016/j.celrep.2017.01.071

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Sylvia Knapp is Director of Medical Affairs at CeMM and Professor of Infection Biology at the Medical University of Vienna. She studied Medicine in Vienna and Berlin, is a board-certified Internist and obtained her PhD at the University of Amsterdam. Sylvia's research focuses on the innate immune response to bacterial infections in general, focusing specifically on the comprehensive repertoire of macrophage functions in health, development and disease.

The mission of **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is to achieve maximum scientific innovation in molecular medicine to improve healthcare.

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