PAUL EHRLICH-STIFTUNG

Der Vorsitzende des Stiftungsrates

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Background • Background • Background

Frankfurt, January 27, 2021

Embargo: January 27, 2021, 10am CET

Background on the award of the 2021 Paul Ehrlich and Ludwig Darmstaedter Prize for Young Researchers to Professor Elvira Mass, Ph.D

Conductors from the yolk sac

Immune cells from the yolk sac help embryos to develop properly.

After an egg cell has been fertilized, every step in the development of an embryo must be well coordinated. Heart, lung, liver, and the other organs have to follow their developmental trajectories and all organ-specific cells must follow their respective fate. This year's recipient of the 2021 Paul Ehrlich and Ludwig Darmstaedter Prize for Young Researchers Professor Elvira Mass has shown that this mission is accompanied by specialized immune cells, so-called macrophages that are derived from the yolk sac of the early embryo. Like law enforcement officers, they spring into action when the developmental steps are not on schedule or flawed. Later in life, they contribute to organ health; hence, if these macrophages fail to execute their function, organs might fail too.

Most of the time, new research expands existing knowledge, but sometimes new research results in rewriting the textbooks. Developmental biologist Elvira Mass from the Life and Medical Sciences Institute (LIMES) in Bonn is one of those scientists who has turned existing knowledge on its head. The award winner has revised our understanding of organ development in early mouse embryos. She discovered that most of the macrophages that colonize all growing tissues of the embryo derive from a yolk sac precursor; once in place, they mature together with their organ of residence. For decades, scientists were firmly convinced that tissue-resident macrophages are exclusively derived from haematopoietic stem cells in the bone marrow. Mass has shown that yolk sac-derived tissue-resident macrophages make a life-long contribution to the health of organs; when they don’t live up to expectations, organ functions may fail.

Dr. Hildegard Kaulen • E-Mail: h.k@kaulen-wissenschaft.de
www.paul-ehrlich-stiftung.de

More than a cleaning crew

Macrophages belong to the innate immune system of mammals. They are part of their permanently active surveillance system that, like a radar, constantly scans the body for threats. If the innate immune system encounters a problem, it sounds the alarm and calls the specialized immune system with its tailor-made antibodies and killer cells to the scene. Macrophages work as a cleaning force, remove cell debris and scavenge dead or damaged cells. However, they are more than just phagocytes. Macrophages also produce a large range of bioactive molecules and growth factors. In doing so, they ensure that tissues are not only tidied up, but are also provided with essential support for their morphogenesis. To achieve this feat, each organ has its own set of tissue-resident macrophages. These cells are called microglia in the brain, Kupffer cells in the liver and Langerhans cells in the skin, to name just three examples.

Mass created a map for the differentiation and migration of macrophages in the mouse embryo as the cells progress from their immature stage in the yolk sac to fully developed tissue-resident macrophages in the organs where they live on to adulthood. Apart from phagocytosis, one of their main tasks is in sculpturing tissues and supporting their functions.

If indeed these macrophages are so important for the development and health of an organ, the question arises as to what happens when they or their progenitor cells in the yolk sac are mutated or damaged. Observations in patients suffering from tumours in which the tissue-resident macrophages proliferate in an uncontrolled manner helped Mass in answering this question. Often, these so-called histiocytoses exhibit a specific mutation. Mass introduced this mutation in yolk sac-derived tissue-resident macrophages in mice and monitored the development of these genetically manipulated animals. The ill effects of the mutation were particularly evident in brain microglia, which shifted from a homeostatic to a pro-inflammatory phenotype and began to eliminate neighbouring neurons. Eventually, all mice showed damage to the brain that led to paralysis, indicating that mutated microglia caused neurodegeneration. This finding mirrors the clinical phenotype of patients with histiocytosis who often also develop signs of neurodegeneration or behavioural deficits.

New approach to neurodegeneration

“These experiments show that macrophages with certain molecular changes may contribute to the development of neurodegenerative diseases,” says Mass about her results. "Even though our results currently only pertain to mice, we ask ourselves what these findings mean for the development of neurodegeneration in humans, such as Alzheimer's or Parkinson's disease. In the light of our findings, it is possible that malfunction of microglia, due to mutation or faulty epigenetic imprinting, may contribute to neurodegeneration. I am firmly convinced that, when looking at the development of diseases, we have to pay much more attention to possible malfunctions of the tissue-resident macrophages than before. "

Mass was also interested in the role of macrophages in other tissues, such as osteoclasts in bones. In healthy bones, bone formation and bone loss are in balance. So-called osteoblasts are responsible for building bones, whereas osteoclasts are breaking them down. Mass was able to show that a defect in the growth and differentiation programme of the yolk sac-derived precursors specifically in osteoclasts impairs their function. This leads to an imbalance between bone formation and bone loss, osteoblasts gain the upper hand and harden the bone. In response, mice with a defect in osteoclast formation recruit new macrophages from the bone marrow, a situation that is not possible in patients, in whom germ-line mutations affect all cells in the

Dr. Hildegard Kaulen • E-Mail: h.k@kaulen-wissenschaft.de
www.paul-ehrlich-stiftung.de

body, including the haematopoietic stem cells which give rise to an alternative lineage of macrophages. However, a blood transfusion from healthy donors may represent a therapeutic option for these patients, soon be tested in clinical studies.

What could harm macrophages?

In the future, Mass plans to investigate which environmental factors change the epigenetic imprinting of yolk sac-derived tissue-resident macrophages and how these changes influence their function. "I am firmly convinced that many diseases are caused by such changes," says Mass about her research. For example, she wants to study the influence of maternal obesity in mice. Mass speculates that the offspring of overweight mice develop a fatty liver disease due to malfunctioning Kupffer cells. With financial support from the European Union, she will also investigate the influence of nanoplastics on macrophages. Particles smaller than 500 nanometers can pass the human placenta and would therefore be able to damage the support function of yolk sac-derived tissue-resident macrophages during organ development.

Further information

You can obtain the full resume, selected publications, the list of publications and a photograph of the prize winner from the Press Office of the Paul Ehrlich Foundation (c/o Dr. Hildegard Kaulen, phone: +49 06122/52718, email: h.k@kaulen-wissenschaft.de and at www.paul-ehrlich-stiftung.de.