New path of origin for macrophages

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Macrophages play a key role in the immune response, protecting organisms against infection and regulating the development of inflammation in tissue. Macrophages differ depending on where they are located and which tasks they perform. A scientist at TUM has been investigating whether these different types of cells have the same origin – and has come up with some surprising results. His findings reveal that there are two distinct macrophage cell lines that continue into adult life and that these two lineages have different origins. The research was recently published in *Science* magazine.

The organs of vertebrates, including of course humans and other mammals, are made of a multitude of highly specialized cells that are built by embryonic stem cells. This is also true for cells of the immune system. Until recently, it was thought that all macrophages were created from hematopoietic (blood) stem cells. However, some of these immune cells had also been found to exist in the yolk sac prior to the appearance of stem cells. For a long time, the existence of these extraembryonic macrophages was a puzzle to scientists.

During a sabbatical at King's College in London, Dr. Christian Schulz, internist at the Deutsches Herzzentrum (German Heart Center) of the Technische Universität München, and his research colleagues set about investigating the development of macrophages in mice. To determine the extent to which macrophages can develop independently of embryonic stem cells, the scientists carried out experiments on mice without the "myb" growth factor, which plays an important role in cell growth and is thus crucial to the formation of blood stem cells. "To our surprise, we

found that macrophages in the yolk sac also develop without myb. This enabled us to close in on a cell line that can develop independently of stem cells," explains Christian Schulz.

The researchers used cell markers in the early phase of embryonic development to trace the paths of these different immune cells. The investigations led to some unexpected conclusions. The myeloid cells that formed in the yolk sac developed into macrophages that reside in the tissue of various organs in adult mice. The macrophages circulating in the blood stream did not originate in the yolk sac. These macrophages were created exclusively by stem cells. For Schulz, this could only mean one thing: "Yolk sac macrophages obviously migrate to the organs at a very early stage in embryonic development – and remain there. There is evidence to suggest that these cells can survive and regenerate themselves in the organs over a long period of time. By contrast, short-lived macrophages in the blood stream are continually replaced through the stem cells."

Resident macrophages in the brain are known as microglia cells. Macrophages in the skin are known as Langerhans cells and those in the liver are called Kupffer cells. They are non-specific killer cells that eliminate bacteria and other foreign bodies and, as antigen-presenting immune cells, also initiate specific immune responses. Current research indicates that two distinct lines of myeloid cells exist. Both reveal different gene expressions and perform different tasks. "Further studies will establish whether or not there are consequences for inflammatory processes," outlines Christian Schulz. "As a heart specialist, I am particularly interested in the conclusions for arteriosclerosis, an inflammation of the vascular wall that can lead to heart attack or stroke."

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