

Missing link between hemolysis and infection found

CeMM/MedUni Vienna Researchers discovered how hemolysis causes infections and found a new means to prevent it, paving the way to new treatment possibilities.

Worldwide, millions of people suffer from hemolysis, the breakdown of red blood cells, such as those afflicted with sickle-cell disease, malaria or sepsis. These patients face an unprecedented risk of death from bacterial infections and the mechanism for this has remained unclear until now. In the latest edition of Nature Immunology, Sylvia Knapp's Group at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and the Medical University of Vienna, uncovers the molecular mechanisms that explain how hemolysis escalates the risk for infections. This study puts to rest the old belief that iron availability favors bacterial infections in hemolytic disorders, and moreover reveals a new treatment approach to protect patients with hemolysis from infections.

(Vienna, 31. October 2016) For decades, iron has been considered the prime suspect responsible for the high rate of bacterial infections in patients with hemolysis (bursting of red blood cells). Iron is the element, which gives red blood cells their color and moreover, iron has long been established as an essential nutrient for bacteria. Taking that into consideration, the traditional hypothesis predicted that since hemolysis leads to the release of iron-containing heme, the threat of serious bacterial infections in these patients was attributed to the excess availability of circulating iron (heme).

A research group led by Sylvia Knapp, Director of Medical Affairs at CeMM and Professor of Infection Biology at the Medical University of Vienna, was able to refute this conventional way of thinking. They revealed that heme was not only failing to act as a willing nutrient to bacteria, heme was instead paralyzing the very innate immune cells sent to protect the host from the bacteria.

"Using in vitro and pre-clinical models, we could clearly demonstrate that heme-derived iron is not at all vital for bacterial growth," explains Rui Martins, PhD student at CeMM and the Medical University of Vienna, and the first author of the study. "In contrast, we found that heme acts on macrophages, the most significant immune cells that are required for mounting an antibacterial response, and it furthermore prevented these cells from eliminating bacteria."

The scientists discovered a completely unknown mechanism: The heme molecule interfered with the cytoskeleton of macrophages and thereby immobilized them. Describing the effect of heme, Martins explains further: "Heme causes cells to form numerous spikes, like hair standing on end and then "stuns" the cells within minutes. It is reminiscent of a cartoon character sticking his finger in an electrical outlet."

The cytoskeleton is crucial for the basic functions of macrophages. The cytoskeleton consists of long, branching filaments that act as the cell's internal, highly flexible and mobile framework. Through targeted build-up and breakdown of these filaments, phagocytes can move in any direction and 'eat' invading bacteria. However, this requires a finely tuned signaling program in which the protein DOCK8 plays a central role. "Through chemical proteomics and biochemical experiments, we discovered that heme interacted with DOCK8, which led to the permanent activation of its downstream target Cdc42, with deleterious effects", explains Sylvia Knapp, the senior author of the study. In the presence of heme, the cytoskeletal resilience is

lost, as filaments grow rampant in all directions, resulting in macrophage paralysis—in other words, the cells lose their ability to shape-shift and can no longer chase down and ‘eat’ the invading bacteria. The resultant impact is that bacteria can multiply virtually unrestricted.

The loss of cytoskeletal resilience results in life-threatening conditions for millions of people worldwide, which suffer from hemolysis due to systemic inflammation (sepsis) or disorders such as sickle-cell disease, or malaria. In the recently published study, scientists led by Sylvia Knapp, were not only able to clarify the molecular effect of heme on macrophages but moreover discovered that an already available medication can restore the functionality of affected (paralyzed) macrophages. “Quinine, which is clinically used to treat malaria and is suspected to bind heme, blocks the interaction of heme with DOCK8 and thereby improves the outcome from sepsis”, says Sylvia Knapp. “This is very promising. We conclusively demonstrate that it is indeed feasible to therapeutically “protect” immune cells and to restore the body’s immune defense against bacteria in hemolytic conditions.”

The Study “Heme drives hemolysis-induced susceptibility to infection via disruption of phagocyte functions” was published online on October 31, 2016 at 1600 London time / 1200 US Eastern time in *Nature Immunology*, DOI: 10.1038/ni.3590

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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.

CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences is an interdisciplinary research institute committed to advancing the understanding of human diseases through basic and biomedical research. Located at the center of the Medical University of Vienna’s campus, CeMM fosters a highly collaborative and interactive research mindset. Focusing on medically relevant questions, CeMM researchers concentrate on human biology and diseases like cancer and inflammation/immune disorders. In support of scientific pursuits and medical needs, CeMM provides access to cutting-edge technologies and has established a strategic interest in personalized medicine. www.cemm.at

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