MedicalXpress

How ancestry shapes our immune cells

June 1 2017

Virtually the entire population of sub-Saharan Africa, and some 70% of African Americans, carry a gene variant (allele) which results in a trait referred to as Duffy-negative. It has long been known that carriers of this version of the gene are relatively protected from some strains of malaria. In addition, the allele has recently been linked to benign neutropenia—a mild reduction in the numbers of neutrophilic granulocytes (neutrophils), a type of white blood cells present in the circulation. Although neutrophils are known to play an important part in the innate immune defenses against pathogens, Duffy-negative individuals do not show any obvious increase in susceptibility to infections. In a new study led by LMU's Dr. Johan Duchêne, Professor Christian Weber and Professor Antal Rot (also at University of York), an international team of biomedical researchers has now shown how the Duffy-negative variant affects the differentiation of white blood cells and why it leads to a relative paucity of circulating neutrophils. The findings appear in the current issue of the journal *Nature Immunology*.

All blood cell types are generated in the bone marrow. In a process called hematopoiesis, so-called multipotent hematopoietic stem cells and progenitor cells progressively give rise to the different types of cells found in the bloodstream. Among these are the neutrophils and the erythrocytes (aka red blood cells). Duffy-negative individuals lack a specific protein, the atypical chemokine receptor 1 (abbreviated ACKR1), normally found on the surface of the erythrocytes. ACKR1 is known to interact with signal molecules called chemokines that regulate immune responses. However, some pathogens responsible for malaria use this receptor to dock onto and subsequently invade red blood cells.

This explains why people who lack this receptor are more resistant to some types of malaria. "But how the lack of ACKR1 on red blood cells alters the balance of white blood cell types was entirely unknown up to now," Duchêne says.

Using the mouse as an experimental model, Duchêne and his colleagues have now shown that the link between ACKR1 and the white blood cell population lies at the level of the differentiation of stem cells and precursor cells during hematopoiesis. The authors discovered that progenitors of the erythrocytes form a specific "niche" in the bone marrow and support the differentiation of hematopoietic stem cells. Thus, surprisingly the expression of ACKR1 on the surface of these erythrocyte progenitors determines the ultimate fates of the stem cells. "If the erythrocyte precursors do not express ACKR1, the stem cells differentiate into neutrophilic granulocytes that differ both molecularly and functionally from those formed following contacts with ACKR1," Duchêne explains. "Our results indicate that these altered neutrophils readily leave the circulation and migrate to the tissues, primarily into the spleen." The resulting decrease in the number of neutrophils in the bloodstream accounts for the characteristic neutropenia. Whether or not the neutrophils that migrate to the spleen survive there and contribute to immune responses remains unclear.

The researchers believe that the specific properties of the neutrophils produced by Duffy-negative individuals have a positive impact on innate immune responses against microbial pathogens, and that genetic variant provides its carriers with a selective advantage. "But of course, a stronger immune response can also be counterproductive, for example when the immune reaction gets out of hand, and leads to chronic inflammation and autoimmune disease," Weber points out. Researchers now want to obtain a better understanding of the effects of hematopoiesis in the absence of ACKR1 on the immune response in cancer, infectious, autoimmune and inflammatory diseases like

atherosclerosis. "Our discovery is a first step towards the understanding on why diseases may take different courses in people of African ancestry. Therefore potentially different medicines should be developed to treat common diseases for individuals of African ancestry" says Rot. Scientists hope that their work should initiate further research and ultimately open the way to novel, patient group targeted therapeutic strategies for Duffy-negative individuals.

More information: Johan Duchene et al. Atypical chemokine receptor 1 on nucleated erythroid cells regulates hematopoiesis, *Nature Immunology* (2017). DOI: 10.1038/ni.3763

Provided by Ludwig Maximilian University of Munich