Understanding the diversity of immature red blood cells could help protect against malaria

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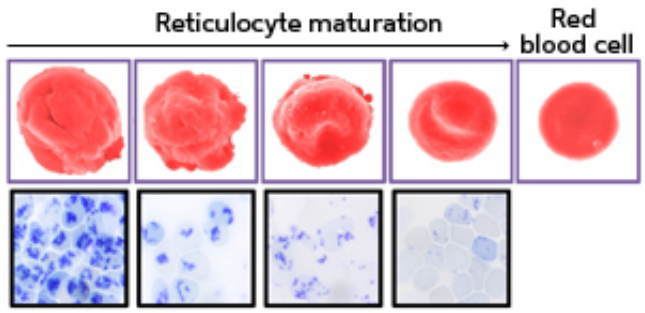

The four subpopulations of reticulocytes show altered external appearances (top) and internal structures (bottom) as they mature into red blood cells. Credit: B. Malleret et al.

Red blood cells are released into the blood stream in their immature form—reticulocytes—from the bone marrow where they develop. Reticulocytes are important markers for certain blood disorders and infectious diseases but their maturation has been poorly understood. Now an international research team led by Laurent Renia from the A*STAR Singapore Immunology Network has characterized, in fine detail, the properties of reticulocytes at different stages of maturation.

Studies in the 1930s identified distinct subtypes of reticulocytes but only provided basic descriptions of their different maturation stages. According to Renia, these early studies have mostly been forgotten, and more detail is needed to better understand the reticulocyte maturation

process.

"The quantity and type of reticulocytes released into the circulation provides important information for the diagnosis and prognosis of certain diseases," explains Renia. "Despite the significance of reticulocytes, limited information is available about their biology and it is incorrectly assumed that reticulocytes are a fairly uniform type of blood cell."

Aided by recent advances in fluorescent staining, Renia and his team set out to describe the properties of reticulocytes at different stages of maturation by studying cells from the reticulocyte-rich blood of the human umbilical cord. They separated the reticulocytes into four subpopulations according to the level of their expression of a specific surface protein which decreases as the cells mature.

"This helped us to fully characterize the chemical and biomechanical differences of these reticulocyte stages," says Renia. They found that as reticulocytes mature, the outer membrane and internal structures are reorganized, creating cells that are smaller, less rigid and have the characteristic concave shape of red blood cells (see image). They also revealed changes in expression levels of specific proteins and the attenuation of metabolic pathways.

"We uncovered an incredible level of reticulocyte heterogeneity characterized by significant chemical, biophysical and metabolic modifications," says Renia. "No-one else has characterized reticulocytes on such a fine scale."

The differences the team noted demonstrate that reticulocyte maturation is a continual process, meaning that reticulocytes should not be grouped together as one cell type. In addition, the finding hints that the maturation process could have direct clinical applications.

"Reticulocytes are important in the study of vivax or 'relapsing' malaria, the most common form of malaria in Asia, because the Plasmodium vivax parasite specifically targets reticulocytes," he says. "We hope our findings will help to develop vaccines that block the blood stage life cycle of vivax malaria parasites."

More information: Malleret, B., Xu, F., Mohandas, N., Suwanarusk, R., Chu, C. et al. "Significant biochemical, biophysical and metabolic diversity in circulating human cord blood reticulocytes." *PLoS ONE* 8, e76062 (2013). dx.doi.org/10.1371/journal.pone.0076062

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