Red blood cell: barometer of cardiovascular health?

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This editorial refers to "Suicidal erythrocyte death, eryptosis, as a novel mechanism in heart failure-associated anaemia" by Mahmud et al., pp. 37–46, this issue.

Anaemia is an important risk factor in a number of conditions, including heart failure.¹ The fact that not only the absolute haemoglobin level but also the change in haemoglobin level over time is related to outcome emphasizes the importance of the underlying mechanism leading to anaemia.¹ Often anaemia is ascribed to reduced sensitivity of erythroid progenitors to erythropoietin,² or bone marrow suppression by inflammatory cytokines such as tumour necrosis factor-alpha or interleukin-6.³ This focus on the production site may be prompted by the seemingly inert nature of the mature red blood cell. Mature red blood cells lack a nucleus and over 95% of their protein cargo consists of haemoglobin. The lack of a nucleus leaves little room to respond to changes in the environment by adjusting cell composition and the vast quantity of haemoglobin appears to underline that gas transport is the sole task of the red blood cell. However, specific properties of the circulating red cell, such as red cell distribution width, a measure of anisocytosis, are associated with outcome, independently of the haemoglobin level. This indicates that not only production and haemoglobin content of the red cell, but also its fate after release into the circulation, is of importance.⁴,⁵

Mahmud et al.⁶ investigate the final stages of the erythrocyte lifespan. Their results suggest increased suicidal red blood cell death (eryptosis) rather than reduced red blood cell birth as underlying cause of anaemia in heart failure.

Their hypothesis is based on the observation that, in a number of conditions, eryptosis has been observed.⁷ Indeed, circulating red blood cells are challenged in the microenvironments that they pass through. Consistent and repeated exposure may alter red blood cell phenotype, in keeping with the notion that the red blood cell may act as a barometer of vascular health, as first pointed out by Allen et al.⁸ In particular, oxidative stress, energy depletion and dysregulated osmotic balance are known factors to increase eryptosis.⁷ Indeed, when the authors look for eryptotic markers in a small cohort of patients with acute heart failure or in rodent models of the disease, an increase in red blood cells that expose phosphatidylserine is observed. This is one of the crucial steps in eryptosis, as the movement of phosphatidylserine from the inner leaflet of the phospholipid bilayer of the cell membrane to the outer leaflet constitutes a powerful ‘eat me’-signal for red blood cell clearance.¹⁰ As a consequence, in healthy individuals the number of circulating phosphatidylserine-exposing red blood cells is negligible. The fact that this increase of circulating phosphatidylserine-exposing red blood cells is observed at all, appears to indicate that a new equilibrium has been set, where a fraction of red blood cells circulate despite suicide markers. This new equilibrium is not the result of impaired clearance. On the contrary, the author’s data indicate that clearance of phosphatidylserine-exposing red blood cells is even enhanced under heart failure conditions. These observations would indicate that phosphatidylserine exposure is increased despite enhanced clearance, implying a dramatically increased rate of eryptosis.

The imbalance is further supported by observations on the remaining red blood cell population that does not expose phosphatidylserine. These cells have become more susceptible to eryptosis when subjected to oxidative stress, hyperosmotic shock and energy depletion in vitro. Taking in vitro, pre-clinical and clinical observations into account, a picture emerges that shows a fragile, suicidal red blood cell population with a substantially reduced life span.

One can only speculate what the exact clinical implications are and whether, for instance, the increased demand for clearance of defective red blood cells and iron load alters the phagocytes phenotype and behaviour.¹¹ Also, phosphatidylserine exposure has been shown to trigger endothelial interactions. For example, in sickle cell anaemia or malaria, phosphatidylserine externalization occurs, leading to binding of red blood cells in capillaries impeding blood flow.¹²,¹³ The continuous presence of circulating phosphatidylserine-exposing red blood cells may even trigger endothelial cells, which would normally not engage in erythropagocytosis, to internalize red blood cells. We have observed that angiogenic endothelium can internalize vast numbers of red blood cells in vitro in the presence of lactadherin, an opsonin that bridges phosphatidylserine on the red blood cell and internalizing alpha v-integrins on the endothelial cell¹⁴ (Figure 1).

A final element in eryptosis that should be mentioned is the formation of vesicles. A natural reaction of the red blood cell after phosphatidylserine exposure is to cluster the phospholipid and shed this small part of the membrane from the surface. The phosphatidylserine-rich vesicles that are shed are usually between 100 and 200 nm in size. They can initiate a multitude of biological reactions, especially
because of the high surface area of phosphatidylserine that is presented on these submicron vesicles. Vesicles have been implicated in thrombosis, activation of complement and consumption of nitric oxide, to name but a few examples.15

Taken all together, the importance of the study by Mahmud et al. is that it provides a strong incentive to further explore the mechanisms leading to anaemia in cardiovascular disease and to focus on the pathophysiology of red cell decay and associated biological consequences.

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References