Platelets beyond their count, as a key element of the innate immune system in the fight against malaria

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Now far from being considered mere contributors to the homeostasis of the circulatory system and vascular integrity, platelets should be seen as protagonists of multiple key roles, even in scenarios other than haemostasis. Among the most extraordinary and unexpected capacities, it is worth remembering how they can act as real effectors of innate immunity, thanks to their ability to interact with blood cells and vessels, and with the system of complement.

One of the most refined pieces of evidence of the interplay between complement and platelets is the demonstration of how the surface of the latter (incredibly protected by complement-mediated proteolysis) provides a scaffold for the activation of C3.[1] Thrombin is the most powerful platelet activator: it can trigger the complement cascade both through the protease-activated receptors (PAR) 1 and 4 present on the platelets, and by direct cleavage of C5. In addition, the expression of FcγRIIa, a surface low-affinity Fc receptor for the constant region of immunoglobulin G (IgG), allows platelets to clear IgG immune complexes from the circulation. Opsonized pathogens can be thus responsible for FcγRIIa-mediated platelet activation.[2]

All the mechanisms mentioned above, in certain complement-mediated diseases such as atypical uraemic-haemolytic syndrome or parasitic infections, result in progressive — more or less rapid — thrombocytopenia, often associated with degranulation and release of microparticles.[2]

Among all infections characterized by thrombocytopenia, malaria represents a particular model for understanding the role that platelets play in the control of infections, even in the long term. Despite a gradual decrease in its number of annual incidences in the period between 2010 and 2018, about 230 million cases of malaria are recorded annually, mainly concentrated in 19 countries of sub-Saharan Africa and India. In its latest report, the World Health Organization estimates that around 24 million children were infected with *Plasmodium falciparum (Pf)* in sub-Saharan African countries in 2018. Approximately 1·8 million of them were likely to have severe anaemia. Moreover, childhood infection with *Pf* is linked to the onset of endemic Burkitt lymphoma (eBL), being the parasite classified as a class 2A carcinogen for this neoplasm.[3]

During a malarial infection, activated platelets appear chronically engaged in aggression against the parasite, against a battleground of inflammation and hypercoagulability. Increased thrombin generation has been found even when parasite density is low.[4] It has been observed that the antiparasitic activity is completely due to the release of Platelet Factor 4 (PF4). This chemokine binds to the Duffy antigen, and is internalized by the infected erythrocyte.[5] As a consequence of the deposition of PF4, intraerythrocytic death of *Pf* is obtained. Mild to moderate thrombocytopenia is present in both symptomatic and asymptomatic patients, and the causes range from immune-mediated depletion to splenic seizure and consumption. Both the risk of bleeds and the presumed need to preserve platelet activation have reignited the controversy over the use of non-steroidal anti-inflammatory drugs in the treatment of malaria symptoms. A manuscript published in 2017 highlights the importance of determining platelet count to improve the clinical management of infections in low-income countries.[6] This laboratory parameter is in fact easily available, and is a good predictor of complications such as sepsis, renal failure and — obviously — haemorrhage. Furthermore, relative changes in values could reflect the patient's immunocompetence status, and consequently the severity of the disease.

But what happens to platelet count in those subjects that develop eBL? The case control study conducted from 2010 to 2016 in Uganda, Tanzania and Kenya, and published in this issue of the Journal,[7] reveals for the first time the differences in terms of platelet count between patients with eBL and controls, with or without active malaria infection. And, above all, it strives to make sense of platelet counts themselves, providing interesting insights for clinical and preclinical research.

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The first important deduction could be represented by the maintenance of the anti-malarial protection offered by platelets. However, the relative increase in the mean platelet count in eBL also deserves special attention. Although this aggressive lymphoma may have heterogeneous clinical and laboratory presentations (circulating proplatelets are common in those presentations that mimic acute lymphoblastic leukaemia), the finding of a tendency toward thrombocytosis could have something to do with the pathogenesis of the disease, given that the data seem to be independent of the presence of *Pf*. The authors hypothesize a role of platelets in promoting the proliferation of pathological B cells. At the same time, it is true that the B cells themselves support the release of platelets in diseases such as essential thrombocythaemia (apparently with a similar expression of some surface receptors compared to eBL) through the production of pro-inflammatory cytokines.[8]

The link between platelets and immunity therefore becomes increasingly close, and it is precisely for this reason that the reading of the article is accompanied by the enthralling satisfaction of imagining what is 'beyond the counts'.

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