Platelets in rheumatoid arthritis: exploring the anti-inflammatory and antithrombotic potential of TNF inhibitors

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Manfredi et al1 explore the relationship between tumour necrosis factor α (TNFα), TNFα inhibition and platelet activation in rheumatoid arthritis (RA). Using elegant systems they demonstrate that TNFα activates platelets and promotes their proinflammatory and procoagulant actions, while TNF inhibition (TNFi) prevents platelet activation. They suggest this is a potential mechanism explaining why TNFi associates with a reduction of cardiovascular (CV) events in patients with RA, as shown in some observational studies. Should we then be (come) interested in platelet biology in RA?

The potential role of platelets in the pathogenesis of RA and related comorbidities has, in fact, received much less attention than it deserves. Platelets are small (1–2 μm) anucleate cells that are intimately involved in thrombosis, angiogenesis, bone remodelling, inflammation and autoimmunity. Their bidirectional, damaging and protective roles across pathophysiological processes have been explored in several clinical and laboratory studies. The discovery of specific platelet markers and agonists, which target a range of membrane-bound receptors, has resulted in better understanding of their role. It is now clear that platelet reactivity throughout their short lifespan (8–10 days) is determined by megakaryopoiesis, which is regulated quantitatively by thrombopoietin; any chemical compound targeting the maturation of platelet precursors in the bone marrow either directly or indirectly can alter the thrombotic, immune and inflammatory potential of circulating platelets.2,3

Activated platelets shed highly active membranous structures—microparticles—and transform from disc-shaped to enlarged cells with pseudopods that facilitate their interaction with other platelets, neutrophils, lymphocytes and other immune cells. Circulating neutrophils, in turn, interact with activated platelets to boost their ‘thromboinflammatory’ potential.4 Circulating cellular complexes of platelets are often found in the blood stream of patients with inflammatory conditions, such as RA, and it is suggested that platelet-derived microparticles along with other biological agents play a more important role in the development of synovitis than activated platelets themselves.5 Indeed, laboratory studies have demonstrated that platelets exert arthritogenic properties through the activation of the collagen glycoprotein VI receptor and subsequent shedding of microparticles.6

As effector cells derived from megakaryocytes, platelets bear a wide variety of membrane receptors of their precursors, autonomous protein-synthesising platform (messenger RNA) and the granular system of accumulated biologically active compounds (ie, α granules, dense granules, lysosomes) facilitating their involvement in diverse immune reactions. α Granules are especially rich in inflammatory cytokines, vasoactive substances, chemokines and stimulators of platelet aggregation, which are abundantly released upon platelet activation. Biological agents of platelet granules propagate inflammation, increase vascular permeability and destroy cells at inflamed sites. Such processes could be involved in the initiation and propagation of the inflammatory response and tissue destruction both in the rheumatoid joint and the vasculature and merit further investigation in RA. At exactly the opposite end, experimental and clinical studies have shown that some components of autologous platelet-rich plasma, particularly ADP of dense granules, are capable of stimulating proliferation of chondrocytes and deposition of collagen I, thereby repairing damaged cartilage and tendons.7,8 There is, therefore, a distinct possibility of regulating various pathophysiological processes in joints and surrounding tissues by suppressing and activating platelets at different stages of the disease.

A variety of specific markers of platelet activation have been tested across inflammatory rheumatic diseases: platelet count, membrane-bound P-selectin and CD40 ligand (CD40L), β-thromboglobulin, platelet factor 4 (PF4), also known as chemokine (C-X-C motif) ligand 4 (CXCL4), platelet aggregates and platelet–neutrophil complexes.5 Reactive thrombocytopenia with elevation of platelet count has been suggested to be of diagnostic importance in the setting of antineutrophil cytoplasmic antibodies-associated vasculitis.9 Mildly elevated platelet count along with decreased platelet size have been viewed as a reflection of inflammatory megakaryopoeisis and activity of RA,10 while the ratio of platelets to neutrophils and lymphocytes has also been suggested to reflect rheumatoid activity.11 A recently emerged important piece of evidence points to the fact that anticitrullinated protein antibodies (ACPA) directly stimulate the expression of P-selectin on platelets, secretion of soluble CD40L and formation of platelet aggregates.12 With the incremental increase of ACPA preceding clinically manifest RA by months and years, it is possible that insidious seropositivity and increase of C-reactive protein determine platelet activation and involvement from the earliest stages of synovial inflammation onwards.

In the era of biological therapy several lines of evidence suggest that agents inhibiting TNFα and interleukin-6 suppress disease activity and decrease platelet counts in RA.13,14 The effect of biologic disease-modifying antirheumatic drugs (bDMARDs) on platelet counts is not matched by nonbiologic DMARDs, which appear to be less effective towards megakaryopoeisis. The exception is bone marrow suppression and related thrombocytopenia as a rare occurrence of sulfasalazine therapy, which however is no longer a frontline choice in RA. Interestingly, the possible effects of bDMARDs on megakaryopoeisis may differ, with reports suggesting that tocilizumab may drop platelet counts in patients with RA more potently than adalimumab.15 This is another area that requires further investigation, as a potential side effect and also as a possible desirable effect. IL-6 is known as a physiological regulator of megakaryopoeisis acting like thrombopoietin,16,17 and blocking IL-6-related pathways may lead to anti-inflammatory and antithrombotic effects.

The present flow cytometric and electron microscopy study by Manfredi et al1 sheds light on the molecular basis of modulation of platelet activity by inflammatory cytokines and their inhibitors. The authors should be congratulated for their extensive work characterising the effects of recombinant human TNFα and the TNF, infliximab, on platelet-rich plasma and isolated platelets of patients with RA (box 1).

One of the important messages of this study is that TNFα can only block the TNFα-dependent activation pathways of
platelets. Other pathways of platelet activation, particularly those regulated by collagen and ADP, can still contribute to proinflammatory and prothrombotic actions. Although platelet count was not analysed in the current study, together with evidence from other sources, demonstrate clearly that the axis of megakaryopoiesis, circulating platelets and platelet cellular complexes, and its modulation by anti-inflammatory therapies, may be very important in the pathogenic mechanisms of rheumatoid synovitis and related CV comorbidity. Despite the many challenges, it merits much more research attention than it has been receiving thus far.

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