Editorial

A Sticky Story for Signal Transducer and Activator of Transcription 3 in Platelets

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The signal transducer and activator of transcription 3 (STAT3) is a cytoplasmic protein that, on appropriate signaling, translocates to the nucleus and binds DNA response elements of target genes.[1] As a result, STAT3 mediates the transcription of key mediators involved in mitogenesis, cell survival, apoptosis, cell cycle regulation, angiogenesis, and metastasis development.[1,2] STAT3 also regulates the transcription of several genes in megakaryocytes that are required for the formation of platelets (Figure).[3]

Article see p 476

As megakaryocytes form platelets, they transfer STAT3 to proplatelet tips. Consequently, STAT3 is found in platelets that circulate in the bloodstream (Figure). The presence of STAT3 in platelets raises the question of whether it regulates functional responses in platelets or is simply a vestigial remnant of megakaryocytes. An argument for the "leftover without function" hypothesis is the anucleate status of platelets: simply stated, with no nucleus and no nuclear DNA there is no place for STAT3 to stick in platelets. The problem with this argument is that "simple" is no longer a common word used to describe platelets. Moreover, why would platelets expend energy to carry a protein that they do not need, especially since previous studies have shown that STAT3 undergoes signal-dependent phosphorylation in these anucleate cytoplasts?[4] Well, any doubt regarding why STAT3 is present in platelets has been cleared up. Using a combination of pharmacological and genetic based tools, Zhou et al[5] demonstrate that STAT3 affects how platelets stick to one another and extracellular matrices. In addition, the authors put forth a new role for interleukin 6 (IL-6) and its soluble receptor in enhancing platelet aggregation.

A major strength of the group's findings is the plethora of evidence presented to make the story stick from men to mice and then back to men. First, they used 2 different types of STAT3 inhibitors to block collagen- and collagen-related peptide-dependent aggregation, as well as the formation of thrombi to a collagen substrate under flow conditions in human platelets. Neutralization of STAT3 also reduced collagen-dependent induction of P-selectin surface expression. STAT3 inhibitors, however, did not block ATP release nor did they dampen aggregation induced by ADP or a thrombin receptor activating peptide. Second, platelets from mice deficient in STAT3 aggregated poorly, had a low level of P-selectin surface expression and calcium influx in response to collagen, and formed smaller thrombi when exposed to a collagen matrix under arterial flow. The same platelets reacted normally to ADP and thrombin receptor activating peptide. Additional studies led to studies implying that glycoprotein VI platelet (GPVI) is the primary collagen receptor on platelets linked to the STAT3 signaling pathway. Finally, Zhou et al[5] provided the first evidence that the IL-6 signaling complex can influence platelet function. They found that platelets constitutively express glycoprotein 130, which is capable of interacting with exogenous IL-6 and the soluble IL-6 receptor (IL-6R). Together, but not individually, these IL-6 family members induce STAT3 phosphorylation and enhance collagen-dependent platelet aggregation.

A transcription-independent role for STAT3 builds on the growing appreciation that previously characterized transcription factors have diverse, noncanonical functions in platelets.[6] In activated platelets, the nuclear factor-κB family member B cell lymphoma 3 interacts with Fyn-related tyrosine kinases to contract fibrin-rich clots.[7] Nuclear factor-κB itself also has roles in limiting platelet activation,[8] and nuclear factor-κB inhibitors attenuate the formation of lipodia in adherent platelets.[9] Much like STAT3, peroxisome proliferator-activated receptor-γ regulates collagen-dependent platelet aggregation that is driven by GPVI.[10] Ligand-dependent binding of retinoid X receptor also controls GTP-binding protein G_q function and thereby aggregation responses in platelets.[11] Cumulatively, these studies point to the sundry function of proteins that were originally thought to have a sole role in transcription.

One of the most intriguing findings of the work of Zhou et al[5] is the identification of an IL-6 signaling pathway that links inflammation to thrombosis. In response to inflammatory cues, IL-6 is synthesized and released by various types of nucleated cells. IL-6 exerts its activities through 2 molecules, the IL-6R (also known as IL-6Rα) and glycoprotein 130 (also referred to as IL-6Rβ).[12] The IL-6R is either membrane bound or soluble. As its name implies, soluble IL-6R is released into the extracellular milieu where it binds IL-6 and then forms a complex with membranous glycoprotein 130. This unique receptor signaling system, termed "IL-6 *trans*-signaling,"[13] induces cellular activation including STAT3-dependent transcriptional responses. Until now there has been no evidence that IL-6 *trans*-signaling occurs in platelets. Zhou et al[5] demonstrate that, in combination with the soluble IL-6R, IL-6 binds membrane-expressed glycoprotein 130 and primes platelets for collagen-induced cellular activation. This

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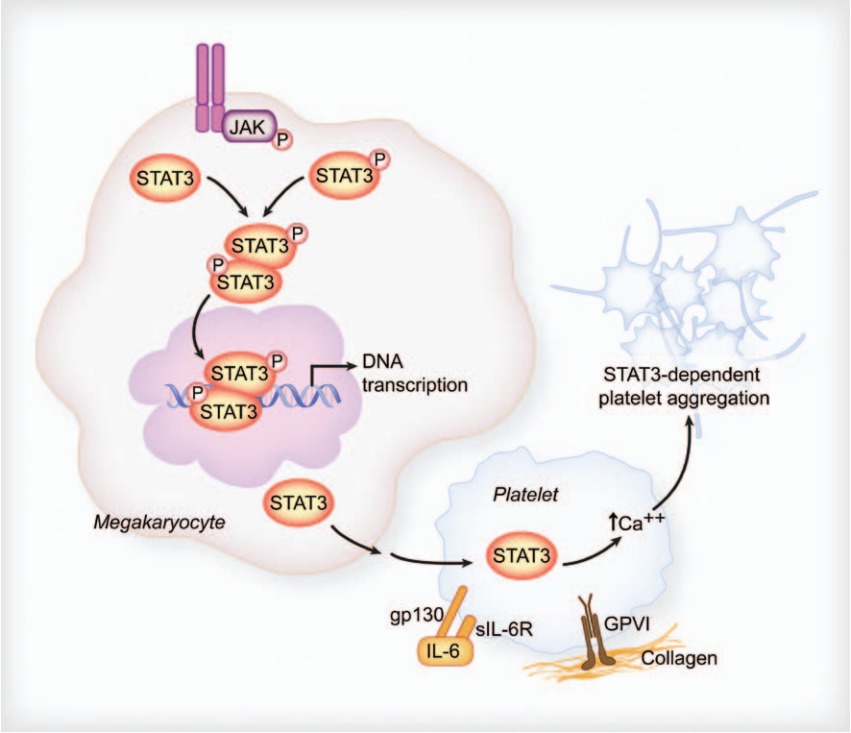

Figure. Schematic representation of traditional and nontraditional roles of signal transducer and activator of transcription 3 (STAT3) in megakaryocytes and platelets, respectively, as described by Zhou et al[5] and reviewed here.

suggests that heightened IL-6 *trans*-signaling in response to inflammation may enhance thrombus formation in a variety of human diseases, such as rheumatoid arthritis, lupus, and sepsis. Conversely, deficiencies in IL-6 production, which have been reported to occur in common variable immune deficiency,[14] may lead to dampened thrombus formation and increased bruising and bleeding that is commonly observed in patients with this syndrome.

Selective inhibition of IL-6 *trans*-signaling has recently received considerable attention for the treatment of cancer, and an IL-6R blocking antibody (tocilizumab) was recently approved for Castelman disease and rheumatoid arthritis (reviewed in References 15 and 16). A STAT3 decoy inhibitor is currently being tested in patients with head and neck cancer, and there is emerging evidence that STAT3 inhibitors may prove useful in treating disorders of cardiac-related inflammation.[15,17] Thus, it will be important to consider off-target inhibition of platelet activity, which may be good or bad, when patients are treated with IL-6 *trans*-signaling and STAT3 inhibitors. Indeed, the authors speculate that inhibition of STAT3 may improve inflammation-induced platelet hyperreactivity and improve the efficacy of aspirin in patients with coronary artery disease. The interplay of IL-6 *trans*-signaling and STAT3 with GPVI will also have to be pondered as the efficacy of GPVI receptor antagonists are screened in the clinic.[18]

Thrombosis is often linked to inflammation, but the reverse has received little attention until Zhou et al[5] unmasked the STAT3 signaling pathway in anucleate platelets.[5] Their results challenge existing paradigms and, in doing so, reveal that we should never underestimate the resolve of platelets to use previously described nuclear-based systems in alternative ways. Identification of a 3-way bridge among IL-6 *trans*-signaling, STAT3, and GPVI that courses to aggregation adds to the fascinating biology of platelets (Figure). It also creates a sticky story for STAT3 in platelets, and potentially the cytoplasm of nucleated cells, with clinical implications for human disease.

Disclosures

None.

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