

Platelet-Derived Interleukin-1 β Fuels the Fire in Blood Vessels in Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the prevalence of autoantibodies in blood, and systemic inflammation affecting multiple organs such as skin, joints, heart, lungs, brain, and kidneys. Given the elevated incidence of cardiovascular diseases in SLE patients (50 times higher risk than healthy individuals)¹ and taking into account the intimate interactions between platelets and the endothelial cells composing blood vessels, Nhek et al² hypothesized that in SLE, platelets could contribute to endothelial dysfunction. They found that platelets were hyper-reactive in SLE and could induce endothelial cell activation through interleukin-1 β (IL-1 β). IL-1 β is a recognized inflammatory cytokine and its presence in blood correlates with increased risk of cardiovascular disease.^{3,4} However, its source(s) remains to be determined. This study suggests that platelets may represent a significant source of IL-1 β in SLE and could contribute to comorbidities associated with this devastating illness.

See accompanying article on page 707

Platelets are small anucleated elements released from the megakaryocytes in the bone marrow and are abundant in blood where they circulate to ensure of the blood vessel integrity.⁵ There is also accumulating evidence suggesting that platelet functions are not restricted to the hemostatic response. Hence, in addition to their set of molecules necessary for the prevention of bleedings, platelets also bear an arsenal of receptors and mediators capable of promoting inflammation.^{6–8} Several studies confirmed that platelets are activated in blood of patients with SLE,^{9,10} and, using a murine model of lupus, it was found that platelets could actively contribute to inflammation in this disease by promoting type 1 interferon production by plasmacytoid dendritic cell.^{9,11}

Cardiovascular diseases are a dominant cause of mortality in adults, and although risks factors such as high blood pressure, cholesterol, obesity, tobacco use, lack of physical activity, and diabetes mellitus are identified, SLE patients have an increased risk of cardiovascular diseases, independently of these traditional risk factors.^{1,12} In their study, Nhek et al²

enrolled 54 well-characterized SLE patients and included 44 healthy controls to assess platelet activation status, with the hypothesis that activated platelets might impact the endothelial cells in SLE. The activation of platelets can promote their interaction with other cells, such as leukocytes and endothelial cells.^{13–15} Consistent with this, the authors found that leukocytes, notably monocytes and neutrophils, were frequently associated with platelets in the blood of SLE patients. Plasma levels of P-selectin and RANTES (regulated on activation, normal T-cell expressed and secreted), molecules abundant in platelets and released on activation, were elevated in SLE and correlated with the severity of disease activity. Interestingly, the authors found that platelets were primed in blood in SLE, because they reacted more efficiently to agonists such as collagen and ADP in aggregation tests in vitro. These observations confirm conclusions made by different groups, that in SLE, platelets circulate in an activated state.

The authors next designed a series of experiments to verify the impact of SLE platelets on endothelial cells. Thrombin-activated platelets triggered expression of mRNA coding for IL-8 and intercellular adhesion molecule 1 by endothelial cells. Furthermore, the authors found that endothelial cells also upregulated the expression of 864 genes, including IL-8 and intercellular adhesion molecule 1, when cocultured with platelets from SLE patients. Conversely, SLE platelets reduced the expression of 552 transcripts, which were found to dampen the proinflammatory role of NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) and endothelial cell activation. Interestingly, sera from SLE patients, but not from healthy controls, promoted the activation of control washed platelets and their adhesion to endothelial cells, which then induced IL-8 and intercellular adhesion molecule 1.

Although platelets express several proinflammatory candidates, including lipid mediators (eg, thromboxane A₂), nucleotides (eg, ADP), S100A8/A9, and damage-associated molecular patterns, such as high-mobility group box 1 and those derived from mitochondria,^{16–18} the blockade of IL-1 β was sufficient to inhibit endothelial cell activation and the adhesion of platelets. In line with these observations, more IL-1 β protein was present in platelets in SLE patients. Together, these data suggest that in SLE, circulatory platelets have an enriched IL-1 β content, which can activate the endothelial cells in the vasculature, thereby promoting platelet attachment to the vessel wall.

How exactly platelets adhere to endothelial cells was not determined in this study, but it strictly required endothelial cell activation by IL-1 β . It might be through P-selectin, exposed on platelets incubated with SLE sera, or even through leukocyte functional molecule 1, which is the counter-receptor of intercellular adhesion molecule 1 and is expressed by

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platelets.¹⁹ Another intriguing observation was the presence of IL-1 β in platelets in SLE. Platelets do not normally contain IL-1 β protein but do bear the necessary mRNA and machinery to produce functional IL-1 β , which was transferred from megakaryocytes during proplatelet formation.²⁰ The authors showed that SLE sera could induce IL-1 β mRNA expression in a megakaryocyte cell line, suggesting that in SLE, megakaryocytes may release platelets enriched in IL-1 β mRNA. The identity of the molecule(s) present in SLE sera capable of activating platelets and megakaryocytes remains unknown. It could be mediated by nucleotide-derived metabolites, which were reported to activate platelets and the levels of which in blood strongly correlates with inflammasome activation and IL-1 β production.³ Because the platelet transcriptional profile is influenced by the type I interferon system, which strongly correlates with vascular diseases in SLE,²¹ we can also speculate that interferogenic immune complexes in sera could mediate these effects.

In the future, it will be interesting to determine whether patients with higher platelet reactivity and IL-1 β content present with increased vascular damage, by reporting Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index and carotid ultrasound plaques and intima-media thickness, for example. Although more studies are still needed to fully understand the mechanisms implicated in endothelial dysfunctions in SLE, this study adds an important piece to the puzzle and suggests that it might be valuable to inhibit platelet activation, or IL-1 β , to reduce the risk of cardiovascular diseases in SLE patients.

Disclosures

None.

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