An oxidase road to platelet adhesion

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Platelet adhesion to collagen via collagen receptors is an important part of thrombosis. In this issue of Blood, Matsuura et al identify collagen receptors as previously unrecognized targets of the extracellular enzyme lysyl oxidase (LOX), the level of which is increased in myeloproliferative neoplasms (MPNs) and other conditions associated with pathological thromboses.1

LOX is a secreted enzyme that stabilizes the extracellular matrix by converting specific lysines to aldehydes, followed by spontaneous crosslinking of these oxidized residues leading to crosslinking of extracellular collagen and elastin.2

Earlier studies showed that excessive LOX expression and activity is associated with pathological bone marrow (BM) fibrosis in mice and humans,3,4 as well as enhanced thrombosis, which is a significant complication in humans and mice with MPN.5,6 Similarly, conditions such as arterial stenosis and chronic kidney disease, which are hallmarkled by increased propensity for thrombosis, also have increased expression of LOX.7,9

Importantly, pharmacologic inhibition of LOX attenuates the fibrotic burden in a mouse model of MPN.3 Using a murine model, the question addressed in this study is whether megakaryocytes (MKs) and platelets can be the source of excess LOX that promotes thrombus formation in MPN.

Matsuura et al from the Ravid laboratory generated a transgenic mouse model (PF4-lox) in which exogenouslox is expressed in MKs and platelets on a wild-type (WT) background to test the direct effect of Lox on this lineage without the compounding influences of pathology.1 They found that mice overexpressing LOX in platelets have more severe thrombosis than normal animals. The authors specifically used PF4-lox mice with LOX activity in the elevated range that occurs in the GATA-1loxlox mouse model of MPN (elevated compared with WT mice). The engineered mice showed a modest increase in MK number and a normal number of platelets. Yet, there was a clear augmentation in thrombus formation following vascular injury in vivo. Exploring underlying mechanisms, they found that LOX-expressing platelets adhere better to collagen, and have greater aggregation response to lower doses of collagen, compared with controls. Enhanced adhesion to collagen was dependent on LOX activity, as shown by in vivo administration of a LOX pharmacologic inhibitor. Using an array of receptor-selective ligands, they found that the collagen receptor integrin α5β1 is affected by LOX. These integrin receptor subunits have just a few highly conserved lysine residues on the extracellular domain, which are likely to be LOX targets.

There are two main novel facets to this study: (1) LOX has never been implicated before in collagen receptor function or in the occurrence of thrombosis; and (2) oxidation of collagen receptors (or associated signaling partners) has not been described previously as a modulator of receptor activity. These findings could potentially lead to identifying collagen receptor lysine residues affected by LOX, or by other oxidative stresses, with lysine being a nucleophilic amino acid and, therefore, vulnerable to modifications. The study lends itself to several lines of new investigation. For example, proteomic approaches could resolve which of the α5β1 collagen receptor subunits is affected, and on which residues, and analysis of MK LOX level and function in murine MPN models might be relevant to adhesion and profibrotic properties of these cells in the BM. Also, analysis of human MPN samples will be important for addressing the application of these findings to human pathology.

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REFERENCES


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