Editorial

New LINE(s) of Evidence for Genetic Regulation of Platelets

Michael Holinstat

Platelets exhibit a complex milieu of signaling pathways that are tightly regulated to allow the platelet to participate in several biological functions in the blood including but not limited to hemostasis and thrombosis.[1] Most cells have the ability to inherently modulate their protein profile and by extension their excitatory or inhibitory activity in part through genetic regulation, including transcription and translation. The platelet, however, being anucleate receives the majority of its translational and post-translational machinery from the megakaryocyte.[2] Recent studies have shown that platelets contain several translational components, including mRNA, microRNA, and initiation and termination factors.[3] These translational components allow the platelet to alter its protein profile on a limited basis which can have far reaching effects on how the platelet functions. In fact, recent work has shown that under certain conditions, platelets can produce cell bodies resembling megakaryocytic proplatelets that are functional and capable of being activated by agonists.[4,5] However, to date, only a limited number of translational control mechanisms have been described in the platelet.

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Although common translational machinery has been described in the platelet, a less common translational regulator is the human transposable element. Only 1 functional autonomous nonlong terminal repeat retrotransposon is known to be expressed in human and that is the LINE-1 (long interspersed nuclear element-1 or L1).[6] This translational element is unique because of the expression in one of its splice variants of a reverse transcriptase domain. This allows LINE-1 to form cDNA from mRNA and exert more control over the gene transcription and protein expression of the cell. Furthermore, reverse transcriptase allows for the generation of intermediates consisting of RNA–DNA hybrids. LINE-1 expression in the platelet may play an important role in platelet reactivity, and understanding its role in the platelet is important because current interventional approaches for viral diseases, including patients with HIV, involves systemic administration of reverse transcriptase inhibitors (Figure).

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Schwertz et al[7] identify the expression of LINE-1 in human platelets for the first time using several confirmatory techniques, including polymerase chain reaction, FISH (fluorescence in situ hybridization), in situ hybridization, and laser capture microscopy. These initial experiments were followed by functional studies showing that the endogenous reverse transcriptase domain of LINE-1 plays an important role in cytoskeletal dynamics and agonist-induced platelet activation both ex vivo and in vivo. Interestingly, the authors were able to convincingly show data supporting an inhibitory role of LINE-1 and endogenous reverse transcriptase in platelets. Inhibition of endogenous reverse transcriptase or LINE-1 resulted in increased platelet activation, integrin activation in the platelet, and proplatelet production. To determine the potential role of LINE-1 and endogenous reverse transcriptase in vivo, nevirapine, a reverse transcriptase inhibitor, was administered to mice, and agonist-induced platelet activation, thrombosis, and death were shown to be increased while the time required for formation of an occlusive clot was decreased. This finding was confirmed ex vivo in platelets from patients with HIV. In these patients, blood treated with reverse transcriptase inhibitors exhibited accelerated agonist-induced platelet activation. This seminal work identifies a critical aspect of platelet regulation not before appreciated and gives significant insight into how therapeutic interventions, previously thought to target nucleated cells, may have untoward effects on the platelet and thrombotic risk in these patients because of expression of LINE-1 and likely other translational and transcriptional regulatory processes. Understanding these mechanisms will enhance our ability to identify potential thrombotic risk as an off-target effect of therapeutic intervention and appreciate the complexity of signaling inherent in the platelet at both the genetic and protein levels.

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Disclosures

None.

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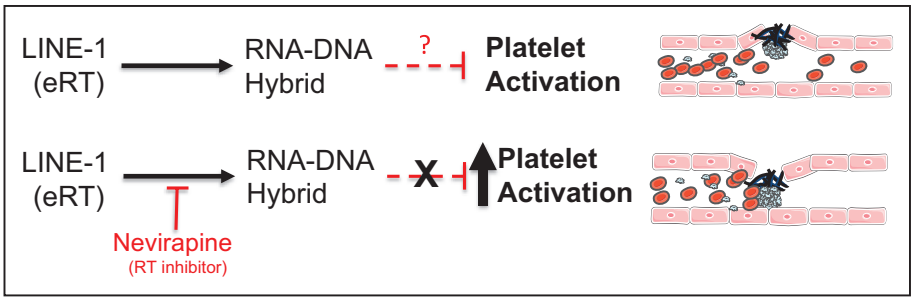

Figure. LINE-1 (long interspersed nuclear element-1; L1) are a primary source of endogenous reverse transcriptase (eRT) activity in human platelets. Expression of LINE-1 in platelets results in RNA–DNA hybrid formation and functions through an as yet undetermined mechanism to limit platelet activation, thrombosis, and vascular injury–related occlusive clot formation. Inhibition of LINE-1 with nevirapine, a reverse transcriptase (RT) inhibitor, used clinically for inhibition of RT in patients with HIV and removes the LINE-1 inhibition of platelets resulting in increased (1) cytoskeletal rearrangement, (2) integrin activation, (3) platelet activation, and (4) occlusive clot formation in vivo.

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