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LETTER TO THE EDITOR

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Thrombopoietin levels in Quebec platelet disorder—Implications for the mechanism of thrombocytopenia

Thrombopoietin (TPO) is the primary regulator of platelet production.[1,2] TPO levels in plasma are increased in disorders that impair megakaryocyte and platelet production, such as aplastic anemia, and are normal in thrombocytopenic disorders that do not reduce the megakaryocyte mass, including those that accelerate platelet clearance.[1,2] We postulated that a detailed analysis of TPO levels in Quebec platelet disorder (QPD) might provide insights into why platelet counts are reduced in this inherited bleeding disorder[3] which is caused by a duplication mutation of *PLAU*, the urokinase plasminogen activator (uPA) gene.[4,5] QPD markedly and selectively increases the production of normal *PLAU* transcripts by the disease chromosome in megakaryocytes but not in leukocytes through unknown mechanisms,[6] and this increases megakaryocyte and platelet uPA levels by more than 100-fold.[7,8] As QPD megakaryocytes and platelets sequester uPA in α-granules,[8] the disorder results in a unique, platelet activation-dependent, gain-of-function defect in fibrinolysis, without systemic fibrinolysis.[9] In QPD, platelet morphology (by light and electron microscopy), size,[3] and dense granule release are normal, and secondary platelet aggregation is absent with epinephrine, with or without reduced maximal aggregation with collagen, adenosine diphosphate, and/or thromboxane analog U46619.[10] Many persons with QPD have thrombocytopenia as platelet counts in this disorder are typically about 50% lower than the platelet counts of unaffected relatives (reported range: ~120-245 × 10^9/L[11]). The reduction in platelet counts in QPD is clinically significant as lower platelet counts are associated with wound healing problems.[11]

To gain insights into the reduced platelet counts in QPD, we evaluated TPO levels and platelet counts with the approval of the Hamilton Integrated Research Ethics Board and the Research Ethics Board of Centre Hospitalier Universitaire Sainte-Justine and written informed consent of blood donors. Platelet-poor plasma for TPO analyses was prepared using EDTA-anticoagulated blood (collected using vacutainers) from QPD (n = 7 representative individuals with the QPD genetic mutation who had often donated samples for research[4-11]) and general population control participants (n = 12). Plasmas were tested using the Quantikine® ELISA Human TPO Immunoassay (R&D Systems, Minneapolis, MN, USA), as recommended, with TPO values below the lowest assay standard (31.3 pg/mL) reported as <31.3 pg/mL.

Although QPD participants had lower platelet counts than control participants (respective medians [ranges]: 143 [116-198] × 10^9/L vs 223 [165-297] × 10^9/L; $P < .01$ based on Mann-Whitney test), all QPD and all but one of the control participants (TPO level: 59 pg/mL) had plasma TPO levels <31.3 pg/mL. Accordingly, all participants had plasma TPO levels within the range of expected results for healthy volunteers, which are typically <31.3 pg/mL but can be as high as 196 pg/mL, according to the ELISA manufacturer.

The reasons for thrombocytopenia in QPD could be complex. TPO cleavage by uPA increases its activity, whereas TPO cleavage by plasmin has the opposite effect.[12] As TPO levels in QPD plasma were <31.3 pg/mL, we were unable to investigate whether QPD causes increased TPO proteolysis. The sequestration of uPA in QPD α-granules (which prevents systemic fibrinolysis)[9] might limit TPO proteolysis by uPA and plasmin in QPD. It is also possible that the increased uPA in QPD megakaryocytes is insufficient to increase TPO effects on megakaryocytes given that there are normal expansion and differentiation of QPD peripheral blood CD34+ stem cells into megakaryocytes in serum-free cultures with added TPO.[8]

While the cause of QPD thrombocytopenia has not been resolved, it is possible that increased plasmin generation is part of the pathogenesis as treatment with fibrinolytic inhibitor drugs, such as tranexamic acid, corrects both the bleeding and wound healing problems of QPD (CPMH and GER, unpublished observations). Most individuals with QPD require only short courses with fibrinolytic inhibitor drugs (eg, 2-10 days) for preventing and treating bleeding (eg, for dental procedures, surgery, complicated childbirth, joint bleeds, and trauma-related bleeding). The possibility that fibrinolytic inhibitor therapy might improve QPD thrombocytopenia led us to examine the platelet count records for 31 individuals with QPD, which included the individuals who donated samples for TPO analysis (n = 10 females, n = 21 males; ages: 4-77 years). The recorded platelet counts for persons with QPD ranged from 92-448 × 10^9/L, after excluding the person whose platelets fell to 19 × 10^9/L during neutropenia unrelated to QPD. Most persons with QPD had fairly stable platelet counts, and while 29% (9/31) had platelet counts below <150 × 10^9/L on the majority of tests, 48% (15/31) had thrombocytopenia documented at least once. A few persons with QPD had ~2.9-fold increases in their platelet counts while on fibrinolytic inhibitor therapy after surgery, and these individuals had the highest recorded QPD platelet counts. As platelet counts normally increase in the postoperative period, more data are needed on QPD platelet counts before, during, and after fibrinolytic inhibitor therapy to determine whether this treatment corrects QPD thrombocytopenia.

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