ATRA-stimulated NB4 cells. Moreover, as opposed to what was observed with NB4 cells, in primary leukemia cells derived from 5 newly diagnosed APL patients, only CCL2 was consistently up-regulated at mRNA and protein levels. Furthermore, increased levels of CCL2, CCL4, CCL7, and CCL24 were found in plasma of an APL patient with DS and not in 2 APL patients without DS. Finally, by adding ATO alone in NB4-cultured cells, only CCL2 and CCL7 were up-regulated more than 5-fold.

These results indicate that CCL2 and CCL7 are elevated in a single patient with DS studied and also in the NB4-cultured cells stimulated with ATRA and/or ATO. However, as only CCL2 was consistently up-regulated by ATRA addition at mRNA and protein levels in the primary leukemia cells derived from 5 newly diagnosed APL patients, it is this chemokine that may play an important role in the development of DS. CCL2 or monocyte chemoattractant protein 1 (MCP-1) is a potent agonist for monocytes, dendritic cells, memory T cells, and basophils.4 Moreover, when secreted from alveolar epithelial cells, it has an important role in the cell-to-cell interaction involved in the chemotactic transmigration of differentiated APL leukemia cells toward alveolar epithelial cells.5 Previous studies have indicated that IL-83 and adhesion molecules5 may also have a role in DS. Because dexamethasone does not efficiently reduce leukemic chemokine production and pulmonary infiltration of leukemic cells may induce an uncontrollable hyperinflammatory reaction in the lung, the therapeutic use of chemokine-receptor antagonists may be a more efficient approach than the use of steroids to treat DS in APL. Among these chemokine-receptor antagonists, CCR2 (receptor for CCL2) and CXCR1 (receptor for IL-8) antagonists, used in phase 1 and 2 studies for treating rheumatoid arthritis and chronic obstructive pulmonary disease, respectively, are the most interesting. Despite the strength of in vitro experimental data, a potential limitation of this paper is that the studies are limited to only one APL patient with DS. Therefore, more APL patients with DS should be studied to evaluate more precisely the role of these chemokines in the pathophysiology of DS.

As in the setting of human migration,6 the chemokine and chemokine receptor production in APL treated with differentiation therapy may act as push (chemokine) and pull factors (chemokine receptors) for migration of leukemic cells from the bloodstream to the tissues, contributing to the development of DS. Moreover, the increased levels of CCL2 during differentiation therapy may become a marker of DS.

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REFERENCES


Robert Flaimenhaft HARVARD MEDICAL SCHOOL

In this issue of Blood, Kunert and colleagues have characterized mice lacking RanBP10, demonstrating an essential role for this β1-tubulin binding protein in platelet microtubule organization. Although not thrombocytopenic, RanBP10−/− mice have a bleeding diathesis and abnormal platelet aggregation and secretion.

Megakaryocytes are charged with the task of generating 0.4 to 2 × 10¹¹ platelets each day. They assemble platelets along pseudopodial extensions termed proplatelets, which are generated by the outflow and evagination of an extensive internal membrane system.1 Several lines of evidence indicate that microtubules drive proplatelet development and form the critical scaffold required for faithful production of platelets. Dynamic microtubule assembly must be tightly controlled to enable the orderly production of nearly identical platelets. Yet the mechanisms that organize microtubules during proplatelet formation are not well understood.

β1-Tubulin is the dominant structural constituent of platelet microtubules. To address the question of how β1-tubulin polymerization is regulated during proplatelet formation, Schulze et al previously used a 2-hybrid system to identify proteins that interact with β1-tubulin.2 RanBP10, which also binds the GTPase Ran, was identified. This was a fascinating result considering that Ran orchestrates mitotic spindle formation,3 another process characterized by a delicate and deliberate dance of microtubules. Further studies showed that RanBP10 serves as a guanine nucleotide exchange factor (GEF) for Ran.2 However, these studies did not directly address whether RanBP10 is important for platelet function.

Schulze’s group has now generated a RanBP10-deficient mouse to determine the role of this binding protein in platelet morphogenesis and function.4 Nearly half of all megakaryocytes isolated from these mice demonstrated shortened, discontinuous microtubulin filaments. Proplatelet formation in RanBP10−/− megakaryocytes cultured in vitro was slightly impaired. This minor defect was compensated in vivo, because RanBP10−/− mice had normal platelet counts. However, electron microscopy and quantitative analysis of the length–versus–width ratio demonstrated that these platelets were more spherical than wild-type platelets. Numbers of microtubule filaments, which vary from 8 to 12 in wild-type platelets, varied from 5 to 26 in RanBP10−/− platelets. These microtubule bundles were disorganized and did not demonstrate the typical cortical localization, giving RanBP10−/− platelets an abnormal morphology. These results showed that RanBP10 functions to prevent platelet anisocytosis.
The investigators next evaluated the effect of RanBP10 deficiency on platelet function. In tail clip studies, RanBP10−/− mice demonstrated increased bleeding times compared with controls. Further evaluation demonstrated that granule secretion was defective. Activation-dependent surface expression of P-selectin and CD63 as well as release of platelet factor-4 were reduced in RanBP10−/− platelets, despite normal granule morphology and content. Platelet aggregation to submaximal doses of thrombin or collagen, but not ADP, was diminished. This observation was consistent with a defect in dense granule release, which would impair responses to submaximal doses of thrombin and collagen, but not responses to ADP.

Patients with mutations in TUBB1 (which encodes for β1-tubulin),5 mice lacking β1-tubulin,6 and mice lacking RanBP104 all have abnormal platelet microtubules and a bleeding tendency. RanBP10−/− mice are unique within this group because they are not thrombocytopenic and still bleed excessively. It remains unclear whether enhanced bleeding results primarily from the defect in platelet granule secretion in RanBP10−/− mice. Furthermore, whether impaired granule secretion results from inhibition by abnormal microtubule structures or impairment of marginal band contraction during platelet activation remains undetermined. In either case, characterization of RanBP10−/− mice indicates that when it comes to hemostasis, it may be detrimental to have platelets that are out of shape.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Getting in shape with RanBP10

Robert Flaumenhaft