To the editor:

LAD III versus LAD I variant

In a recent issue of Blood,1 Kuijpers et al described 9 patients, all from the Anatolia region in Turkey, who suffered from recurrent infections, leukocytosis, and severe bleeding tendency related to abnormal properties of platelet and leukocyte integrins. The syndrome is associated with a defect in granulocyte NADPH oxidase activity triggered by unopsonized zymosan. The authors designated this syndrome leukocyte adhesion deficiency (LAD)-I/variant.

We have previously described an Israeli patient with similar clinical features. We named the human genetic deficiency LAD-III, distinct from LAD-I.2 Whereas LAD-I is a genetic defect in β2 integrin expression or function, LAD-III leukocytes express intact integrins with impaired ability to generate high avidity to their endothelial ligands at vascular endothelial contacts in response to rapid endothelial chemoattractant signals. Notably, Rap-1 activation in the LAD-III lymphoblasts we have characterized was markedly defective in spite of normal Rap-1 expression. In contrast, the Kuijpers studies did not detect any abnormalities in leukocyte Rap-1 and Rap-2 expression as well as in the expression of major Rap regulatory molecules.

Recently, we studied 2 new patients, also from the Anatolia area in Turkey, with similar clinical findings to those described in the Kuijpers study.3 We have been able to show that 4 major leukocyte and platelet integrins from the β1, β2, and β3 subfamilies were severely defective in their ability to become activated upon chemoattractant stimulation. Furthermore, both patients were found homozygous for a splice junction mutation in their CalDAG-GEF1 gene, one of several Rap guanine-nucleotide exchange factors (GEFs).4 Both mRNA and protein levels of this GEF were diminished in LAD-III hematopoietic cells, including platelets, neutrophils, and lymphocytes.

Although the patients described by Kuijpers et al were not analyzed for reduced expression and function of this specific GEF or any other Rap GEFs,1 in light of the growing evidence that Rap-1 is a key regulator of integrin adhesiveness,5 it is very likely that these patients and others with combined integrin activation defects in leukocytes and platelets share different degrees of Rap-1–activation defects. We thus believe that genes encoding this or related GEFs for leukocyte and platelet Rap GTPases are likely to cluster under this severe syndrome. A further support for the role of CalDAG-GEF1 in particular and of Rap-1 activity in general as the primary defect in LAD-III has been provided by 2 murine studies by Crittenden et al6 and Bergmeier et al,7 which demonstrated impaired integrin activation in both platelets and neutrophils derived from CalDAG-GEF1 knockout mice. The Bergmeier paper even stated in its title that CalDAG-GEF1 knockout mice represent a model for LAD-III.7

Whether the molecular pathway defective in this new group of patients are associated with identical Rap-1 effectors or not, we strongly feel that patients with combined integrin activation deficiencies rather than integrin expression deficiencies should be collectively termed LAD-III to avoid confusion with the LAD-I syndrome. LAD-I variant, a terminology used by Kuijpers et al, should be restricted, in our opinion, to rare mutations in the β2 integrin subunit CD18 with retained expression of this integrin subfamily but impaired functions.8 LAD-III should be ascribed to any defect in leukocyte integrin activation that is not the result of an aberrant integrin expression or structure. Although the defects in integrin activation culminating in LAD-III are not restricted solely to leukocyte integrins, as they are shared by the main platelet integrin GpIibβ3, this nomenclature was adopted by the International Union of Immunological Societies Primary Immunodeficiency Diseases classification Committee in 2006.9

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Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References

Response:

Adherence to the LAD variant form

The leukocyte adhesion deficiency type-I (LAD-1)/variant syndrome was coined in 1997.1 At the time, we designated the constellation of clinical symptoms and some laboratory findings a separate entity, and since then some 15 additional patients with this syndrome have been found. As described in our recent paper in Blood,7 the syndrome can be discriminated by increased levels of...
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