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The role of integrins in pathophysiology of myeloproliferative neoplasms

JAK2-V617F-positive chronic myeloproliferative neoplasia (CMN) commonly displays dysfunction of integrins and adhesion molecules expressed on platelets, erythrocytes, and leukocytes. However, the mechanism by which the two major leukocyte integrin chains, β1 and β2, may contribute to CMN pathophysiology remained unclear. β1 (α4β1; VLA-4) and β2 (αLβ2; LFA-1) integrins are essential regulators for attachment of leukocytes to endothelial cells.
Recently, we have shown enhanced adhesion of granulocytes from mice with JAK2-V617F knock-in (JAK2+/VF mice) and from MPN patients to vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1-coated (ICAM-1-coated) surfaces. Soluble VCAM-1 and ICAM-1 ligand binding assays revealed increased affinity of β1 and β2 integrins for their respective ligands. For β1 integrins, this correlated with a structural change from the low- to the high-affinity conformation induced by JAK2-V617F. JAK2-V617F triggered constitutive activation of the integrin inside-out signaling molecule Rap1, resulting in translocation toward the cell membrane. Employing a venous thrombosis model, we demonstrated that neutralizing anti-VLA-4 and anti-β2 integrin antibodies suppress pathologic thrombosis as observed in JAK2+/VF mice. In addition, aberrant homing of JAK2+/VF leukocytes to the spleen was inhibited by neutralizing anti-β2 antibodies and by pharmacologic inhibition of Rap1. Thus, our findings identified cross-talk between JAK2-V617F and integrin activation promoting pathologic thrombosis and abnormal trafficking of leukocytes to the spleen.
Further, integrin stimulation via the adhesion molecules VCAM-1/ICAM-1 activated integrin outside-in signaling including FAK, SYK, NFκB, and JNK. This induced strong mRNA expression of IL-1α, IL-1β, IL-6, TNF and CXCL10. In myeloid 32D cells, the presence of the JAK2-V617F mutation further increased VCAM-1/ICAM-1-induced mRNA and protein levels of IL-1α and IL-1β, and active caspase 1 expression. In primary mouse granulocytes, integrin stimulation resulted in an activated mRNA signature of inflammatory cytokines.
Utilizing the Jak2-V617F knock-in mouse model, we also investigated the role of β1- and β2-integrins in regulating spleen volume and spleen weight. The response to neutralizing antibodies against VLA-4 and the β2-integrin chain, as well as to isotype controls, was evaluated by serial intraindividual magnetic resonance imaging, by assessment of spleen weight and by analysis of the cellular composition of spleens. Short-term anti-VLA-4/β2-integrin treatment (applied on day 1 and evaluated at day 8) significantly reduced the spleen volume by 30% compared with the immunoglobulin G (IgG) control. At the cellular level, anti-integrin treatment led to a substantial 30% decrease in erythroblast counts and a 23% reduction in basophilic erythroblasts within the spleen, as compared with the isotype control. Furthermore, immunohistochemistry analysis of spleen sections revealed that CD71 (= Transferrin receptor protein 1) expression in spleen remained largely unchanged, whereas there was a clear reduction in Ter119 expression upon anti-integrin treatment. These data suggest that the substantial decrease in erythroblasts following anti-integrin treatment is a primary

factor contributing to the overall reduction in spleen size. To study the spleen architecture, multiepitope ligand cartography (MELC) analysis of spleen sections was applied. This demonstrated that the spatial distribution of the marginal zone, red pulp, and white pulp remained unaltered upon anti-integrin treatment in JAK2-V617F knock-in mice.

In conclusion, our data show a previously unrecognized role of the β1-integrin VLA-4 and of β2-integrin chains in development of JAK2-V617F induced venous thrombosis, in induction of inflammatory cytokines in MPN and in extramedullary erythropoiesis of the spleen in JAK2-V617F-induced disease.

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