Oncogenic JAK2V617F requires an intact SH2-like domain for constitutive activation and induction of a myeloproliferative disease in mice.

The oncogenic JAK2V617F mutation is found in myeloproliferative neoplasms (MPNs) and is believed to be critical for leukemogenesis. Here we show that JAK2V617F requires an intact SH2 domain for constitutive activation of downstream signaling pathways. In addition, there is a strict requirement of cytokine receptor expression for the activation of this oncogene. Further analysis showed that the SH2 domain mutation did not interfere with JAK2 membrane distribution. However, coimmunoprecipitated experiments revealed a role for the SH2 domain in the aggregation and cross-phosphorylation of JAK2V617F at the cell membrane. Forced overexpression of cytokine receptors could rescue the JAK2V617F SH2 mutant supporting a critical role of JAK2V617F abundance for constitutive activation. However, under physiologic cytokine receptor expression the SH2 domain is absolutely necessary for oncogenic JAK2V617F activation. This is demonstrated in a bone marrow transplantation model, in which an intact SH2 domain in JAK2V617F is required for the induction of an MPN-like disease. Thus, our results points to an indispensable role of the SH2 domain in JAK2V617F-induced MPNs.