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Comment on Melzner et al, page 2535

Holes in SOCS in primary mediastinal large B-cell lymphoma

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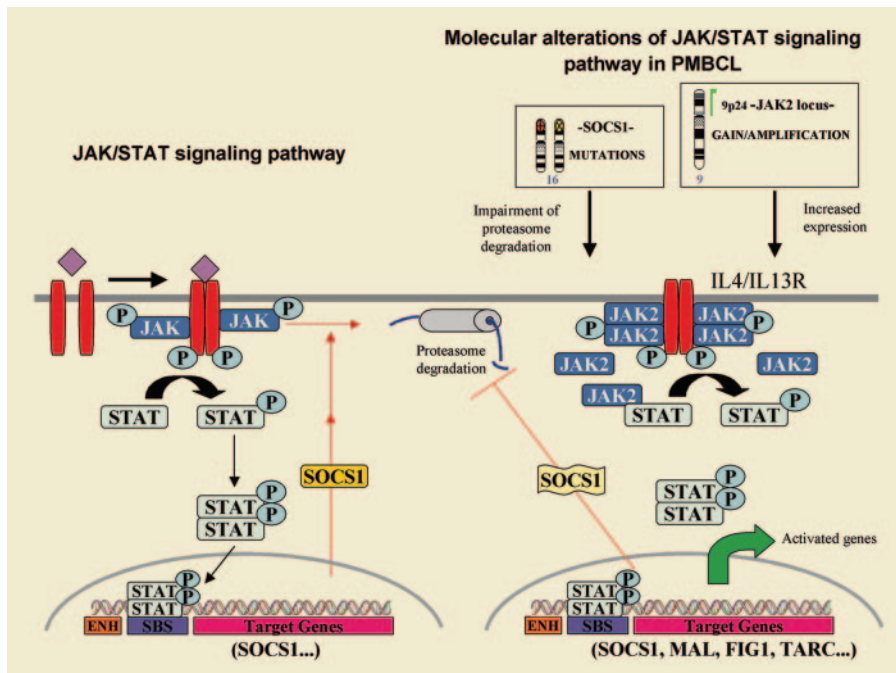
Primary mediastinal large B-cell lymphomas have frequent inactivating mutations of *SOCS1* that impair JAK2 degradation and in turn maintain a constitutive activation of the JAK2/STAT pathway in these lymphomas.

Primarily mediastinal large B-cell lymphoma (PMBL) is an aggressive lymphoid neoplasm thought to arise in thymic B cells that typically presents in young women as a bulky mediastinal mass. PMBL is characterized by a diffuse proliferation of large B cells, often with clear cytoplasm, low or negative immunoglobulin, and HLA class I and II expression, and is associated with a variable degree of sclerosis. These tumors often carry overrepresentation of the chromosomal region

9p24 containing Janus kinase 2 (*JAK2*).¹ JAK tyrosine kinases, activated by cytokines, phosphorylate signal transducers and activators of transcription (STATs), which subsequently dimerize and translocate into the nucleus, promoting gene transcription (see figure). Transcriptional analyses of PMBL have detected a marked overexpression of several elements in the interleukin-4 (IL-4)/IL-13 pathway, including the receptor interleukin-13 receptor alpha-1 (IL-13R α 1), JAK2 and STAT, and

several downstream target genes, suggesting that this pathway may play an important role in the pathogenesis of these tumors.^{2,3} Moreover, a recent study revealed constitutive activation of STAT6 in PMBL associated with *JAK2* gene amplification, overexpression, and protein hyperphosphorylation.⁴

In this issue of *Blood*, Melzner and colleagues provide exciting new insights into JAK2 signaling in PMBL. The authors were intrigued by the fact that the Hodgkin lymphoma cell line L428, also carrying *JAK2* gene amplification and overexpression, showed virtually no phosphorylation of JAK2 and STAT proteins, in contrast to the PMBL cell line MedB-1. In addition, JAK2 protein degradation in MedB-1 seemed delayed, whereas JAK2 half-life in the L428 cell line was much shorter and similar to the turnover observed in physiologic conditions. Searching for possible alterations in the mechanisms regulating JAK2 degradation, the authors detected biallelic inactivating mutations of the suppressor of cytokine signaling 1 (*SOCS1*) in MedB-1 that were not present in the germ line of the original patient. *SOCS1* is a transcriptional target of STAT that inhibits JAK2 signaling by mediating its proteasome degradation (see figure). The functional role of these mutations was confirmed by transfection of wild-type *SOCS1*, which reduced the proliferation rate of the cells and the levels of phosphorylated JAK2 and STAT. In addition, *SOCS1*-inactivating mutations were also found in 9 of 20 primary PMBL cases, indicating that they represent a frequent molecular aberration in these tumors. Further studies should clarify the downstream genes deregulated by these alterations. Although Melzner et al show the transcriptional modulation of cyclin D1 by JAK2, its role in PMBL is questionable since cyclin D1 mRNA up-regulation does not always translate into protein⁵ and, in addition, cyclin D1 is not usually expressed in B lymphocytes or B-cell lymphomas other than mantle cell lymphoma.⁶ It is noteworthy that PMBL appears to carry 2 putative oncogenic alterations targeting the same signaling pathway, namely *JAK2* amplification and *SOCS1*-inactivating mutations (see figure). Intriguingly, these 2 alterations do not seem to be mutually exclusive, since almost all primary tumors with *SOCS1* mutations also carry gains of chromosome 9 and, therefore, presumably *JAK2*



The JAK/STAT signaling pathway and its main oncogenic alterations in primary mediastinal large B-cell lymphoma. On the left, the JAK tyrosine kinases are activated by cytokines and phosphorylate the signal transducers and activators of transcription (STATs), which subsequently dimerize and translocate into the nucleus where they promote the transcription of target genes. One of these genes is the suppressor of cytokine signaling 1 (*SOCS1*) that inhibits the pathway in an autoregulatory loop by binding to the phosphorylated JAK and promoting its degradation through the proteasome pathway. On the right, PMBL carries 2 putative oncogenic alterations in the JAK2/STAT pathway. *JAK2* is amplified and overexpressed and the protein is phosphorylated. Prolonged JAK2 half-life is sustained by *SOCS1* mutations. Expression profiling of PMBL has detected overexpression of the IL-4/IL-13 receptor, JAK2 and STAT, and several target genes of this pathway.

gains or amplifications. These findings may suggest that the alterations have a synergistic effect or, given the role of SOCS1 in maintaining JAK2 activation, 9p gains may be selected for the presence of additional targets such as *PDL2*, usually coamplified and overexpressed with JAK2 in PMBL.²

I thank Itziar Salaverria and Lluís Hernández for their collaboration in the design of the figure. ■

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IMMUNOBIOLOGY

Comment on Piccio et al, page 2421

CD47 and SIRPs: new openings

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In the present issue of *Blood*, Piccio and colleagues report that a member of the signal-regulatory protein (SIRP) family, SIRPβ2, is expressed by T cells, binds to CD47, and costimulates T-cell proliferation.

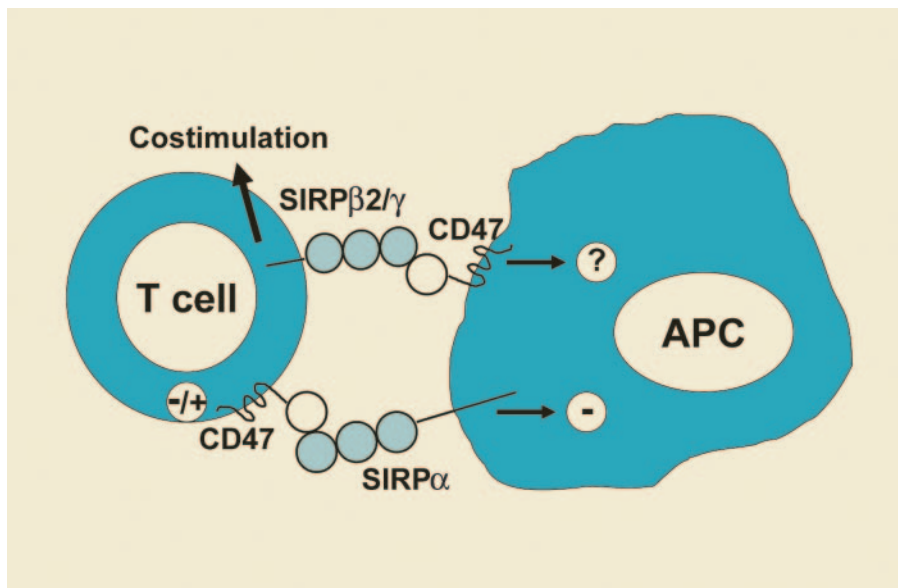
Within the SIRP family of cell-surface glycoproteins, SIRPα and SIRPβ1 have hitherto been identified and studied. SIRPα is highly expressed by myeloid cells and neurons, but expression has also been

found on endothelial cells and a subpopulation of B cells. In myeloid cells, SIRPα has been reported to inhibit phagocytosis and cytokine production when ligated by its ubiquitously expressed cell-surface ligand CD47, a function

mediated by the cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs) of SIRPα.^{1,2} The CD47-SIRPα interaction can also support cell-cell adhesion and cell migration. SIRPβ1, on the other hand, does not have any intracellular signaling motifs of its own, but functions by signaling through recruitment of the adaptor protein DAP12, resulting in stimulation of myeloid cellular functions.³ In contrast to SIRPα, SIRPβ1 does not seem to bind CD47.⁴

The present report on SIRPβ2 significantly extends the understanding of this family of receptors, showing that SIRPβ2, in contrast to SIRPα and SIRPβ1, is not expressed by myeloid cells, but rather by T cells and activated natural killer (NK) cells. Similar to SIRPα, SIRPβ2 binds CD47 on other cells, in this case antigen-presenting cells (APCs). However, the CD47 binding affinity is lower for SIRPβ2 than that for SIRPα. The cytoplasmic domain of SIRPβ2 does not have ITIM motifs or the capacity to bind DAP12. Instead, the authors suggest that the SIRPβ2-CD47 interaction may function to strengthen the T-cell-APC binding, thereby supporting T-cell activation. These data are supported by a recent report, where the SIRPβ2 protein was referred to as SIRPγ, and shown to bind CD47.⁵ That study showed that, by binding to CD47, both SIRPβ2/SIRPγ and SIRPα fusion proteins could induce CD47-dependent apoptosis in CD47-expressing cells.⁵

The present findings raise new, interesting questions about the ability of CD47 to regulate immune reactions by binding to SIRPα and SIRPβ2. Although the APCs in the present study were B cells, which may not express SIRPα, other important APCs such as dendritic cells and macrophages express this receptor. Bidirectional signaling following binding of CD47 on the T cell to SIRPα on the APC was reported to inhibit both T-cell and APC activation.² However, it has also been shown that this interaction might have the opposite effect, resulting in costimulation of T-cell activation.^{1,4} Since the CD47-SIRPα interaction could theoretically operate in parallel with the SIRPβ2-CD47 interaction reported by Piccio et al (see figure), further investigations are needed to understand how these interactions can regulate T cells and APCs in various settings of immune activation. ■



Possible effects of dual interactions between CD47-SIRPα and CD47-SIRPβ2 upon contact between T cells and APCs.