Increased expression or activity of PTPN22 may compromise negative selection of autoreactive CLL cells

The finding of Hebbring et al that the PTPN22 R620W autoimmune risk allele is present at a higher frequency in chronic lymphocytic leukemia (CLL) patients originating from northern/western Europe than in matched controls is very interesting and provides further support to the recent findings of Negro et al suggesting an important role for PTPN22 in the pathogenesis of CLL.2

The study by Negro et al investigated the expression of PTPN22 in a large series of CLL patients from Italy, where the PTPN22 R620W autoimmune risk allele is relatively infrequent, and showed that PTPN22 is markedly overexpressed in the majority of investigated CLL samples.2 Additional experiments showed that overexpression of PTPN22 attenuates BCR signals that can potentially induce leukemic cell apoptosis while simultaneously increasing the activity of the AKT kinase, a key survival signaling molecule in CLL cells. This selective uncoupling of AKT from downstream proapoptotic BCR pathways was shown to protect CLL cells from activation-induced cell death. Overall, these data suggested that the purpose of PTPN22 overexpression in CLL could be to protect the malignant B cells, which frequently express autoreactive BCRs, from immunologic tolerance mechanisms that eliminate autoreactive lymphocytes.

A similar mechanism is believed to be responsible for the increased risk of autoimmune disease in subjects carrying the PTPN22 R620W variant interferes with the removal of developing autoreactive B cells in humans. J Clin Invest. 2011;121(9):3635-3644.


Response

References


increased expression and increased activity of PTPN22 could play a role in the pathogenesis of CLL. It will be interesting to investigate in future studies whether these 2 mechanisms operate in the same or different patients. Given the possibility of targeting PTPN22 or PTPN22-regulated pathways, this issue could be of considerable importance.

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

To the editor:

CLL B-cell receptors can recognize themselves: alternative epitopes and structural clues for autostimulatory mechanisms in CLL

Chronic lymphocytic leukemia (CLL) may be driven by antigen recognition through the B-cell receptor (BCR). A recent paper in Nature suggested a new mechanism for such antigenic drive by functionally characterizing an epitope previously identified by our group as being recognized by virtually all CLL BCRs within a large cohort of CLL patients. This epitope has now been shown to be part of the CLL BCR itself, thus conferring apparently autonomous signaling of BCRs within the cell membrane that may promote growth and survival of the leukemic cell. This provides an entirely new view on CLL pathobiology and its mechanism of disease that appears to apply to the majority of CLL patients.

We describe herein an additional epitope involved in self-recognition of CLL BCRs. We screened random phage display peptide libraries for peptides specifically binding to the CLL BCR (expressed as a Fab fragment) of a randomly chosen patient (Fab007). We identified peptides mimicking the epitope recognized by Fab007 and validated their strong binding to this BCR (data not shown). The consensus amino acid sequence of this epitope (YYC) is homologous to Ig heavy and light chains of different gene families used by Igs of the IgG, IgM, IgA, IgE, and IgD isotype, including the respective CLL Fab007 itself (data not shown). Binding of the CLL Fab007 to the Fab part of Igs was verified in a protein array (Figure 1A) and in ELISAs (Figure 1B). Further binding assays indicated that CLL Fab007 recognizes itself and other CLL BCRs even in patients (eg, CLL Fab005) in whom the recently described epitope VRQ is not present (Figure 1C). A large binding study on primary CLL samples indicated that approximately 50% of CLL cases interact with the YYC motif, most of them showing also considerable reactivity with the VRQ motif, suggesting redundant recognition of alternative epitopes. Interestingly, our new epitope, which is located in framework region 3 of the variable part of Igs, is sterically adjacent and builds a structural continuum with the VRQ epitope located in framework region 2 that was recently suggested as driving autonomous BCR signaling in most CLL patients (Figure 1D bottom right panel). This remarkable colocalization of different epitopes mediating self-recognition of CLL BCRs may explain how autonomous signaling can occur even at a single-cell level (Figure 1D blue circles) and not just in the context of 1 CLL cell recognizing receptors in adjacent cells (Figure 1D red circles). This is because the region containing both described epitopes is (1) structurally exposed on the surface of the protein and (2) approximately the same distance from the cell surface as the CDR3 region mediating this autorecognition (Figure 1D). This allows interaction of adjacent BCRs within the membrane of the same CLL cell. Our data support the recently established theory of autostimulatory mechanisms in CLL pathobiology and point out redundant recognition profiles and structural explanations that provide the basis for self-recognition of the BCR and self-antigen binding despite the low-affinity typically attributed to CLL BCRs.

References

Response: increased expression or activity of PTPN22 may compromise negative selection of autoreactive CLL cells

Dimitar G. Efremov