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Marginal zone B-cell dysfunction in ALPS

Joao Bosco Oliveira  INSTITUTO DE MEDICINA INTEGRAL PROFESSOR FERNANDO FIGUEIRA

In this issue of Blood, Neven et al report that patients with autoimmune lymphoproliferative syndrome (ALPS) have poor production of antipolysaccharide immunoglobulin (Ig) M antibodies and an elevated risk of pneumococcal sepsis and demonstrate that this is caused by infiltration and disorganization of the splenic marginal zone by the prototypical double-negative T cells.1

ALPS is caused by genetic defects that prevent appropriate lymphocyte cell death.2,3 Most patients harbor mutations in the FAS (TNFRSF6) death receptor gene and present with the predictable consequences of abnormal lymphocyte removal: chronic splenomegaly, lymphadenopathy, autoimmunity, and increased risk of lymphomas.4,5

Although under normal conditions these patients can handle perfectly well infections by viral, fungal, and bacterial agents, they seem to be exceedingly sensitive to spleen removal.

Sepsis by encapsulated bacteria is a well-known complication after splenectomy or during functional or congenital asplenia, but splenectomized ALPS patients have even higher complication rates compared with these populations.1,6,7 In fact, the rate of invasive bacterial infections after splenectomy in ALPS reported here and in a recent publication by the National Institutes of Health ALPS group was as high as 30% and 50%, respectively.1,6

Currently, postsplenectomy sepsis is the main cause of death in ALPS and not lymphoma development.6,6

In their article, Neven et al provide a plausible explanation for these findings and incriminate a cell population typically seen in ALPS: the TCRβ+CD4+CD8-T cells, also termed double-negative T cells (DN-Ts). They report that DN-Ts infiltrate and disorganize the splenic marginal zone (MZ) during periods of disease activity, leading to abnormal MZ B-cell function.

The splenic MZ is a specialized area at the interface between the circulation and the immune system, thought to be a prime site for the generation of first-line low-avidity IgM antibodies against blood-borne pathogens.8 These antibodies are produced by local MZ B cells, which in humans have a IgMhiIgDlowCD1c+CD21bCID27+ phenotype and seem to be particularly important for mounting T-cell independent anti-polysaccharide antigen responses.8

However, for their proper function, MZ B cells have to be correctly placed within the MZ, as antigens entering the spleen through the perifollicular zone are trapped by neutrophil extracellular trap-like structures emanating from unusual B-cell helper neutrophils inside the MZ.8,9 The MZ B cells are then exposed to the trapped antigen and initiate antibody production locally, mostly IgM but also IgG or IgA.9

Neven et al demonstrate that the spleen MZ in ALPS patients with active disease is packed with DN-Ts, resulting in a paucity of MZ B cells in situ and in the peripheral blood. They go 1 step further by demonstrating that DN-Ts seem to be attracted to and retained within the MZ by the interaction between their αβ β integrin and a thick layer of MAdCAM-1 expressed by MZ stromal cells. This disruption of the normal MZ B-cell responses seems to result in a mild B-cell immunodeficiency that is aggravated by the removal of the spleen. These data could also explain findings of low numbers of circulating memory and MZ-like B cells and reduced serum IgM levels occasionally seen in ALPS patients with active disease.1

Although not explored here, it is also plausible that the susceptibility of ALPS patients to pneumococcal sepsis after splenectomy may be further enhanced by DN-T infiltration into additional functional reserves of MZ B cells in humans, such as

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lymph nodes, tonsils, and intestinal Peyer’s patches. 

In addition to shedding light into the pathogenesis of the B-cell defects in ALPS, the data from Neven et al further strengthen the arguments against the removal of the spleen for the treatment of the autoimmune cytopenias seen in this disorder. Alternatives such as mycophenolate mofetil and sirolimus have recently been used with great success for disease control and are viable alternatives to the deadly splenectomy.

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B-cell development: COX-1 joins the game

Cosima T. Baldari  UNIVERSITY OF SIENA

In this issue of Blood, Yang et al contribute to fill in the gap of our understanding of cyclooxygenases (COXs) in adaptive immunity by identifying COX-1 as a central player in B-cell development.1

COXs, which catalyze the rate-limiting step in the biosynthesis of prostaglandins (PGs) and thromboxanes (TXs), are among the most popular molecules in the biomedical literature, with close to 30 000 references in PubMed since 1975, when the biological activities of these lipids in inflammation and coagulation were first identified. The seminal discovery that COX exists as 2 functionally different isozymes, COX-1 and COX-2, implicated in tissue homeostasis and inflammation, respectively, provided an explanation to the adverse side effects of aspirin on the gastric mucosa, setting the foundations for the development of nonsteroidal anti-inflammatory drugs selectively targeting COX-2.2 This finding, however, faced the scientific community with the difficult challenge of elucidating the mechanisms by which COX-1 and COX-2 play different roles using the same toolbox of lipid mediators, which is confounded by accumulating evidence that the homeostatic vs disease-related function of the 2 enzymes is not as black and white as initially inferred from the effects elicited by their pharmacological blockade.3 Moreover, the widespread expression of COX-1 poses a limit to a full understanding of the growing array of biological functions subserved by this enzyme. The report by Yang et al brings us a step closer to this important objective by implicating COX-1 in the pathway that regulates B-cell development in the bone marrow (BM), on which the ability of the organism to raise an adaptive immune response to pathogens crucially depends.

Although PGs have long been known to suppress T- and B-cell activation in vitro,4 the role of COX-1 in lymphocyte development, activation, and differentiation has been to date largely limited to the T-cell compartment. COX-1 has been shown to participate in thymocyte development, promoting the prostaglandin E2 (PG2)–dependent transition from the double negative (CD4−CD8−) to the double positive (CD4+CD8+) stage.4 At nonimmunosuppressive concentrations, PG2 also modulates the differentiation of CD4+ T cells in the periphery, impacting on the T-helper (Th)1/Th2 balance and promoting their polarization to Th17 effectors.5 The relevance of these activities to diseases such as allergic asthma and inflammatory bowel disease has been established with mice lacking the main T-cell PG2 receptors EP2 and EP4.6,7 As with T cells, PG2 affects peripheral B-cell differentiation, promoting their maturation to immunoglobulin (Ig)E-secreting cells7 and participating in interleukin (IL)-21–dependent B-cell death during terminal cell selection.8 In a recent report, the roles of COX-1 and COX-2 in the humoral immune response have been addressed in vivo in a model of infection with the Lyme disease pathogen Borrelia burgdorferi.9 This study confirmed the implication of COX-1 in the control of class switching, as assessed by the lack of Borrelia–specific IgG in infected COX−1/− (but not COX−2−/−) mice, which correlated with defective germinal center formation and production of the cytokines IL-6 and IL-17. The report by Yang et al completes this picture by investigating the function of COX-1 in developing B cells.

Starting with the observation that COX−1−/− mice have a reduction in the number of peripheral B cells compared with their wild-type counterparts, which does not result from increased apoptosis, the authors hypothesize an implication of COX-1 in B-cell development, demonstrating that COX-1 regulates the pro-B cell to pre-B cell transition. This was found to correlate with a peak in COX-1 expression in pre-B cells and to be independent of BM stromal cell–derived prostanooids. The maturation of pro-B to pre-B cells is controlled by the cytokine IL-7, which promotes expression of the master transcription factor
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