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Bregging rights in ITP

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Just as we all have had our fill of the many articles on the T regulatory cell (Treg) abnormalities in immune thrombocytopenia (ITP), in this issue of *Blood* Li et al have identified a new regulatory player; the B regulatory cell (Breg).[1] They find that Bregs have similar properties to Tregs in ITP; they are deficient in active disease and therapy that raises platelet counts also rescues the underachieving B-cell subset.

Immune thrombocytopenia is an autoimmune bleeding disorder due to enhanced peripheral platelet destruction and reduced bone marrow platelet production. Antibodies and T cells are involved in the pathogenesis of the disease and, like other autoimmune diseases, patients with ITP have a peripheral deficiency of Treg numbers and function that may be responsible for loss of tolerance.[2] Li et al now report an additional defect in the peripheral immune regulatory compartment of ITP patients, namely in the Bregs.[1] Accumulating evidence from mouse models of autoimmunity and infections suggest that like Tregs, Bregs are potent suppressive lymphocytes for maintaining peripheral tolerance and abating pathogenic immune responses.[3] Furthermore, it has recently been shown that Bregs are important for the control of Tregs, promoting their differentiation and/or recruitment to tissues through an IL-10–dependent mechanism.[3] This suggests that there is a hierarchy in immunoregulatory circuits with Bregs controlling Tregs for maintenance of peripheral immune tolerance. This suppressive B-cell subset has also been identified in humans. For example, Blair et el reported the first description of human Bregs within the $CD19^{+}CD24^{hi}CD38^{hi}$ immature transitional B cells.[4] They showed that this subset had the ability to reduce $CD4^{+}$ T-cell activation via production of IL-10 and that the subset had compromised suppressive function in patients with active systemic lupus erythematosus. In addition, renal transplant patients found to have an increased frequency of the same B-cell subset appeared to have better transplant outcomes.[5] Bregs have also been implicated to negatively regulate monocyte cytokine production through both IL-10–dependent and –independent pathways.[6] Taken together, these studies suggest that, like mice, humans harbor Bregs and these cells have the ability to suppress T-cell and monocyte activation and thus play a critical role in maintaining immune tolerance.

Here, Li et al show, for the first time, reduced Breg populations at the level of phenotypic as well as functionality in patients with chronic refractory ITP. Specifically, the authors examined the $CD19^{+}CD24^{hi}CD38^{hi}$ Breg subpopulation and found a lower frequency of Bregs in the peripheral blood of nonsplenectomized patients with chronic ITP with low platelet counts. In addition, IL-10 expression was significantly decreased in all B cells and inhibition of monocyte TNF-α expression by activated B cells was reduced, suggesting that Bregs are functionally impaired in ITP. What is fascinating is that when thrombopoietin (TPO) therapy increased platelet counts in the ITP patients, it also increased the Breg numbers and function, just like the authors' previous analogous observations showing that TPO can rescue the Treg deficiency in ITP.[7] While the ITP patient population studied was composed of primarily chronic refractory patients, the question remains as to the in vivo relevance of the reduced Breg frequency in ITP pathogenesis. Is the deficiency causal or a result of the antiplatelet autoimmunity? Does it occur over time as the disease progresses? More intriguing is the question of how the Breg, or for that matter, the Treg frequency/activity[7] are improved after treatment and, are they linked; does one deficiency or its rescue depend on the other? Furthermore, although TPO, particularly the small molecule–based drugs, are believed to be devoid of immunomodulatory activities, the indirect or even direct effects of TPO on Bregs cannot be ruled out and, as the authors stress, require further investigation.

Other therapies such as dexamethasone,[8] rituximab,[9] and intravenous immunoglobulin have all been shown to improve the Treg deficiency in patients with ITP, so is this also true for Bregs? As the authors point out, this raises an important issue concerning ITP therapies. Do all of them, having vastly different mechanisms of action, affect both the Breg and Treg regulatory compartments the same way? Or, because platelets have immunomodulatory effects themselves,[10] does the increase in their mass induced by the different therapies have a role to play in modulating Bregs? Understanding the relationship between Bregs and Tregs will definitely shed light on how the two immunoregulatory networks interact in ITP and this knowledge may guide development of future therapies to perhaps restore long-lasting tolerance in ITP. One thing is for sure, however: the novel finding of this Breg deficiency in ITP has clearly shown that the immunopathogenesis of this disorder is complex and raises numerous questions that need to be addressed.

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