Human autoreactive plasma cell characterization in multiple organs

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Abstract

80% of immune thrombocytopenia (ITP) patients possess anti-integrin αIIbβ3 IgG autoantibodies causing platelet opsonization and phagocytosis. The spleen is considered the primary site of autoantibody production by autoreactive B cells generated in germinal centers, and platelet destruction by macrophages. The immediate failure in ~50% of patients to recover a normal platelet count after anti-CD20 Rituximab-mediated B cell depletion and splenectomy suggest that autoreactive, rituximab-resistant, IgG-secreting B cells (IgG-SC) reside in other anatomical compartments. We analyzed single IgG-SC from spleen, bone marrow and/or blood of patients with ITP revealing high inter-individual variability in affinity for αIIbβ3 with variations over 3 logs. IgG-SC dissemination and range of affinities were however similar per patient. Longitudinal analysis of autoreactive IgG-SC upon treatment with anti-CD38 mAb daratumumab demonstrated variable outcomes, from complete remission to failure with persistence of high-affinity anti-αIIbβ3 IgG-SC in the bone marrow. This study demonstrates the existence and dissemination of high-affinity autoreactive plasma cells in multiple anatomical compartments of patients with ITP that may cause the failure of current therapies.