Destroying dysfunctional immune systems with autologous HSCT and then closely observing how they are rebuilt from scratch via thymic and other pathways not only helps us to ameliorate intractable disabling and life-threatening states, but also has also provided useful insights into the pathogenesis of autoimmune diseases. By highlighting the ability of autologous HSCT to generate a naive, functional, and diverse donor-derived Treg compartment, Delemarre and colleagues add a further piece to van Bekkum's visionary jigsaw.

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

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Comment on Melenotte et al, page 113

Identifying risk factors for B-cell lymphoma

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In this issue of *Blood*, Melenotte and colleagues provide an interesting and provocative analysis of a potential novel risk factor for B-cell non-Hodgkin lymphoma (NHL).[1]

This is one of the first studies to focus on *Coxiella burnetii* (the infectious agent associated with Q fever) as an inciting factor for lymphomas. Building on the identification of an incident case, the authors examined the incidence of lymphoma among individuals within a cohort of patients with Q fever. These analyses provide clinically meaningful insights that may aid in the identification of a novel risk factor for diffuse large B-cell lymphoma (DLBCL) and other B-cell NHLs and support the development of a comprehensive understanding of factors associated with lymphoma incidence. Utilizing a French National Referral Center for Q fever database of 1468 consecutive patients diagnosed from 2004 to 2014, and accounting for differences in age and sex distribution between the Q fever cohort and the general French population, the authors identified an increase in the incidence of DLBCL and follicular lymphoma (FL) in individuals who had Q fever compared with the general population, with standardized incidence rates of 25.4 (95% confidence interval [CI], 11.4-56.4) and 6.7 (95% CI, 0.9-47.9), respectively. Moreover, a diagnosis of Q fever with a persistent focal infection was noted to have a greater risk of lymphoma with a hazard ratio of 9 over the period of observation. For these analyses, acute Q fever was defined by the association of clinical symptoms (fever, hepatitis, and/or pneumonia) with the serological criteria of a phase 2 immunoglobulin G (IgG) titer ≥200 and a phase 2 IgM titer ≥50, seroconversion or a positive polymerase chain reaction (PCR), and no endocarditis. Supporting these epidemiological data were findings that interleukin-10 production was significantly increased in patients with lymphoma, particularly those with Q fever. Moreover, *C burnetii* was detected in $CD68^+$ macrophages within lymphoma and lymphadenitis tissues in patients with and without lymphoma, but infection was localized in plasmacytoid dendritic cells in lymphoma tissues only providing early evidence for a possible pathway to lymphomagenesis. Although the selection process for assembly of the cohort of patients and serological samples for the Q fever database may introduce biases that could influence the strength of association between *C burnetii*/Q fever and the incidence of B-cell NHLs, this analysis provides insight for a new infectious disease linked to lymphoma. Further validation of these observations would add Q fever to the list of infectious agents such as Epstein-Barr virus, *Helicobacter pylori*, and hepatitis C infection involved in the pathogenesis of B-cell lymphomas.

These findings must be considered in the context of numerous other analyses examining infectious and other risk factors for B-NHL, most notably the recent large international pooled InterLymph Subtypes Project.[2-5] The International Lymphoma Epidemiology Consortium (InterLymph) was formed in 2001 to perform pooled case-control studies that maximize statistical power to identify common as well as distinct risk factors among NHL subtypes. This group has identified numerous demographic, medical history, environmental, and genetic risk factors for lymphoma, exposing the common threads and heterogeneity in etiology across NHL subtypes. Of relevance to the present study, the subtype study of DLBCL performed a pooled analyses of 4667 cases and 22 639 controls from epidemiological studies in Australia, Europe, and North America and

identified that B-cell–activating autoimmune diseases (odds ratio [OR] = 2.36), hepatitis C virus–positive status (OR = 2.02), first-degree family history of NHL (OR = 1.95), and greater body mass index (BMI) as a young adult (OR = 1.58 for BMI ≥30 kg/m^2) were significantly associated with increased DLBCL risk, whereas higher socioeconomic status (OR = 0.86), medical history of any atopic disorder (OR = 0.82), and increased recreational sun exposure (OR for highest quartile = 0.78) were significantly associated with decreased risk of DLBCL.[2] In addition, there were DLBCL site-specific and sex-specific risk factors related to occupation, hormone use, and alcohol consumption. Of note, in a pooled analysis restricted to occupational exposures,[6] InterLymph investigators found a relationship between farming and DLBCL for field crop/vegetable farmers, but not for exposure through farm animals, which could mediate exposure to *C burnetii*. Thus, confirmation of the findings from Melenotte and colleagues also would benefit from additional data examining the route of exposure to *C burnetii*.

In addition, the InterLymph subtype study of FL involved 3530 cases and 22 639 controls.[4] First-degree family history of NHL (OR = 1.99), higher BMI as a young adult (OR = 1.21, per 5 kg/m^2 increase), and work as a spray painter (OR = 2.66) were associated with increased risk of FL, whereas any atopic disorder (OR = 0.87), previous blood transfusion (OR = 0.78), increased sun exposure (OR for highest quartile = 0.74), occupation as a baker (OR = 0.51), and occupation as a higher education teacher (OR = 0.58) were associated with decreased risk of FL. As with DLBCL there were sex-specific risks for FL with Sjögren syndrome and history of cigarette smoking being associated with increased risk, and history of alcohol consumption, hay fever, and food allergies being associated with decreased risk of FL in females. Of particular note, these multivariable analyses determined that these risk factors are mutually exclusive, suggesting that FL and DLBCL can have a multifactorial etiology. Separate InterLymph analyses have investigated genetic risk factors for DLBCL and FL. Cerhan et al identified several gene variants with genome-wide significant associations in the HLA region of chromosome 6 and new loci near *EXOC2*, *MYC*, *NCOA1*, and *PVT1*.[7] Genome-wide association studies (GWAS) of FL, including a large-scale 2-stage GWAS in 4523 cases and 13 344 controls of European ancestry identified numerous highly statistically significant HLA risk alleles and 5 non-HLA loci near *CXCR5*, *ETS1*, *LPP*, *BCL2*, and *PVT1*, which also suggests overlap between genetic risk for DLBCL and FL.[8] Integrating the findings of Melenotte et al with prior epidemiological studies in B-NHL,[2,4] and studies investigating the genomics of the host[7,8] and the tumor, will be critical to defining novel treatment and prevention strategies for FL and DLBCL in the future.

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● ● ● PLATELETS AND THROMBOPOIESIS

Comment on Yu et al, page 132

FcγRIII in ITP: it ain't over 'til it's over

Keith R. McCrae CLEVELAND CLINIC

In this issue of *Blood*, Yu et al describe a novel anti–Fcγ receptor III (FcγRIII)-albumin fusion protein that inhibits the development of thrombocytopenia in a murine model of immune thrombocytopenia (ITP).[1] The unique aspect of this protein is that it blocks FcγRIII-mediated uptake of antibody-coated platelets without activating FcγRIII and the associated inflammatory response.

Antiplatelet glycoprotein antibodies induce thrombocytopenia in patients with ITP by impairing platelet production and enhancing the clearance of platelets by the reticuloendothelial system.[2] Platelet clearance may be the dominant pathophysiology in many patients with ITP, though this aspect of the disorder has received less attention over the past decade, reflecting increased use of thrombopoietin receptor agonists.

Studies performed more than 30 years ago demonstrated that intravenous immunoglobulin delayed the clearance of radiolabeled, opsonized red blood cells in patients with ITP, suggesting that intravenous immunoglobulin impaired the function of Fcγ-expressing phagocytes.[3] Subsequent studies using isolated Fc fragments as well as anti-D coated red cells confirmed the ability of the Fc region of immunoglobulin G to cause reticuloendothelial blockade and suggested the therapeutic potential of inhibiting Fcγ receptor function.[4] In 1986, significant increases in the platelet count of a patient with refractory ITP were observed in response to treatment with a monoclonal antibody against FcγRIII (3G8).[5] Responses, however, were brief, and infusion of 3G8 was accompanied by severe neutropenia as well as chills, nausea, and vomiting. The expectation that these toxicities were induced by binding of the Fc region of 3G8 to Fcγ receptors, resulting in cellular activation and an ensuing inflammatory response, led to the development of GMA161, a version of 3G8