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/m²) 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. 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, 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 et al 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. First-degree family history of NHL (OR = 1.99), higher BMI as a young adult (OR = 1.21, per 5 kg/m² 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. 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 CXCRI, ETS1, LPP, BCL2, and PVT1, which also suggests overlap between genetic risk for DLBCL and FL. Integrating the findings of Melenotte et al with prior epidemiological studies in B-NHL, and studies investigating the genomics of the host and the tumor, will be critical to defining novel treatment and prevention strategies for FL and DLBCL in the future. Conflict-of-interest disclosure: The authors declare no competing financial interests.

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PLATELETS AND THROMBOPOIESIS

Comment on Yu et al, page 132

FçγRIII in ITP: it ain’t over ’til it’s over

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In this issue of Blood, Yu et al describe a novel anti–Fçγ receptor III (FçγRIII)—albumin fusion protein that inhibits the development of thrombocytopenia in a murine model of immune thrombocytopenia (ITP). The unique aspect of this protein is that it blocks FçγRIII-mediated uptake of antibody–coated platelets without activating FçγRIII and the associated inflammatory response. A platelet glycoprotein antibodies induce thrombocytopenia in patients with ITP by impairing platelet production and enhancing the clearance of platelets by the reticuloendothelial system. 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 Fçγ-expressing phagocytes. Subsequent studies using isolated Fç fragments as well as anti-D coated red cells confirmed the ability of the Fç region of immunoglobulin G to cause reticuloendothelial blockade and suggested the therapeutic potential of inhibiting Fç receptor function. 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 FçγRIII (3G8). 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 Fç region of 3G8 to Fç receptors, resulting in cellular activation and an ensuing inflammatory response, led to the development of GM1A161, a version of 3G8
in which Fc function was inhibited by deglycosylation. A pilot study in 2009 confirmed the activity of 3G8 and GMA161 in ITP; however, both antibodies were associated with a similar toxicity profile.6 These studies provided proof of principle that FcyRIII contributed to clearance of antibody-coated platelets in ITP. However, toxicity from FcyRIII activation halted their further consideration as ITP therapeutics.

Humans express several Fcy receptors in a cell-specific manner. FcyRI, FcyRIIa, FcyRIIc, and FcyRIIIa are “activating” receptors, whereas FcyRIIB is inhibitory.7 FcyRI and FcyRIIa contain a ligand-binding α chain, but signal through the associated γ chain dimer, which contains an immunoreceptor tyrosine-based activation motif. FcyRIIA is a low-affinity receptor that preferentially binds immune complexes; ligation of FcyRIIA leads to phosphorylation of the immunoreceptor tyrosine-based activation motif, recruitment of SYK, and activation of downstream targets including SOS, RAS, and phosphatidylinositol 3-kinase, causing cellular activation, phagocytosis, and cytokine release.

Though it had been assumed that the toxicity of 3G8 was a consequence of FcyR activation by the Fc region, Yu et al reasoned that the parallel toxicity of GMA161 suggested that these responses were due instead to ligation of FcyRIIia by the bivalent F(ab’)2 region. To test this hypothesis, they produced a monovalent 3G8 single chain variable region (scFv) fused to human serum albumin (HSA) (see figure). This fusion protein specifically bound and blocked binding of human immunoglobulin G to the extracellular domain of human FcγRIIIa. The investigators then created a murine counterpart of the 3G8 scFv-HSA fusion protein using an scFv from monoclonal antibody 2.4G2, which targets murine FcγRIII/IIh, and murine serum albumin (MSA). This construct specifically bound its target and inhibited development of thrombocytopenia in mice treated with the antiplatelet antibody MWReg30, which induces thrombocytopenia by stimulating platelet clearance through FcγRIII.1 In contrast, 2.4G2 scFv-MSA did not impair platelet clearance in response to 6Ab, a murine antiplatelet antibody that mediates clearance through FcγRI.1 Importantly, the 2.4G2 scFv-MSA fusion protein had an extended half-life and did not cause the systemic drop in temperature or activation of basophils seen with the bivalent parental antibody, which resulted from activation of FcγRIII.

This study extends previous work demonstrating the role of FcγRIII in ITP and suggests the feasibility of a monovalent FcγRIII scFv-fusion protein as an ITP therapeutic. However, many questions remain. For example, human ITP is a complex disorder with a heterogeneous array of antiplatelet antibodies that may cause platelet clearance through different Fc receptors. Moreover, a recent report suggests a role for an entirely different receptor, the hepatocyte Ashwell-Morell receptor, in clearance of platelets bound by antibodies to GPIbα that cause Fcγ-independent activation and desialylation.8 Finally, it is likely that inhibition of platelet production is of primary importance in at least some cases of ITP.

The late baseball legend, Yogi Berra, was famous for his “Yogi-isms,” the most well-known of which is “It ain’t over ’til it’s over,” meaning that a baseball game was not over until the last out, and there was always a chance for a comeback. In this report, Yu et al show that this also applies to treatment of ITP through inhibition of FcγRIII. Future studies of the 3G8 scFv-HSA fusion protein or its derivatives in human ITP will be of great interest.

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● ● ● RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Canli et al, page 139

Unconventional cell death in erythroid cells

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In this issue of Blood, Canli et al demonstrate that reactive oxygen species (ROS) and lipid hydroperoxides can function as unconventional upstream signaling activators of receptor-interacting protein 3 (RIp3) kinase-dependent necroptosis, causing anemia in mice lacking erythroid glutathione peroxidase 4 (Gpx4).1
FcγRIII in ITP: it ain't over 'til it's over

Keith R. McCrae

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