EDITORIALS

A BAFFling Association between Malaria Resistance and the Risk of Multiple Sclerosis

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B cells are increasingly recognized as a therapeutic target in autoimmune diseases. B-cell–depleting therapy with the use of rituximab, a monoclonal antibody to CD20, is approved for the treatment of rheumatoid arthritis and antineutrophil cytoplasmic antibody–associated vasculitis and is frequently used off-label to treat lupus nephritis.[1] The rationale for targeting B cells in multiple sclerosis has remained controversial, particularly because major animal models of the disease do not involve B cells.[2] Nevertheless, rituximab and its almost fully humanized successor, ocrelizumab, were tried in patients with multiple sclerosis and appear to be exceedingly potent in suppressing signs of inflammation in the central nervous system and slowing disability progression.[3] Anti-CD20 therapy does not target plasma cells, and, accordingly, the amount of immunoglobulin in patients treated with rituximab was not decreased. Thus, it is considered unlikely that rituximab acts by reducing autoantibody levels. Rather, several reports in experimental models and in humans suggest that B cells might play an important role as antigen-presenting cells for autoantigens in multiple sclerosis. Steady-state survival and maintenance of B cells is regulated by several means, including a network of B-cell growth factors such as B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL).[4]

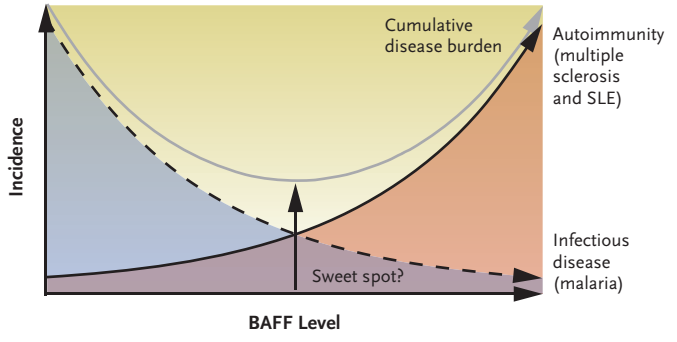

Figure 1. Selection Pressure for "Optimum" BAFF Level.

When disease incidence in a population is plotted against levels of B-cell activating factor (BAFF), the area under the curve represents the disease burden of a given disease entity as a function of BAFF levels. In the Sardinian population, genetic variants of *BAFF* that lead to increased BAFF levels were selected because they result in greater protection against malaria infection. Increased levels of BAFF would result in a decrease in the disease burden due to malaria but an increase in the disease burden due to autoimmune diseases. Thus, there might be an "optimum" BAFF level (sweet spot), at which the cumulative primitive function of both incidence curves reaches a minimum (gray curve). SLE denotes systemic lupus erythematosus.

Although Sardinians have one of the highest rates of centenarians in the world, they also have the highest incidence rates of multiple sclerosis. To date, the genetic factors associated with multiple sclerosis in Sardinia have not been fully defined. In this issue of the *Journal*, Steri et al.[5] report on a novel insertion–deletion variant of *TNFSF13B* (encoding BAFF), which results in higher BAFF levels owing to resistance of *TNFSF13B* messenger RNA (mRNA) degradation by microRNA. This variant results in enhanced humoral immunity and is associated with an increased risk of multiple sclerosis or systemic lupus erythematosus. The increased incidence of this variant of *TNFSF13B* in the Sardinian population appears to be the result of a selection process (Fig. 1). The authors speculate that carriers of the variant have an increased fitness in host defense against malaria, which was endemic in Sardinia until the 1950s. These findings are in line with studies that have shown that plasma levels of BAFF increase during acute malarial disease and that mice that overexpress BAFF are protected from lethal malaria infections.[6]

Examples of selection processes due to advantages in the fitness of mutants, which cause monogenetic diseases, are well appreciated. A mutation in the *HBB* locus leads to sickle cell anemia but lowers disease burden in malaria.[7] Resistance to activated protein C owing to a mutation in the *F5* gene leads to thrombosis but confers protection against certain forms of sepsis.[8] However, more recently, certain single-nucleotide polymorphisms (SNPs) that are associated with complex genetic diseases were also shown to be maintained in the genetic pool of distinct populations owing to selective pressure: besides BAFF, the adaptor protein SH2B3, which is a key negative regulator of cytokine signaling, may be an example of this phenomenon. A variant of SH2B3 (missense mutation), which is associated with an increased risk of celiac disease, leads at the same time to increased responses of the pattern recognition receptor NOD2 on stimulation with muramyl dipeptide and thus improved host defense against certain bacteria.[9]

The BAFF system is complex. It has three receptors: BAFF receptor (BAFF-R), B-cell maturation antigen (BCMA), and transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI). Soluble trimeric BAFF binds to BAFF-R, which is expressed on B cells. Trimeric APRIL, an alternative ligand, binds to BCMA, which is expressed on plasma cells. TACI, which is expressed on B cells and in particular on innate-like B1 cells, is only engaged by higher-order oligomers of BAFF and APRIL. Although BAFF and APRIL generally promote the expansion and differentiation of B cells and plasma cells, respectively, signaling through TACI can have complex outcomes. Unexpectedly, mice deficient in TACI exhibit increased B-cell proliferation and autoimmunity.[10] Therefore, the effects of blocking BAFF are difficult to predict. Indeed, a large phase 2 trial of atacicept, a blocking agent against BAFF and APRIL, that involved patients with multiple sclerosis had to be halted because those in the treatment group had twice as many relapses as those in the placebo group.[11] This was unexpected because atacicept appears to be beneficial in rheumatoid arthritis and lupus. However, because one of the BAFF receptors (TACI) conveys inhibitory (proapoptotic) signals into B cells, adverse net effects might be inherent to this interventional strategy. An intense biomarker program showed that high levels of *BAFF* mRNA were associated with a shorter time to first relapse, suggesting that BAFF expression is under a negative feedback control.

It will be a challenge for the future to assess whether the insertion–deletion variant of *TNFSF13B* can be used to stratify patients for a specific therapy. Although the data from the current study clearly point in this direction, the discriminatory power of this solitary SNP may not be sufficient for clinical decision making. However, it seems reasonable to study whether stratification of patients according to the variant of *TNFSF13B* could be useful for clinical trials that assess B-cell–directed therapies.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe1700720