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Commentary

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Treating MS: getting to know the two birds in the bush

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Current therapies for immune-mediated diseases, such as rheumatoid arthritis and MS, could represent the proverbial bird in the hand — a known entity, yet limited in potential. Emerging biologic therapeutics for these diseases carry with them the potential for known as well as unknown adverse effects. Alemtuzumab, a biologic that depletes leukocytes, shows great promise for the treatment of MS. However, a significant number of patients develop autoimmunity after treatment, raising the level of caution for the use of this drug. In this issue of the *JCI*, Jones et al. describe a link between IL-21 levels and alemtuzumab-associated autoimmunity (see the related article beginning on page 2052). They show that proliferation of lymphocytes in those patients with autoimmunity is higher than in those without autoimmunity and suggest that the lymphopenia-driven proliferation of T cells, in combination with higher IL-21 levels, results in autoimmunity. This study helps inspire new enthusiasm for making a grab for the proverbial two birds in the bush — representing undiscovered therapies — with greater confidence.

Emerging therapies in MS

MS is an immune-mediated disease characterized by inflammatory areas of demyelination in the brain and spinal cord. Patients typically experience episodes of neurologic disability (termed relapsing-remitting MS [RR-MS]), which often evolves into unrelenting disability progression. MS is at the forefront of diseases being treated with biologic therapeutics that modulate the immune system. Given the limited reduction of relapses and disability induced by current treatments, these emerging therapies are highly anticipated. However, caution must be exercised, as current MS therapies are on the whole safe and well tolerated.

Among the monoclonal antibodies that have had significant promise is alemtuzumab (also known as Campath-H1). Alemtuzumab targets the leukocyte antigen, CD52, which is ubiquitously expressed on T and B lymphocytes, monocytes, and macrophages. A single treatment causes profound leukopenia. In preliminary clinical trials, alemtuzumab has shown much greater efficacy in the treatment of RR-MS than that of a currently approved drug, IFN-β1a (1). While it may have greater efficacy in the treatment of MS, a major concern with alemtuzumab is the not-infrequent adverse effect of autoimmunity. Notable among the adverse events in early trials were autoimmune thyroiditis and idiopathic thrombocytopenic purpura (ITP) (1). One patient enrolled in the study cited above in fact died from ITP. While the trial resumed after safety measures were implemented, it is of particular importance to understand why some MS patients succumb to autoimmune disease after alemtuzumab treatment, while others do not, in order to gain maximal benefit from this potential therapeutic.

Lymphopenia-driven autoimmunity

It has long been recognized that autoimmunity develops in patients who develop significant leukopenia (2). This led Jones et al., authors of the related study in this issue of the *JCI* (3), to consider the factors that predispose to autoimmunity in the setting of lymphopenia/leukopenia. Experimentally, the association between lymphopenia and autoimmunity was clarified by Sarvetnick and colleagues using the diabetes-prone mouse strain, NOD (4). They demonstrated that NOD mice are lymphopenic and that correction of lymphocyte numbers prevented immune-mediated damage of the pancreas. Lymphopenia was associated with a deficit in the pro-survival proteins Bcl-2 and Bcl-XL; a striking association between IL-21 and IL-21 receptor levels and autoimmune diabetes was also reported. Given the role of IL-21 in homeostatic proliferation, elevated IL-21 levels likely promote T cell proliferation and favor the expansion of self-reactive lymphocytes. Further work by others has extended this observation to show that IL-21 is critical for autoantibody production in a mouse model for lupus (5). Thus, IL-21 provides a mechanistic link between lymphopenia and autoimmune diseases in mice.

RR-MS patients treated with alemtuzumab are optimal subjects for the study of whether autoimmunity observed following the induction of lymphopenia is a result of IL-21–driven lymphocyte expansion. Typically, lymphocyte numbers do not recover until 6–12 months after alemtuzumab administration, and the percentage of patients experiencing autoimmune disease is around 30% (3). In their current study, Jones et al. examined RR-MS patients enrolled in two separate alemtuzumab trials and found that lymphocytes reemerging after alemtuzumab treatment not only had a greater tendency to proliferate, but also exhibited higher degrees of apoptosis (3). These features were more frequent in patients with autoimmune disease (defined as persistent autoantibodies or clinical disease with or without autoantibodies) 9 months after treatment with alemtuzumab, compared with patients without autoimmune disease after treatment. Jones et al. also report that in an overlapping cohort of patients, serum IL-21 levels were more than 2-fold higher in patients with thyroid autoantibodies than in those with no serologic evidence of autoimmunity. These results fit nicely with our understanding of the process by which lymphopenia drives autoimmunity in mice.

Predicting autoimmune disease in patients

Jones and colleagues took a further step in defining the risk for developing autoimmune disease after alemtuzumab treatment (3). They asked whether the predisposition for developing autoimmunity following lymphopenia induction could be identified

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Nonstandard abbreviations used: ITP, idiopathic thrombocytopenic purpura; RR-MS, relapsing-remitting MS.

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prior to treatment. Interestingly, the difference in serum IL-21 levels was found even before alemtuzumab administration. In fact, serum levels of IL-21 were used to generate a sensitivity of 66% and specificity of 67% in predicting the development of autoimmunity after alemtuzumab administration. Can this predisposition to higher IL-21 levels, and accompanying autoimmunity after alemtuzumab treatment, be explained genetically? The authors examined this possibility by looking at several SNPs within the *IL21* gene. They found that in a small group of subjects, a higher percentage of those carrying a risk allele developed autoimmunity. While there was only a trend toward statistical significance, this strategy represents a major advance in defining the predisposition toward complications arising from alemtuzumab therapy, based on a defined immunologic mechanism.

The report by Jones et al. (3) heralds a new era of medicine in which genetic analysis of patients can be used to tailor treatments that may otherwise have unacceptable adverse effects. A clear example of the utility of this approach is the recent clinical practice of screening patients prior to initiation of anticoagulation therapy with warfarin. To anticipate the rate of warfarin metabolism, allelic differences in the cytochrome P450, family 2, subfamily C, polypeptide 9 (*CYP2C9*) and vitamin K epoxide reductase complex, subunit 1 (*VKORC1*) genes can be used to predict dosing requirements, helping prevent the under- or overdosing of anticoagulant that can lead to disastrous consequences (6). Genetic predisposition toward benefiting from disease-specific treatment is also under intense scrutiny. For example, in rheumatoid arthritis, genetic analysis has been performed, with the goal of predicting who will respond well to treatment with anti-TNF molecules (7). From limited studies, no genetic basis for treatment response has been clearly demonstrated, although some studies suggest that alleles within the MHC complex may influence response to anti-TNF therapy in rheumatoid arthritis (7). Overall, employing drugs more effectively based on the genetic makeup of each patient — a pharmacogenomic approach — appears to be on the horizon.

Further questions

Jones et al. raise several questions as a result of their study (3). First, why do some forms of autoimmunity predominate after lymphopenia-induced proliferation? In alemtuzumab trials, a vast majority of affected patients develop autoimmune thyroiditis (1). This could be due in part to the high prevalence of this condition (clinically as well as subclinically) in the general population. Alternatively, factors that are suppressive for the development of other autoimmune diseases may contribute to organ-specific autoimmunity. In their study, Jones et al. purposely excluded patients who developed transient autoantibody elevation from the "autoimmunity" group. Perhaps other mechanisms are employed in patients that transiently develop autoantibodies, suppressing the emergence of disease. It should be noted that a major concern with alemtuzumab treatment is the handful of patients who develop ITP. Certainly ITP is more critical clinically than thyroiditis, and it will be important to determine whether IL-21 levels are also associated with antiplatelet antibodies, even if this is clinically not evident.

Second, is the benefit from alemtuzumab treatment in MS related to IL-21 levels? IL-21 has been identified as a critical regulator of Th17 lineage commitment (8). These proinflammatory $CD4^+$ T cells, characterized by their production of IL-17, are thought to play a crucial role in MS and its experimental models (9, 10). If IL-21 levels are higher in some patients with RR-MS, it could be posited that the result of alemtuzumab treatment would be less effective in disease suppression, as greater proportions of Th17 cells would emerge upon lymphocyte recovery. The authors note by means of personal communication that there was no relationship between the development of autoimmunity in MS patients treated with alemtuzumab and the degree of disease suppression. However, whether or not patients with higher IL-21 levels and autoimmunity respond less favorably to alemtuzumab needs further exploration.

A third question — less biologic, yet broader — is how to deal with the changing landscape of risk/benefit analysis in the use of biologic therapeutics. Current MS therapeutics (e.g., IFN-β1a and glatiramer acetate) are considered relatively safe. Faced with several deaths resulting from progressive multifocal leukoencephalopathy after natalizumab treatment (11), the MS community had to make a large adjustment to how therapies with far greater risks are used. Again, addressing the potentially fatal adverse reaction of ITP after treatment with alemtuzumab inspires a long hard look at the bird in the hand, namely the current immunomodulatory agents used to treat MS. Armed with a greater degree of knowledge, on behalf of the patient, as to who will optimally respond to treatment, it may be easier to embrace the potential benefit of reducing disease burden, rather than fearing a complication that is not likely to occur. Clearly, pharmacogenomic profiling will aid greatly in this pursuit. Thus, instead of being content with one bird in the hand, perhaps we can begin to see the value of reaching for two birds in the bush.

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Restraining order for dendritic cells: all quiet on the fetal front

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The paradoxical ability to launch effective immunity against pathogens while avoiding the horror autotoxicus of autoimmunity is one of the most remarkable features of the mammalian immune system. This assumes a particular evolutionary significance at the maternal/fetal interface, where avoidance of immune reactivity to the fetus is vital to the propagation of the species itself. Several mechanisms of suppressing maternal immunity against the fetus have been described. The article by Collins et al. in this issue of the *JCI* describes a novel mechanism of avoiding immune surveillance in which the migratory capacity of dendritic cells at the maternal/fetal interface is restrained (see the related article beginning on page 2062).

In eutherian mammals, the implantation of an embryo in a mother's uterus creates an incongruous immunological paradox. The hemochorial placenta provides optimal nourishment and protection to the embryo; however, persistent and intimate contact between the uterine lining (decidua) and the semi-allogeneic fetus (sharing some but not all genes of the mother) should evoke significant immunologic responses akin to a mismatched organ transplant. During pregnancy, however, a seemingly harmonious temporary coexistence of two immunologically distinct multicellular organisms occurs so that the fetus remains protected from any maternal immune responses. Understanding this evolutionary adaptation of immune evasion in the placenta will be pivotal to understanding the induction and maintenance of tolerance from conception to senescence and may provide useful insights into the immunologic role of the placenta during prematurity and recurrent abortions, and during acute and chronic maternal viral infections.

Medawar's postulates

In 1953 Sir Peter Medawar proposed three general mechanisms of immune evasion within the uterus, which when gravid constitutes an immune-privileged site (1). First, there could be induction of immunological tolerance of the mother for fetal antigens. Second, an anatomical and physiological barrier between mother and fetus might prevent access of maternal immune cells to fetal antigens, a mechanism similar to that in effect in other immune-privileged sites, including the testes, eyes, and brain. Third, fetal cells might suppress the expression of alloantigens. These postulates remain plausible but do not explain the paradox of how the maternal immune system acquires unresponsiveness to fetal antigens, while maintaining immune reactivity against infections. A corollary to Medawar's postulates has been put forward to explain this paradox: one that involves site-specific suppression of maternal immune responses at the maternal/fetal interface, thus controlling immune reactivity to the fetus without compromising immunity to pathogens elsewhere (2). The mechanisms underlying site-specific immune suppression facilitating fetal engraftment have been the subject of intense research, and several have been proposed. These include: (i) the expression of FasL by the fetus, which induces Fas-mediated deletion of maternal T cells reactive to the fetus; (ii) expression of nonclassical HLA-G major histocompatibility molecules in cytotrophoblast cells at the maternal/fetal interface, where they maintain a tolerogenic status between the mother and fetus; and (iii) the presence of cells expressing immunosuppressive molecules such as indoleamine 2,3-dioxygenase (IDO), IL-10, TGF-β, and PGE_2 (3–5). In addition, $CD4^+Foxp3^+$ Tregs, which suppress the activation of the immune system, have been documented to increase in number during early human pregnancy (6).

Maternal/fetal détente

The study by Collins et al., reported in this issue of the *JCI*, presents new insights into the role of DCs in mediating this site-specific suppression (7). DCs represent a rare population of APCs that have long been known to play a key role in sensing pathogens as well as initiating and tuning the quality of the subsequent immune response (8). Like lymphocytes, DCs also comprise distinct cell subsets, which are functionally specialized to produce distinct cytokines that differentially regulate the type of immune response induced. Immature DCs are scattered at the portals of pathogen entry, such as at the mucosal surfaces of the intestine, lungs, and reproductive tracts, and are equipped to sense conserved molecular patterns of pathogens through receptors such as TLRs (9, 10). Upon sensing a pathogen, immature DCs rapidly migrate to the draining LNs and stimulate the naive antigen-specific T cells, thus launching an immune response. Recent work demonstrates that DCs can also suppress the immune response, through the generation of Tregs, and DCs exhibiting this immune-suppressive property have been observed at mucosal sites such as the gut, lung, and decidua (9, 10).

The study by Collins et al. (7) examines the effect of decidualization (encasement of the fetus and placenta in a stromal cell–derived structure called the decidua) on decidual DC migration and function in a murine model of pregnancy (Figure 1). The authors first used flow cytometry to characterize populations of cellular subsets expressing MHC class II (MHCII) in the uterine tissues of virgin mice that had been treated with a high-dose regimen of progesterone designed to simu-

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