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Tolerance, immune regulation, and autoimmunity: cells and cytokines that make a difference

Roberta Pelanda and
Integrated Department of Immunology, National Jewish Health, 1400 Jackson Street, K814a, Denver, CO 80206, USA, pelandar@njc.org

Ciriaco A Piccirillo
Department of Microbiology and Immunology, and Center for the Study of Host Resistance, McGill University and the Research Institute of the McGill University Health Center, Montreal, QC, Canada, ciro.piccirillo@mcgill.ca

Adaptive immune responses are based on the random generation of immunoglobulin and T cell receptors to create repertoires that cover the complete spectrum of potential foreign antigens. Because of the random nature of the immune adaptive receptors and their extensive diversity, a large fraction of the antibodies and T cell receptors that are generated every day by our B and T cells are reactive to self-components. If we add to this self-reactive capacity the notion that the immune system harbors an incredible ability to cause tissue damage and destruction, we can forever marvel how it is that most of us do not develop autoimmunity during our life. In fact, a permanent battle for balance takes place in our body to ensure that the immune system is active and effective against dangerous foreign and self (i.e., cancer-related) proteins, while it remains non reactive against us. Maintaining this balance is not, indeed, an easy task as the battle is lost resulting in overt autoimmunity in approximately 3% of the human population.

The onset of autoimmunity is a dynamic, multi-factorial process that requires the breaching of multiple checkpoints. Immune regulation is effected via regulatory cells and via regulatory membrane and soluble molecules that can be potentially manipulated to prevent autoimmunity and achieve tolerance. Manipulating the immune system for therapeutic purposes is a difficult but important goal, and recent findings propose a variety of novel targets for clinical intervention that are just starting to be explored.

In this Autoimmunity issue of *Current Opinion in Immunology*, we have collected short reviews covering recent findings on what are the cells and factors that maintain tolerance or, conversely, promote autoimmunity.

In the last few years B cells have moved to the forefront of basic and clinical research in autoimmunity due to the substantial amelioration of autoimmune patients when treated by B cell depletion therapies in recent clinical trials. The role of B cells in autoimmunity could simply depend on the fact that autoimmune individuals may have a predisposition for producing and/or maintaining more autoreactive B cells than healthy individuals. Detailed studies of human B cells have been lacking due to the difficulty of analyzing human samples with the same rigor and sophisticated tools that are available for animal studies. Few years ago, Michel Nussenzweig and colleagues took up the difficult job of examining levels of self-reactivity of single human B cells at various stages of differentiation. Meffre and Wardemann summarize the findings of these elegant studies in the first review. The intriguing results of these studies are that lupus (SLE) and rheumatoid arthritis (RA) patients have a significantly higher number of autoreactive B cells in the mature naïve, but not in other, stages of B cell differentiation. Indeed, SLE patients and healthy controls bear the

same frequency of autoreactive and polyreactive IgG^+ memory B cells. These findings open up questions that need to be addressed in the future. We need to understand whether the difference in the numbers of mature autoreactive B cells play an important role in the induction and/or maintenance of these autoimmune responses. These cells may be important in regulating the function of pathogenic T cells or be the progenitors of effector B cells. Moreover, further studies are necessary to investigate whether IgG^+ autoreactive memory B cells that are at similar frequency, differ functionally between healthy and autoimmune individuals.

Jan Erikson and collaborators (Mandik-Nayak *et al.*) summarize recent mouse and human studies that aimed at pinpointing the specific role of B cells in autoimmunity. Studies that analyzed the effect of anti-CD20 antibodies, which target mature B cells, bortezomib, a novel synthetic reagent that targets plasma cells, and FcγRIIb, which was recently shown to be expressed also in plasma cells, suggest that both mature and terminally differentiated B cells may play a role in the establishment and maintenance of autoimmune processes. Thus, B cells appear to have multi-faceted functions in the pathogenesis of autoimmunity that remains to be cleared and exploited for therapy. Of particular interest is the potential role of B cells in regulating the activity of other blood cells via expression of cytokines and other immuno-modulatory factors. Clinical trials of novel reagents such as bortezomib will hopefully elucidate the relative importance of B cells and plasma cells in human autoimmunity. Furthermore, additional basic studies that characterize the phenotype of autoreactive B cells in animal models (such as [1]) and autoimmune patients are required to provide novel clinical targets to more specifically attack autoreactive B cells leaving other B cells to cope with potential infections.

Human primary immunodeficiencies (PID) can be considered as immunological anomalies of nature. PID are characterized by an increased susceptibility to infections, and are often associated with a high prevalence of autoimmune manifestations. Thus, PID offer immunologists a peculiar enigma since the immune system of PID individuals remains unresponsive to pathogen-derived antigens while responding robustly to self-antigens. Snapper and colleagues provide compelling evidence to support the link between immunodeficiency and autoimmunity. Recent findings in patients and animal models of PID have shown that the breakdown in self-tolerance may be in part related to defects in negative selection of self-reactive T lymphocytes in the thymus, disturbances in the ability of regulatory T (Treg) cells to dominantly suppress self-reactive T cells, or possibly due to decreased clearance of pathogens. A more in depth understanding of the defined causes for the autoimmune predisposition in PID patients may lead to the development of more effective therapeutic strategies.

The human specie more than any other has a predilection for controlling its surrounding environment. Thus, it is not surprising that many immunologists nowadays focus their studies on understanding how to control the master regulators of immune responses. It is one thing being able to direct the movement of a puppet, but being capable of controlling the master puppeteer holds a much greater appeal and potential. In recent years, $CD4^+Foxp3^+$ Treg cells have forcefully moved to the forefront of immunological research as regulators of immune responses and potential suppressors of autoimmunity. Ciriaco Piccirillo and collaborators give us a comprehensive and intriguing update on recent studies that focused on understanding the mechanism of development and action of Treg cells. Importantly, these studies have identified ways to differentiate Treg cells from naïve peripheral T cells, and they have uncovered multiple mechanisms of action that mediate Treg function in suppressing immune responses. These findings are starting to be tested in the contest of mouse and human autoimmunity, such that in the future we may be able to control local and

systemic autoimmune processes by increasing Treg cell numbers, directing the specificity of Treg cell function, or suppressing effector T cells using Treg cell mechanisms.

Cytokines can exert distinct signals on a wide variety of cells depending on their genetic program and activation status. A considerable body of evidence shows that IL-17-producing $CD4^+$ T cells, also known as Th17 cells, have been implicated in host defense to a variety of pathogens but also in the exacerbation of autoimmune pathology. This unique subset of Th cells develops along a pathway that is distinct from the Th1-and Th2-cell differentiation pathways. The review by Diveu *et al.* focuses on recent advances made in cytokine regulation of inflammatory responses, particularly with regards to the antagonistic functions of two members of the IL-12 family, IL-23 and IL-27. IL-23 promotes RORγt-dependent Th17 cell development and function that, in turn, supports skin, lung, and mucosal immunity. However, Th17 responses can also become critical mediators of autoimmune inflammation *in vivo*. In stark contrast, IL-27 has been documented to induce IL-10 production and, concurrently, to downregulate Th17 and Th1-mediated immune pathologies. Although this emerging and vibrant area of research is still dissecting these complex cell differentiation pathways, it has nonetheless identified important targets for therapeutic intervention for various inflammatory diseases.

Peripheral immune tolerance requires a finely controlled balance between maintaining tolerance to self-antigens, mounting protective immunity against enteric and invading pathogens, and dampening effector immune pathology. Although mucosal immunology and autoimmunity have often been perceived as being independent fields of study, it is now clear that many mechanisms maintaining tolerance to gut-related flora or dietary antigens are actually operative in assuring tolerance to a variety of systemic self antigens, as recently shown by Chervonsky and colleagues [2]. Thus, research into the cellular and molecular pathways underlying tolerance induction in mucosal environments has often cross-fertilized research in autoimmunity and advanced our collective understanding of immune self-tolerance. Researchers from both disciplines are attempting to identify the innate and adaptive cellular mechanisms that control aberrant inflammation, including Treg cells, as well as the factors that enable self-reactive lymphocytes to breach these mechanisms. The tissue architecture and regional immune system of the gut makes it a unique environment to study these questions. It is well accepted that a diversity of immune cells located in the gut actively contribute in the discrimination between commensal/invading microbes and dietary constituents, in the generation of protective IgA responses, and in the dampening of potentially, chronic inflammatory responses provoked by intestinal bacteria. How does the regional immune system of the gut integrates this symphony of signals is ill-defined, but emerging evidence suggests an interaction between luminal bacteria, epithelial cells and immune cells, including dendritic cells and macrophages, is essential to maintain intestinal homeostasis. The review by Rescigno *et al.* focuses on the role of these critical cell types in determining the balance between inflammation, immunity and tolerance.

The onset and pathological consequences of autoimmune diseases are often associated with disturbances in the functional balance between immunoregulatory/modulatory and pro-inflammatory cytokines. It is thought that manipulation of cytokine pathways may represent a valid mean to re-establish a balance between immunity and tolerance, and consequently achieve therapeutic success. The review by Strom and Koulmanda reports recent evidence suggesting that effector/pathogenic and protective/Treg T cells vary in their response to a variety of cytokines and may be selectively modulated by distinct cytokine pathways. In particular, several studies show that IL-2 can simultaneously provide vital survival signals to $Foxp3^+$ Treg cells, trigger activation-induced death of effector T cells and abrogate IL-15 driven expansion of memory cells. The ability of pro-inflammatory cytokines like IFNγ,

TNFα/β, IL-17 and IL-23 to exert selective effects upon critical lymphocyte subsets *in vivo* may also enable the development and application of novel therapies.

In conclusion, ongoing research in immunology continues to increase our understanding of the mechanisms that the immune system utilizes to maintain tolerance to self while mounting an effective and rapid response to non-self. Recent advances have shed light into the cellular mechanisms dictating immune tolerance, and have identified important events that define critical checkpoints in the regulation of autoimmune disease onset, progression and treatment. A more global understanding of the development and function of the various cell players and their cytokine mediators throughout the evolution of an autoimmune response will hopefully lead to insights for therapeutic approaches. Moreover, recent exciting studies that reveal identity and function of microRNAs in controlling the genetic programs of regulatory and effector lymphocytes [3–6] will provide a more global and basic understanding of the immune system in the next few years. However, difficulty remains in translating these findings into effective clinical methods. Nonetheless, recent clinical trials with B cell-depleting agents show promising results in more than one autoimmune disease, and new findings in the cytokine field are expected to increase our capacity of modulating immune responses toward self-tolerance.

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