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Editorial

Towards an integration of mathematical models, theories and observations concerning autoimmune diseases

The purpose of this special volume on models and theories of autoimmunity is to suggest that our understanding of autoimmunity and autoimmune disease is inadequate and has not kept up with our changing knowledge of immunology as a whole. The inadequacy is most apparent in the some dozen competing theories that currently exist, ranging from hidden and modified antigen theories, to molecular mimicry and anti-idiotype theories; from T-cell–B-cell mismatch and failed clonal deletion, to bystander and antigenic complementarity. The fact that none of these has clearly swept the field is evidence that each has serious limitations. Indeed, most current theories of autoimmunity were proposed between 1900 and 1985, some before the clear delineation of the roles played by different types of antigen presenting cells (APC), B cells and T cells; most before the discovery of the Toll-like receptors (TLR), nucleotide-binding oligomerization domain receptors (NOD), and other mechanisms of innate immunity; and all before the experimental investigation of how sex hormones and genetics affect immunity. These are crucial lacunae because recent research has demonstrated important roles for all of these in predisposing people to, and regulating the development of, autoimmune diseases. Many of the essays in this volume attempt to address one or more of these lacunae, or at least to better define them, so that more comprehensive theories and models can be developed and more incisive experiments can be planned and executed.

Another oddity of autoimmune disease research revealed by this volume is a disjunction, but also an unexpected synergy, between mathematical models and theories. While significant effort has been put into modeling the ways in which molecular mimicry may trigger, and anti-idiotype networks may regulate, autoimmune disease, few of the competing theories of autoimmunity have had more than cursory investigation through mathematical modeling. These include the hidden antigen theory, epitope spread theory, bystander effects, innate regulation of autoimmunity, antigenic complementarity theory, co-infection models, and the dual-affinity T cell receptor theory. Surprisingly, the strengths of the existing literature on mathematical models of autoimmunity lie in two areas for which there is no explicit theory. One is the role of idiotype–anti-idiotype networks in controlling susceptibility and progression to autoimmune disease. The other is the investigation of how T regulatory cells (T_{regs}) might determine susceptibility to autoimmune disease. Where most theories of autoimmunity start with the assumption that there has been a failure of the regulatory system (often in some unstated manner), thereby permitting the immune system to attack its host, mathematical modelers have very explicitly investigated the conditions under which network and/or T cell disregulation would permit autoimmune disease to develop. Mathematical modelers of autoimmunity have played an extraordinarily important role in providing the underpinning for what most of the specific theories of autoimmune disease take for granted.

The volume therefore starts off with a series of articles examining various mathematical models of how various environmental triggers might induce an autoimmune disease response. Saeki, Doekes and De Boer utilize a probabilistic model to investigate the conditions under which T_{reg} suppression of antigen-presenting dendritic cells would permit a successful specific immune response to be mounted while preventing initiation of autoimmune disease by pathogens that mimic host antigens. Their conclusion, which is consistent with a number of recent papers in the field, is that for values of T-cell cross-reactivity that are within current estimates, a successful pathogen response is very unlikely. In order to produce an effective immune response to a pathogen, the system they modeled is optimized when T cells are much more specific than current estimates suggest and also when there are no T_{regs} produced. These unintuitive results strongly suggest that our common-sense notions of how the immune system regulates autoimmune responses may be incorrect and that different mechanisms must be sought.

Blyuss and Nicholson provide one possible alternative. They suggest that there are two sets of T cells in any healthy individual, one composed of potentially autoreactive T cells, with one activation threshold, and the other of relatively non-specific T cells, with different activation thresholds. Modeling these two sets of T cells as separate compartments, each having “tunable” thresholds that detect different levels of infection and different antigen specificities, yields a model of how viruses can potentially induce a variety of states in the host depending on the various relationships between the thresholds: an acute infection that is rapidly cleared; a chronic infection; or a remitting–relapsing infection with autoimmunity.

The Blyuss–Nicholson model explicitly ignores any contribution of B cells to autoimmune disease, which makes the next paper by Agliari, Barra, Del Ferraro, Guierra and Tantari all the more interesting. Agliari et al., address the question of how B-cell mediated autoimmunity can be initiated. Their approach is quite novel, utilizing a statistical mechanics perspective to compare two of the dominant theories of how clonal anergy might normally be maintained. One is Varela’s theory that anergy results from the orchestration of the entire B cell repertoire through intensive feedback systems similar to those proposed decades ago by Niels Jerne. The other is the cognate response model, which proposes that potentially self-reactive clones are not stimulated by helper T cells and are therefore rendered anergic. The authors reach the surprising and interesting

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conclusion that under many conditions, the two theories are not only compatible, but produce identical results.

Menshikov, Beduleva, Frolov, Abisheva, Khramova, Tolyarova and Fomina also model Jerne's network theory, but using a series of partial differential equations rather than statistical mechanics. One assumption of the model is the identity of the idiotype and paratope in such a network, so that the active site of the antigen and that of the anti-idiotypic lymphocyte receptor are identical. Their results are similar to those of Agliari et al. in suggesting that regulation of autoimmunity resides in the interactions between potentially self-reactive clones and helper T cells, but Menshikov et al., identify this regulation as residing in the interaction of anti-idiotypic antibodies down-regulating helper T cell activity rather than in helper T cells controlling clonal activation. The Menshikov et al. paper is unique to this volume in including novel experimental results testing some of the predictions made by their mathematical model.

The overall impression that one gets from reading these mathematical modeling papers is that self-reactive clones are omnipresent and normal; that they are required for a normally functioning immune system to respond adequately to pathogens; that a distribution of lymphocyte and antibody reactivities ranging from highly specific to relatively non-specific may be required to produce such a normally functioning immune system; and that intensive feedback systems (whether composed of idiotype-anti-idiotype networks or other types of specific lymphocyte interactions) are a requirement of such systems.

Now, if autoimmunity is normal (that is to say, if auto-reactive lymphocytes and antibodies exist in every normal individual without causing pathogenic effects), what tips the regulatory systems described by the mathematical modelers from benign to disease-causing? Mathematical modelers tend to assume that there is a firm distinction between the pathogen or other environmental triggers of autoimmune disease, the host immune system, and possible host targets of autoimmunity. Thus, each becomes an independent variable. But is the issue that clear? On the one hand, Cohn writes in his contribution to this volume that, "any physiological system that has as its output an activity that is biodestructive and ridding must have a way of distinguishing the host (self) from that which is other (nonself). The setting in which autoimmunity can be analyzed depends, in part and unavoidably, on the way in which the normal self (S)–nonself(NS) discrimination is accomplished." Cohn provides a pair of penetrating propositions that can form the basis by which such self–nonself discrimination might be performed. Tauber, on the other hand, challenges us to consider the possibility that there is no clear demarcation between "self" and "nonself", suggesting instead that "all immunity is 'autoimmunity'". The evolutionary drive that resulted in the immune system, he contends, was to perform housekeeping activities that can, under a variety of conditions, escalate through a continuum of states to overt pathologies. So where Cohn proposes that autoimmunity results from "defects" in the immune system, Tauber asserts that it results from exacerbation of normal functions. The differences in Cohn's and Tauber's approaches bring us face-to-face with some of the most important elements of modern immunology, such as whether autoreactive lymphocytes are deleted or tolerized during development, as would be required to distinguish "self" from "nonself", or whether there is, instead, active positive selection *for* autoreactive lymphocytes so that they can maintain host integrity.

Vaz and Carvalho take the problem of whether it is possible to discriminate "self" from "non-self" a step further, noting that the recognition that a healthy human being is host to "an enormous and diversified commensal microbiota [poses] a new and pressing problem: how to explain the harmonic conviviality with trillions of foreign macromolecules." Like Tauber, Vaz and Carvalho argue that we need both a new evolutionary perspective and new linguistic conventions to address the difficulty in talking about the immune system of an organism that hosts commensal microbes and is in constant contact through its gut with myriad additional ingested foreign molecules to which it is orally tolerant. Could immunopathologies, they ask, result from the decrease in clonal diversity that must result from the adaptation of the immune system to these myriad molecules, leading in turn to a loss of stabilizing connectivity among the lymphocyte populations? This proposition certainly ties in nicely with some of the mathematical models of network regulation developed earlier in the volume.

Rose adds yet another twist to the microbiota issue raised in Vaz and Carvalho's article by examining the ubiquity of molecular mimicry between microbes and their hosts. Molecular mimicry is the sharing of epitopes among "self" (e.g., pathogen) and "nonself" (host) antigens that has evolved through a "Red Queen" process to produce microbes that camouflage themselves by producing antigens as similar to their hosts as possible. As Rose points out, the fact that molecular mimicry is extremely common raises an important problem for our understanding of mechanisms of immunological self-tolerance. If the immune system effectively deleted or tolerized any clone that could potentially attack the host, it would inevitably become unreactive to a wide range of pathogens as well, creating serious "black holes" in immune competence. We can, Rose contends, understand the trade-offs that the immune system makes in allowing some degree of auto- or cross-reactivity by placing clonal selection within the evolutionary context of molecular mimicry. Any theory of autoimmunity must address these trade-offs.

Rose's approach, of course, assumes that the immune system is itself an entity that can be treated as if it were independent of the host and the microbial mimics it encounters, which is consistent with Cohn's point of view, but with neither Tauber's nor Vaz's and Carvalho's. Thus we begin to see how the philosophy of immunology can have a significant impact on what problems we recognize and how we formulate them for investigation. In that vein, it is also interesting to note that reading Vaz and Carvalho along with Rose raises yet another conundrum for theoreticians of immunology, which is the question of what happens to the concept of molecular mimicry if we include in our concept of "self" the host's microbiome? Since the immune system must normally tolerate the microbiome, and presumably performs normal "housekeeping" on it as well as the host itself, could the same triggers that activate a pathological attack on the host also cause the microbiome to become a target for "autoimmunity"? Alternatively, could the microbiome be the initial target of autoimmunity and the host an unwitting, secondary participant? How would such "autoimmunity" against commensal molecular-mimics be manifested? Without an appropriate theory and the proper concepts, would we recognize it if was happening?

The final four papers in the volume use a different strategy to evaluate current approaches to understanding autoimmunity than do the mathematical modelers and general theorists whose papers make up the first two-thirds of the volume. The last set of papers focus on attempts to model and understand the pathogenesis of specific autoimmune diseases as case studies in the applications of various theories of autoimmunity.

Jaberi–Douraki, Schnell, Pietropaolo and Khadra use an ordinary differential equation model to parse the pathogenesis of type 1 diabetes mellitus (T1DM). Unlike the generalized mathematical models opening this volume, the Jaberi–Douraki model explicitly integrates the details of pancreatic beta cell turnover, cellular physiology, responses to stresses of immune attack, the varying avidity of anti-beta cell antibodies over the course of the disease, and lymphocyte turnover rates. One of the most interesting

outcomes of their analysis is that contrary to expectation, it appears that direct cell killing plays a minimal role in the development of T1DM. Rather, the autoimmune destruction of a small number of beta cells leads to physiological stresses on the remaining beta cells strongly affecting endoplasmic reticulum function and leading to massive cell suicide due to improper protein processing. Not only does this model provide novel insights into the possible pathogenesis of T1DM, but if generalizable to other autoimmune diseases, could causes us to rethink the degree to which autoimmune pathologies are indirect, rather than direct, consequences of immunological attacks.

Pendergraft, Badhwar and Preston also ask us to look at the pathogenesis of autoimmune diseases from a new angle. Many theories of autoimmunity assume either directly or indirectly that the disease trigger is an antigen that mimics a host target so that the antibodies to the trigger cross-react with the host. Pendergraft et al., propose instead that the "immunogen causing disease is a protein complementary (antisense) to the self-antigen, rather than a response to the native protein." More specifically, Pendergraft et al. develop their theory from the clinical observation of patients with anti-neutrophil cytoplasmic autoantibodies (ANCA), in whom they have found not only antibodies against the proteinase 3 of ANCA (PR3-ANCA), but also antibodies against peptides that were encoded in the non-coding strand of gene encoding PR3-ANCA. Using ANCA as a specific case, the authors develop a general theory that antisense peptides or proteins may play a critical role in initiating autoimmune diseases. This is an exciting proposition in light of the mathematical models of the Jerne's network theory developed by Aglieri et al. and Menshikov et al., since complementary antigens could potentially have quite different effects on such networks than do the single epitopes generally used to explore the behavior of such models. Hopefully, this volume will lead to collaborations in which these effects are investigated.

Merrill and Mu also take us into new territory, addressing one of the most interesting and least modelled realms of autoimmune disease: the effect of sex differences on the prevalence of these diseases. In only a handful of mostly quite rare autoimmune diseases do men acquire autoimmune diseases more frequently than women. Overall, approximately 80% of autoimmune diseases occur in women and much of that figure is due to a significant degree to the fact that nearly half of all cases of autoimmune disease involve thyroid autoimmunity; women predominate among these cases. While there is significant clinical and laboratory research being focused on the mechanisms underlying these sex differences, theories are generally lacking. Merrill and Mu propose that adipokines such as leptins, tumor necrosis factor-alpha and interleukin 6, which are significantly elevated in women as compared with men, activate various elements of the innate immune system through receptors on thyrocytes. Merrill and Mu also suggest that the thyroid is an unusually common target for autoimmune disease because it is particularly rich in these adipokine receptors and that these can provide an "adjuvant-like signal" that stimulates exogenous triggers of disease. Once again, Merrill and Mu's hypothesis, like those of Pendergraft et al. and Jaberi–Douraki et al., may provide more general insights into autoimmune disease pathologies if their work can be extended to other autoimmune diseases.

Finally, the volume concludes with a paper by Fairweather and myself examining the ability of half-a-dozen of the most cited autoimmune disease theories and their mathematical models to account for the clinical and experimental data concerning autoimmune myocarditis. Specifically, we evaluate the hidden or cryptic antigen theory (that autoimmunity is due to release of host antigens to which the host is not tolerized because the antigens are normally "hidden" from the immune system); the epitope spread theory (that autoimmunity is induced by a very weakly cross-reactive immune response that is progressively amplified by shifts in the epitope targets over time); the anti-idiotype theory (microbes use cellular receptors to target host tissues; antibodies against the microbe will mimic the receptors and anti-idiotype antibodies will mimic the microbe, therefore attacking the host); molecular mimicry (cross-reactivity between foreign antigens that mimic host antigens results in cross-reactivity producing autoimmune disease); the bystander or adjuvant effect (inflammatory processes, mainly involving innate immunity, create cellular destruction causing the release of host proteins that become targets of autoimmunity—see, e.g., Merrill and Mu); dual-affinity T cell receptors (a significant proportion of T cells exhibit multiple TCR which can cause the clone to be activated by one signal but target another); complementary antigen theory (simultaneous activation of the immune system by a pair of molecularly complementary antigens abrogates network regulation leading to autoimmunity—see, e.g., Pendergraft et al.); and co-infection or co-exposure (tissue destruction due to infection may be exacerbated non-specifically by a co-infection). A number or surprising facts emerged from this overview. First, most of these theories lack mathematical models, providing a rich field of possibilities. Second, there is significant evidence for each of the theories, but every observation can be accounted for by some subset of the other theories. This fact explains why no single theory has thus far dominated the field. Third, every theory lacks critical tests of some of its key assumptions, so there is a great deal of experimental and clinical work that remains to be done. Fourth, every theory is significantly deficient in failing to account for basic phenomena such as why the incidence of autoimmune diseases varies so greatly, is sex-dependent, and how autoimmunity is regulated by innate immunity. Thus, the volume ends with a set of challenges for the next generation of modelers and theoreticians to devise more robust, complete, and experimentally or clinically testable concepts.

The ultimate goal of such studies is, of course, to develop sufficient understanding of autoimmune diseases that we can actively and effectively intervene to prevent, better treat, or even cure them. So far, both mathematical models and theories are far from providing the kinds of information necessary for such interventions. Thus, we have to admit that although we are living in a golden age of data and techniques appropriate to the study of such diseases, our conceptual and theoretical ideas are not yet up to the task of understanding and explaining what we can observe. It is my hope that this volume will help to redefine the kinds of questions we ask and the way we ask them so that our concepts and theories can begin to lead the way toward treatments and cures of autoimmune diseases rather than following in the wake of the experimentalists and clinicians who are more or less blindly feeling their way forward. The contributors to this volume have boldly challenged us to take up this task by questioning what we think we know and knowing what we need to question.

Robert Root-Bernstein
Department of Physiology, Michigan State University, East Lansing, MI 48824, USA
E-mail address: rootbern@msu.edu

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