

The Role of Innate Immunity in Autoimmunity

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During the 2004 International Congress of Immunology in Montreal, a panel of experts gathered for an “Ideashop” discussion on the potential role of innate immunity in autoimmunity and the ways in which this might be targeted in future therapies.

Given the importance of innate immunity in the activation of conventional immune responses, a role for innate immunity in the development of autoimmunity is anticipated. The challenge is to identify which cells, receptors, and mediators are critical in different autoimmune settings. Recently, it has been suggested that the TLRs, which are classically thought of as sensors of microbial components, may have the potential to recognize self-antigens and trigger autoimmune disease (1). And the activating NK receptors expressed on CD8⁺ T cells may have a hand in the development of autoimmune diabetes (2). The inherent, low-level autoreactivity of certain specialized immune cell types which have both innate and adaptive characteristics, such as the CD1-restricted NKT cells, $\gamma\delta$ T cells, and B1 cells, suggests that they may also have the potential to stimulate autoimmunity, but there is little direct evidence at this stage. What was more unexpected, and still controversial at this point, is the potential regulatory role of these innate lymphocytes, with some groups reporting that NKT cells can protect against the development of autoimmune disease (3). Ideashop organizers, Matthias Von Herrath and Eli Sercarz, and sponsor, Kirin Brewery, hoped that a roundtable discussion of the new data and concepts would help clarify some of the uncertainties, suggest new research di-

rections, and stimulate ideas for future therapies. Sadly, not all of the topics that were discussed could be presented, but here are some of the highlights.

NKT Cells as Regulators of Autoimmunity

Jean-François Bach: There are data, and we contributed to it initially, showing that autoimmune strains—NOD mice, SJL mice (4), and lupus-prone mice—are somewhat deficient in NKT cells, both in number and function (5). In addition, one can prevent autoimmunity by a number of maneuvers that aim to boost NKT cells (6, 7). But there are also discrepant data. It would be nice to hear the opinion of the experts on this topic which relates to the more general problem of what is the involvement of NKT cells in regulation of immune responses?

Albert Bendelac: We have tried to explore this area and have had several results that are conflicting with others. Some of the most crucial data indicating that NKT cells are important in type-1 diabetes relies on crossing CD1d-deficient mice to the appropriate background, and there are different results from different laboratories. Obviously, one of the major issues here is the carrying of background genes that modify these diseases. That is very much true for diabetes, I think, and explains why there is such a discrepancy in the field.

J-FB: The NOD mice, when they are backcrossed to CD1d knock-out mice have been claimed to show enhanced disease expression, which indicated that NKT cells play a role in the physiological control of autoimmunity. But more recently, when we backcrossed the mice further we lost that difference (8, 9). Now, in collaboration with Masuru Taniguchi, we have crossed V α 14-deficient mice

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and NOD mice, and again, there was no disease acceleration (unpublished data). A complicating factor is the extremely important influence of sanitary conditions on the expression of this autoimmune disease. Were the sanitary conditions different (10), or was there a problem with the initial backcrossed mice? I don't know.

Matthias G. von Herrath: Let us say there is no difference in diabetes incidence between CD1d-deficient mice and NOD mice. This doesn't mean that NKT cells would not be a useful therapeutic tool. A similar consideration applies to the role of IL-4 in the diabetogenic process. Data in NOD mice and RIP-LCMV mice models are very clear in showing that physiological IL-4 production does not play any role during the diabetogenic process. However, IL-4 has been shown to have strong beneficial effects in both models (11, 12). Regarding NKT cells, the efficacy of therapy may depend on the set point in the peripheral blood. As I understand, there is considerable variation in NKT cell numbers between human individuals (13). So if we enhance NKT cells therapeutically, will we have to watch these set points and subclassify the patients in order to define those that might be responsive to this form of therapy?

AB: When we looked at humans with specific probes to identify NKT cells, we found extravagant differences (as much as a thousand-fold) between individuals. Some have virtually no NKT cells and others have 1–3% of peripheral blood lymphocytes (13). We looked at identical twins and they have exactly the same frequency of NKT cells. I have looked at my own for a couple of years now—they don't change, and it is the same for many other people. So everybody has a set frequency of NKT cells; it is genetically determined and it is set for life. Going to clinical trials, we will have to be extremely careful in terms of first determining the frequency of the cells and understanding the consequences of having a low or high level of NKT cells.

J-FB: There was some data initially in favor of the role of NKT cells in immunoregulation, particularly in the context of the Th1/Th2 paradigm (7). What would you say today?

Mitchell Kronenberg: Our research suggests that these cells are poised or programmed to make both IL-4 and IFN- γ , and that puzzles us. When we stimulate them through the T cell receptor, their immediate response is to make both cytokines (14, 15). Even with compounds that are reported to stimulate a Th2 response such as OCH we see immediately that NKT cells will make both cytokines. But we do find that the sustained IFN- γ that we expect to see in the serum is diminished with OCH compared with α -gal-cer. Perhaps they have communicated differently with DCs and ultimately with NK cells, which are the major producers of IFN- γ , we believe, following the activation of NKT cells. So it may be possible to manipulate the NKT cell response by using different ligands. The other thing that is important is that if you activate NKT cells not through the T cell receptor solely or primarily but through

other receptors, such as the IL-12 receptor, they don't make much IL-4 and they make more IFN- γ (16). So perhaps NKT cells can integrate the signals from different receptors that in the end might push the overall immune response in the Th1 or Th2 direction.

Are Innate Lymphocytes Drivers of Autoimmunity?

Michael B. Brenner: It's very important to keep in mind that NKT cells are there primarily to fight infection. We need to learn how they are activated in a variety of microbial encounters in order to understand the circumstances in which they are activated under physiological conditions. We also have to think about cognate antigen recognition. All evidence indicates that they are largely reactive to self-antigens. A variety of studies have underscored that the CD1d molecule picks up self-lipids based on where it traffics. This is a set up for cognate antigen recognition where the autoimmunity is not so much determined by the immunoregulatory aspects of NKT cells, but the cross-reactivity or over-activity on self-antigens in the context of molecular mimicry of foreign antigens. Thus, I would emphasize that there are two ways that NKT cells might be involved in autoimmune disease: the one that has just been discussed, and the other where they are actually the driver of autoimmunity through self-reactivity.

Mark J. Shlomchik: What cell types do you imagine NKT cells are recognizing CD1d on, in that case?

MBB: Most of what we know, with a few exceptions, comes from studies in mice, which have only CD1d. In humans, we must also consider CD1a, b and c. All of these molecules are known to recognize foreign microbial antigens. Yet, there is evidence that they also recognize self-glycolipids. Correspondingly, there is the potential for CD1a, b, and c foreign reactive T cells to also be self-reactive and to mediate autoimmunity, again based on cognate antigen reactivity. CD1a, b, and c are expressed almost exclusively on professional APCs, mainly dendritic cells, CD1c is also on B cells, and thus expression is more similar to MHC class II than MHC class I. In contrast, CD1d has a broader distribution including expression on both myeloid cells and some epithelial cells.

MGvH: What is known about these self CD1 ligands in terms of their potentially pathogenic presentation during inflammatory processing?

MBB: I don't have any data on that, perhaps Gennaro [GDL] does?

Gennaro De Libero: First, I would like to broaden the discussion to include not only NKT cells but also other T cells that recognize other types of self-antigens. We must not forget $\gamma\delta$ T cells in humans, for example, which recognize phosphorylated metabolites. We should also not forget MAIT cells in the gut and other types of autoreactive T cells that recognize other types of self-ligands such as gly-

cosphingolipid. We have recent data showing that if you stimulate antigen-presenting cells, like dendritic cells or macrophages, with pathogenic bacteria or different types of microbial components which are known to stimulate TLRs, you end up with a complete change in the metabolism of lipids (unpublished data). This leads to up-regulation of the synthesis of defined glycosphingolipids, and these APCs become capable of stimulating autoreactive T cells. There is an effect due to up-regulation of costimulation molecules; however, it is not sufficient. What we need for activation is this modification of lipid metabolism.

MBB: This is the concept of neo-self epitopes.

GDL: Yes, this is a kind of induced self-recognition. More self or perhaps slightly modified self is induced and so you get activation of these autoreactive cells.

AB: To extend what Gennaro [GDL] is saying, the notion of innate lymphocytes is a bit paradoxical when we talk about T cells, B1 cells, $\gamma\delta$ T cells, and NKT cells. They express rearranging receptors, so why would we call them innate? The innate characteristics come from several aspects. One is the sequence of the antigen receptor, which is germline encoded. You don't need any special manipulation of the genome to make the sequence, which has been likely evolutionarily selected from an ancient receptor. Then, there is the autoreactivity. They do not explode when you put them in presence of antigen-presenting cells, but there is a degree of autoreactivity. I believe that this autoreactivity is under the control of inhibitory receptors, such as NK inhibitory receptors in $\gamma\delta$ T cell and NKT cells. Finally, another aspect that brings them together very nicely is the fact that if you take the antigen receptor from a B1 cell, $\gamma\delta$ T cell, or NKT cell and make a transgenic mouse, you get back the lineage of the original cell. So the structure of the antigen receptor determines a number of characteristics of these lineages, and I think that is what brings them together under the innate-like lymphocyte denomination.

MK: One of the types of cells that I want to add to the list is CD8 $\alpha\alpha$ -expressing IELs that have the $\alpha\beta$ TCR receptor. We were involved a couple of years ago in showing that these cells require self-recognition in the thymus in order to develop (everybody used to think that they were extrathymic) (17). One of the unusual things about the CD8 $\alpha\alpha$ IELs is that although they are oligoclonal in their repertoire, they do not always have a conserved repertoire between individual mice. Another population that is supposed to be self-reactive is the CD25⁺ CD4⁺ regulatory T cells. At least those that are in the thymus are supposed to have gone through a self-recognition process, but they apparently have a very broad repertoire of receptors. So not all self-reactive cells that escape negative selection necessarily fit into something that is obviously an innate type lymphocyte. An extreme would be the $\gamma\delta$ cells that live in the mouse skin: they have one receptor and there is no N region diversity in the rearrangements, so there is very little

overall antigen receptor diversity. Other $\gamma\delta$ T cells have substantial structural diversity. It is useful to think about how these different cells might relate to autoimmunity. The idea used to be that they might be forming a bridge between innate and adaptive immunity. But what most people are thinking now, at least for NKT cells, is that they are components of what we might call the innate immune system, like dendritic cells and other cell types that have adjuvant-like effects on the adaptive immune response.

MBB: You can appreciate the innate features that stand out, and Albert [AB] emphasizes that these cells share. But I also agree with Mitch [MK] that these cells are somewhere in the middle between innate and adaptive. We don't have a perfect word to describe them. The other point I'd like to make comes from the K/BxN arthritis model of Diane Mathis and Christophe Benoist. Everyone has always thought that autoimmunity may result because the adaptive response is in some way perturbed under particular circumstances of innate stimulation. The K/BxN model has shown us that things can also go the other way, that if you have autoimmune T cell-B cell cognate self-antigen reactivity, the autoantibodies that are generated can activate the innate immune system through Fc receptors and complement receptors (18). I always thought about autoimmunity being initiated during or following an innate reaction. Now you also have to appreciate it the other way round: when self-reactivity occurs in adaptive immunity it may drive activation of NKT cells, $\gamma\delta$ T cells, mast cells, macrophages, and other innate cells that drive the inflammatory response.

Can Innate Immunity Link Cell Death to Autoimmunity?

J-FB: In the NOD mouse, there is a wave of β -cell apoptosis at 2–3 weeks of age, and it has been claimed that this could play a role in stimulating the anti- β cell response (19). There has been a similar observation in lupus where apoptotic cells seem to be stimulatory in various conditions (20). How do the apoptotic cells stimulate the autoimmune response?

MJS: The key, at least the way we are looking at it in lupus, is that the focusing on particular autoantigens is because these are the autoantigens that can provide B cells with an innate immune signal. Although B cells are not considered to be innate cells, they have innate receptors. Even in the K/BxN model, the question is still how do you get that productive T-B interaction in the first place? My feeling is that you need an innate immune signal to get that interaction. Our hypothesis has been that antigens like DNA are capable of providing B cells with a TLR signal at the same time. With Ann Marshak-Rothstein, we have shown that rheumatoid factor B cells and anti-chromatin B cells in vitro can be stimulated to give an unusual B cell immune response: a lot of autoantibody right away and not very much of a germinal center type response (1, 21). I think that may be down stream of the failure to clear apop-

otic cells or situations that create a lot of apoptotic cells. But there's no published data that really shows, at least in lupus, the role of TLRs in the onset of autoimmune disease. Our lab has been trying to test this.

Harvey Cantor: I've been impressed by the finding that uptake of apoptotic cells by plasmacytoid dendritic cells in association with ligation of TLR9 induces the cell to produce very high levels of interferon- α (22), which seems to stimulate the activity of conventional dendritic cells and enhance their ability to present autoantigen. I wonder if a common thread in the development of autoimmunity, particularly after viral infection, might be these fascinating sequelae that seem to occur after subpopulations of DCs are activated.

NK Cells and NK Receptors in Autoimmunity

Lewis L. Lanier: CD8⁺ T cells express a lot of NK receptors, and many of their ligands are in fact self molecules: for example, the ligand of the 2B4 (CD244) receptor is CD48, a cell surface glycoprotein expressed on many normal tissues (23). In addition, a lot of the NK cell receptors recognize MHC class I itself. Normally, NK cells are held in check by negative regulation by inhibitory receptors for MHC class I. To overcome that you can either diminish the ligands of the inhibiting receptors (that is MHC class I), or you can just jack up the density of the ligands for the activating receptors. In general, many of the autoimmune phenomena we are talking about maybe explainable by a tipping of that balance in T cells.

J-FB: What do you know about the regulation of expression of these ligands?

David H. Raulet: For MICA/B there is evidence suggesting there is some transcriptional level regulation of the ligands for the NKG2D receptor (24), but I also think that there may be some protein level regulation of other ligands.

LLL: TLR signals certainly regulate this family of ligands for NKG2D. We looked at mouse peritoneal macrophages and demonstrate up-regulation of the RAE-1 ligands (25), but many other types of cells in tissues that are involved in autoimmune disorders have TLRs. There is a nice paper from Tom Spies' group looking at the synovial tissues of rheumatoid arthritis patients (26). They saw overexpression of MICA/B. It's phenomenology, but it's suggestive.

HC: In terms of the concept of an autoimmune attack against a particular subset of cells through decreased inhibitory receptor activity, you find that if you knock out the ligand that normally interacts with inhibitory NKG2A, -C, and -D receptors, the activated CD4 T cells, which normally express these ligands, are no longer allowed to become memory cells because now they are susceptible to NK cell activity (unpublished data). The result is an inability to generate immunological memory.

LLL: The most striking inhibitory receptor I know about is SIRP α , which is an inhibitory receptor expressed on macrophages. Its ligand is CD47, which is found on lots of tissues. If you take red blood cells from CD47 knockout mice and put them into wild-type animals, the macrophages eat them immediately and cause autoimmune hemolytic anemia (27).

MK: What about the NK cell itself? Do you find evidence for a role in autoimmunity?

DHR: I don't have any specific evidence in terms autoimmunity, but certainly there is a lot of evidence that NK cells regulate dendritic cells in positive and negative ways.

LLL: Diane Mathis had a paper where they depleted NK cells in NOD mice and they prevented diabetes (28). The reason Diane did this was that NK cells are one of the first infiltrating cells in the pancreas. Obviously, they can't cause disease by themselves because NOD-SCID mice don't get sick, so there must be some back and forth with T cells. But it changed my opinion because I previously had thought NK cells were bystanders in the disease process.

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Glossary

α -gal-cer: α -Galactosyl ceramide; a glycosphingolipid originally isolated from a marine sponge, which binds to CD1d and is recognized by a subset of NKT cells in this context.

CD1d: MHC class I-like molecule that can present nonpeptide antigens and is recognized by NKT cells.

IEL: Intraepithelial lymphocytes; found within the intestinal epithelium.

K/BxN: Mice transgenic for a TCR recognizing an epitope of bovine RNase bred onto a NOD background, which develop a disease resembling rheumatoid arthritis. Disease is transferable by autoantibodies in the animals' sera specific for the ubiquitous self-antigen glucose-6-phosphate isomerase.

MAIT cells: Mucosal-associated invariant T cells; located in the gut lamina and restricted by the MHC class I-like molecule MR1.

MICA/B: Human MHC class I-like ligands for the activating NK receptor NKG2D, which may be induced under conditions of cellular stress.

NOD mice: Nonobese diabetic; a spontaneous mouse model of autoimmune diabetes.

OCH: A synthetic variant of α -gal-cer that has been reported to induce Th2-like responses.

RIP-LCMV mice: Rat insulin promoter-LCMV glycoprotein transgenic mice; a viral-induced model of autoimmune diabetes.

SJL mice: Mouse strain highly susceptible to the induction of experimental autoimmune encephalitis, an animal model of multiple sclerosis.

TLRs: Toll-like receptors; a family of innate immune receptors that recognize various molecular patterns associated with pathogens.

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