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Different modes of pathogenesis in T-cell-dependent autoimmunity: clues from two TCR transgenic systems

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Summary: T lymphocytes constantly flirt with reactivity to self peptides, a price they pay for their ability to recognize foreign peptides presented by self-MHC molecules, and autoreactivity in the T compartment occasionally gives rise to autoimmune disease. Pathology from T-cell autoimmunity can manifest itself through radically different strategies, as we have observed recently in two transgenic models. In the BDC2.5 diabetes model, T cells express a transgene-encoded T-cell receptor (TCR) with reactivity against a pancreatic antigen. This leads to a massive, if often controlled, infiltration of the pancreatic islets. Target cell destruction then results from the local consequences of this local immune/inflammatory process. On the other hand, the arthritic manifestations of the KRN transgenic model are indirect: the transgenic TCR confers a broad autoreactivity, through which T cells stimulate B cells to produce arthritogenic immunoglobulins. These molecules are then sufficient to produce the disease, even in the complete absence of any lymphocytes. Although important questions subsist in this model – how the KRN T cells interfere with B-cell tolerance, what the target of arthritogenic IgG is – its implication is that an isolated T-cell dysregulation may manifest itself through an Ig-mediated disease.

Introduction

Dysregulated reactivity of T lymphocytes is a primary determinant of several organ-specific autoimmune diseases. Some of these diseases have an endogenous origin, reflecting a qualitative or quantitative breakdown of tolerance induction mechanisms: a leakiness of central tolerance in the thymus, allowing clones with high affinity for self to emerge into the peripheral circulation, or a failure of peripheral tolerance, resulting in an inability to control clones reactive to organ-specific antigens. In other cases, the suspected trigger is exogenous: antigenic mimicry, where a foreign antigen activates and amplifies T cells fortuitously cross-reactive with a self-component, or bystander activation, where T cells expressing an autoreactive receptor but previously kept in check are activated in the context of the inflammatory state created by a microbiological infection, which modifies the manner in which antigen is presented and how T cells respond to it (1–3). Many such scenarios have been proposed, and evidence for their possible existence has been provided in rodent model systems (4–9).

The terminal step of the autoimmune process, destruction of the target tissue, is generally assumed to represent directly deleterious consequences of T-lymphocyte activation. T cells are equipped to produce a range of toxic cytokines, to carry granule-loads of pore-drilling factors and proteases, and to express surface ligands for death receptors on target cells. It is not surprising, then, that they are prime suspects when found in an activated state at the scene of tissue inflammation and destruction. Some of the evidence incriminating T cells in rheumatoid arthritis (RA), for example, is of this nature (10, 11). As discussed previously (12), T-cell toxicity when in close apposition to the target tissue can be direct, with recognition of antigen presented by the target cell leading to immediate killing (recognition-linked). It can also be indirect, with the activation of T cells by local antigen-presenting cells (APCs) leading to destruction of epithelia in the immediate vicinity through production of toxic cytokines, triggering of death receptors on the target by ligands induced on the activated T cells, or through stimulation of cytocidal properties of macrophages (activation-linked).

Yet organ lesions in autoimmune diseases instigated by T cells may not always correspond to such local-action scenarios. We have recently obtained evidence, in a transgenic mouse model of arthritis, that autoreactive T cells can provoke damage indirectly and at a distance (13, 14). Once the process has been initiated, the contribution by autoimmune T cells is accessory and dispensable.

We will illustrate here these two different modes of tissue destruction induced by autoreactive T cells, taking as examples two transgenic mouse models that have been studied extensively in our lab. Both transgenic lines express a rearranged T-cell receptor (TCR) specific for a self-antigen. Their modes of aggression of the target tissues are radically different: in the first case, destruction follows the classical scenario, with a massive infiltration by T cells that eventually destroys the tissue. In the second case, the mode of action is very indirect, the T cells acting at a distance.

Local destruction: diabetes in the BDC2.5 mouse

This transgenic line represents a simplification (and an exaggeration) of the non-obese diabetic (NOD) mouse model of autoimmune diabetes, in which T cells reactive to antigens expressed by pancreatic β cells are the major causal element. The line was derived from a $CD4^+$ T-cell clone reactive to an islet-specific antigen presented in the context of the A^{g7} MHC molecule, and isolated by Haskins and colleagues from the peripheral lymphoid organs of a diabetic NOD mouse (15, 16). The TCRα and β-chain genes of this clone were isolated and used to produce transgenic mice (17). Due to the dictates of allelic exclusion, essentially all $CD4^+$ T cells in these transgenic animals express only the transgenic TCRβ ($V\beta4^+$) chain, and many the TCRα chain.

The rationale of this experiment was to follow the selection and/or tolerization of T cells reactive to an antigen exclusively expressed in peripheral tissues. On the NOD background, which provides the A^{g7} MHC molecule appropriate for positive selection of transgene-expressing T cells and presentation of the β-cell antigen, thymic selection and export of $CD4^+$ T cells expressing the transgene-encoded TCR proceed normally (17). There is no sign of central or peripheral tolerance induction. Autoimmune attack is rapid and vigorous: transgene-expressing T cells are first activated in the draining pancreatic lymph nodes, and then quickly migrate to the islets, which they infiltrate massively (17, 18). Interestingly, though, destruction of the insulin-producing β cells does not necessarily follow. In some instances, and depending on the genetic and environmental status of the mice (see below), the insulitis is immediately aggressive and destructive, and overt diabetes appears at 3 to 6 weeks of age; in others, a stable and balanced state of insulitis sets in and persists for long periods of time, and the mice remain normoglycaemic. This state of equilibrium does not represent anergy in the infiltrating cells. The infiltrating $CD4^+$ cells express activation markers and turn over rapidly through active cycling and apoptosis (*Fig. 1*, (17–19)); there is evidence for production of cytokines of both Th1 and Th2 types.

The first few days of infiltration by T cells seem to condition the type of insulitis. Several factors determine which path is followed:

- There is a strong influence of the genetic background of the mice. On the NOD background, regulated and stable insulitis is the most frequent mode of evolution of BDC2.5 autoimmunity, while on the $B6.H2^{g7}$ background insulitis is most frequently aggressive (20). This strain association appears paradoxical at first, since NOD is the prototype diabetes-prone mouse. On further consideration, however, the result makes sense, since the NOD strain was isolated in a long breeding scheme, selecting for diabetes; genes predisposing to a fast onset of disease would be incompatible with breeding, and would have been eliminated in this protocol. This genetic influence is complex, involving several loci. The interest shown in a leading candidate locus, TGFβ, has recently been downgraded, as its sequence and expression appear to be identical in NOD and C57Bl/6 strains (L. Poirot, unpublished).

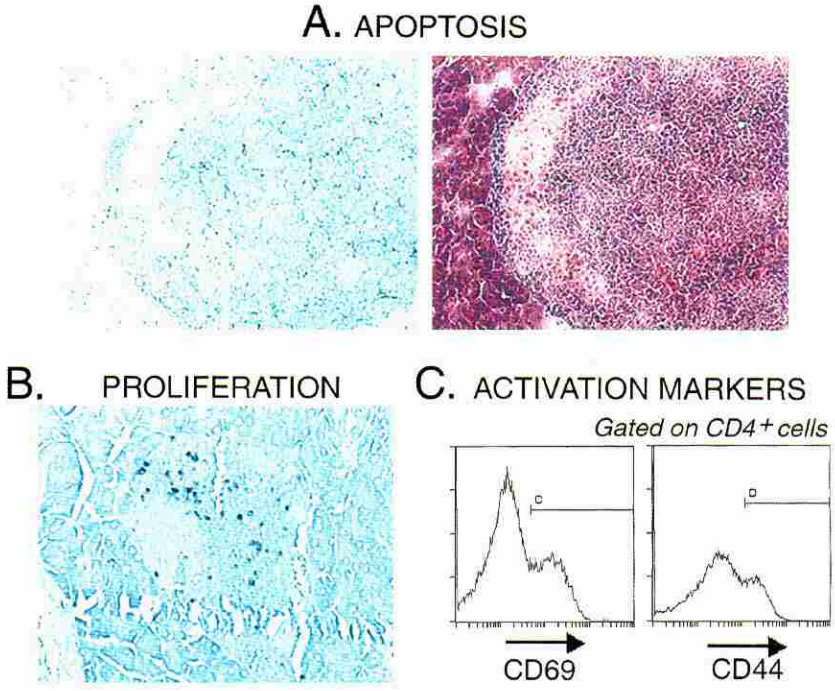

Fig. 1. Active T cells in stable BDC2.5 insulitis. A. Active apoptosis. Serial sections of pancreas from 8 week-old BDC2.5/NOD mice were stained by the TUNEL technique for the presence of apoptotic cells (left) or haematoxylin/eosin. Note the presence of many apoptotic cells (brown spots) which are almost all localized in the lymphoid/monocytic infiltrate, but not in the surviving β-cell region of the islet. Objective: ×20. **B. Active proliferation.** An adult BDC2.5/NOD mouse was injected with ^{3}H-thymidine; pancreatic sections were prepared 12 hours later and exposed to emulsion. Dividing cells are identified by the accumulation of grains, here again in the lymphoid infiltrate. Objective: ×10. **C. Activation markers.** Infiltrating cells were prepared from an adult BDC2.5/NOD mouse and analyzed by multiparameter flow cytometry. A high proportion of gated CD4-positive cells display early (CD69) and late (CD44) activation markers. In control lymphoid organs of the same mouse, only 5–10% of CD4^{+} cells express the same activation markers.

- The overall composition of the lymphocyte compartments in the transgenic mice also has a major influence. BDC2.5/NOD transgenic mice crossed onto severe combined immunodeficiency disease (SCID) (21) or recombinase-activating gene (*RAG*)-deficient (our unpublished data) backgrounds, and thus devoid of B cells and unable to express any other TCR (αβ or γδ), show a most aggressive disease. Overt diabetes appears in a matter of days after the onset of insulitis. It is not known whether this phenomenon denotes the existence of a clonotype-specific mode of immunoregulation (hypothetical 'suppressor cells'?) or less specific influences (microenvironment crowding, non-specific cytokine consumption). Analogy with the experimental allergic encephalomyelitis system might argue for the former (22, 23).
- Manipulating co-stimulatory pathways in T cells has a profound effect on the degree of aggressiveness. Timed injection of anti-cytotoxic T-lymphocyte-associated antigen (CTLA)-4 monoclonal antibody in BDC2.5/NOD mice elicits an aggressive and destructive evolution (24). This is most readily interpreted as preventing negative signalling through this molecule (25). Interestingly, the time window in which this effect is observed is very narrow, corresponding to the phase in which the activated T cells begin to infiltrate the islets (24) (F. Lühder, unpublished data).

Once stable insulitis sets in, its equilibrium can still be upset. This can occur spontaneously, and a proportion of BDC2.5/NOD transgenic mice develop late diabetes, beyond 15 weeks of age. This proportion varies with the colony, even among otherwise genetically identical and thoroughly backcrossed animals (J. Katz, R. Flavell, N. Sarvetnick, L. Chatenoud, personal communications). Other factors can disrupt the equilibrium, in a catastrophic fashion:

- Infection of BDC2.5 mice with Cocksakie B4, a virus with tropism for neighbouring cells of the exocrine pancreas, induces the stable insulitis of BDC2.5/NOD mice to become aggressive and destroy islet cells (8). Most likely, the inflammatory conditions induced by the nearby viral infection destabilize the regulatory balance of the established insulitic lesion. Local cytokine and chemokine production likely modifies the conditions of antigen presentation and/or of T responses within the islets.
- A dramatic shift in the characteristics of the insulitis can also be induced by low-dose treatment with cyclophosphamide (Cy) in BDC2.5/NOD mice with established insulitis, resulting in complete islet destruction and overt diabetes in a matter of days. The profound histological changes are accompanied by a marked increase in the production of inflammatory cytokines, and these are essential for the progression of the destruction (19).

In this transgenic model of diabetes directed against natural autoantigens, throngs of autoreactive T cells are thus in close proximity to the target organ. It is only there and in the immediate draining lymph nodes that activated cells are found. Sev-

eral of the results mentioned above indicate that these local T cells do play an immediate role in tissue destruction: 1) the aggressive insulitis of BDC2.5/NOD mice crossed onto SCID or RAG-deficient backgrounds, which shows that variations in T-cell populations condition the outcome; 2) the effect of anti-CTLA-4, which modifies regulatory signalling in T cells at the time of antigen recognition and lymphocyte activation; and 3) the blocking of Cy-induced disease by concomitant administration of anti-CD4 monoclonal antibodies, indicating that T cells are involved in this process.

The mode of β-cell killing in autoimmune diabetes is unknown at present (for reviews see (12, 26)). There is evidence for the participation of perforin from $CD8^+$ T cells, but diabetes in its absence is only partially reduced (27). A role for the fas-fasL pair has been proposed (28), but on the basis of arguments which have since been refuted (29–31). In fact, we do not know whether the T cells themselves deliver the lethal hit, and it is conceivable that the local destruction involves unleashing by T cells of macrophage cytocidal activity (32, 33), or even the recruitment of γδ or natural killer cells, as elsewhere (e.g. (34)). Yet, whatever the molecular details, and even if T cells must enlist the help of macrophages, it is clear that in the BDC2.5 system, and in NOD mice in general, the destruction is provoked by local T cells infiltrating the tissue.

Long-range destruction: arthritis in the KRN mouse

Tissue destruction in the KRN model of arthritis follows a very different path. This mouse model is again based on a transgene-encoded rearranged TCR with reactivity to a self-component (13). All KRN TCR transgenic mice produced on the B6xNOD genetic background (K/BxN mice) develop an inflammatory joint disorder, beginning at 3 to 4 weeks of age, and rapidly evolving until the joints are severely deformed; the disease is chronic, progressive, symmetrical and has a proximal to distal gradient of severity. It shares all of the major histological features of human RA: leukocyte invasion, synovitis, pannus formation, cartilage and bone destruction and anarchic remodelling of joint structures. K/BxN mice, like patients, show several immunological abnormalities, in particular polyclonal B-cell perturbation with an increase in B-cell numbers and hypergammaglobulinaemia, but with the noted absence of IgM anti-IgG immunoglobulins (rheumatoid factor (RF)).

The initiating element of the KRN model lies in the reactivity of the TCR against NOD-derived MHC class II A^{g7} molecules. Recognition of A^{g7} molecules by the KRN TCR does not appear to involve particular joint-specific antigenic peptide(s), and can be elicited by APCs from spleen or thymus, or by cells grown *in vitro*. An autoreactive situation is thus generated in K/BxN mice* which express both the transgenic TCR and its stimulatory target. This situation is similar to other autoreactive transgenic systems described previously (35–38), but in which arthritis was never observed. Multiple levels of tolerance induction in the T-cell compartment can be observed in K/BxN mice – thymocyte clonal deletion, diminished levels of TCR clonotype due to selection of cells exhibiting incomplete allelic exclusion and clonal inactivation of peripheral cells (13). However, these are not completely effective, and a low level of transgene-specific reactivity persists (13).

How does organ-specific autoimmune disease develop in the context of systemic self-reactivity, and where do T cells come into play? T cells, and the self-reactivity due to the KRN transgene, are at the root of the disease because of the very nature of the transgene involved (recently derived KRN mice on a RAG-deficient background have confirmed that disease is due to the KRN specificity itself), because the disease is manifest only in the presence of the MHC molecule able to stimulate this TCR, and because anti-CD4 mAbs block disease if administered before clinically overt arthritis. Yet anti-CD4 reagents have no effect later in disease course, suggesting that T cells exert their major role in the initiation rather than the effector stages. It is also quite obvious that the local lesion involves very few T cells. They represent a very small minority of the cells that invade the articular cavity and are also rare in the synovial infiltrates (Fig. 2). In both locations, they are grossly outnumbered by macrophages or granulocytes.

B cells are also required in the K/BxN model since introduction of the μM° mutation, which causes an absence of B cells, results in a block of arthritis development (13). We have recently dissected the role of B cells (14). After testing several possibilities – indirect effects, antigen synthesis by B cells and synthesis of a particular cytokine – we established that B cells engage in a critical A^{g7}:TCR-mediated, CD40:CD40L-dependent interaction with T cells, and ultimately act by secreting arthritogenic Igs. Transferring as little as 100 μl of serum from arthritic K/BxN mice into healthy B-cell-deficient, or even lymphocyte-deficient, animals provokes arthritis within days. The induced disease exhibits all of the major histological features of the spontaneous one. It is transient after a single inoculation of serum, essentially resolving in 20 to 30 days, but can be made to persist by repeated injections. The arthritogenic activity in K/BxN serum resides in the IgG fraction and depends on particular Ig specificities: disease can be prevented

* In truth, the autoreactivity was only discovered when seeking the cause of the unexpected and unexplained arthritis.

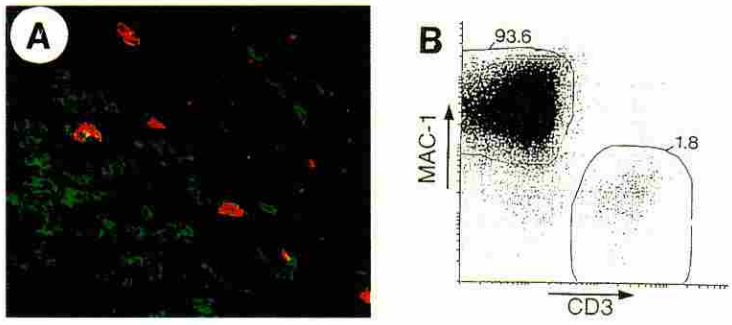

Fig. 2. T cells (or lack thereof) in the KRN arthritic lesion. A. A cryostat section of synovial tissue from a K/BxN mouse stained with mAbs against T cells (CD3, red) and macrophages (Mac-1, green). Note the rarity of T cells (the few cells seen here are actually an exception, as most fields on such sections contain even fewer T cells). **B.** Flow cytometric analysis of the synovial fluid of a K/BxN mouse showing active arthritis, in which the huge majority of cells are of the myelo-monocytic lineage (Mac-1 positive).

by crossing K/BxN mice with Ig 'knock-in' mutants, which carry IgH and Igκ loci altered so as to encode Igs of a single, irrelevant, specificity. This arthritogenic Ig specificity is not RF, nor anti-collagen-II. Although disease can be precipitated by serum transfer into BxN-μM$^{o/o}$ mice not expressing the KRN TCR transgenes, it is more severe in K/BxN-μM$^{o/o}$ animals, suggesting that KRN T cells may have a secondary influence on the later stages of disease.

Taking into account all of the data accumulated to date (detailed in (13, 14)), we hypothesize the following scenario to account for the development of arthritis in K/BxN mice: 1) T cells expressing the KRN receptor recognize a self-peptide in the context of A^{g7} molecules displayed on peripheral APCs, and become activated. The critical APCs are probably dendritic cells and/or macrophages as this process does not require display of A^{g7} on B cells or on synovial fibroblasts or chrondrocytes. 2) Activated KRN T cells interact with B cells through TCR:A^{g7} and CD40L:CD40 engagements, promoting broad activation of the B cell compartment and Ig overproduction. 3) Amongst the Igs produced, some possess arthritogenic potential, this process depending critically on particular Ig specificities. They could be pathogenic via several mechanisms: direct perturbation of joint structures; activation of the complement cascade, resulting in cell lysis and/or production of inflammatory mediators; and engagement of Fc receptors, inducing activation of local cells.

This scenario raises two main questions. First, what are the specificities of the arthritogenic Igs? Prime candidates might have been RF and anti-collagen-II antibodies but we have ruled out both of these (13, 14). This question thus remains open. Second, how do these particular Ig specificities come to be produced? T cells expressing the KRN receptors can recognize essentially any cell displaying A^{g7} molecules. Thus, KRN T cells should be able to stimulate the entire repertoire of B cells, as they all display MHC class II molecules and CD40. However, polyclonal B-cell activation is too simple an explanation for disease in the K/BxN model: other polyclonal activators do not elicit the aggressive and isolated arthritis characteristic of these mice. There has to be selectivity to the stimulation, at least at the level of Ig production. There are several possible explanations here:

- Reactive T cells may interfere selectively with early phases of B-cell tolerance induction. The generation and maintenance of a B-cell repertoire that is tolerant to self-constituents is known to be a complicated affair, relying on multiple mechanisms (reviewed in (39, 40)): clonal deletion of pre-B cells in the bone marrow or in secondary lymphoid organs, anergy induction and receptor editing. It is easy to imagine that some of these could be prevented by concomitant engagement by activated T cells. Some B cells undergo arrest of differentiation in the bone marrow, but do not die until some time later in the periphery; this process is reversible in the presence of T-cell help (41). Clonal deletion can also be thwarted by T-cell help (42–44). Alternatively, KRN T cells may awaken anergized B cells. Thus, engagement by T cells may preferentially lead to the appearance of 'forbidden' autoreactive immunoglobulin specificities, or to the expansion of the autoantibodies normally found in 'natural antibodies' (45).
- It is also conceivable that KRN T cells react against a single ubiquitous self-peptide presented by A^{g7}, derived from a protein present in only moderate amounts, such that those B cells that can internalize this molecule through their surface Ig receptor receive more help than do the bulk of B cells. This scenario parallels the classical demonstrations of preferential processing and presentation of antigens by B cells that can internalize them through cognate surface receptors (46). It predicts that KRN T cells and arthritogenic Igs recognize different epitopes on the same self-protein. Why Igs directed against a ubiquitous self-protein generate exclusively arthritis would still need to be explained in this hypothesis.

Whatever the interpretation, it is clear that autoreactive T cells, in the KRN model, lead to joint lesions in a manner that is fundamentally different from that of islet destruction in the BDC2.5 model. This basic dichotomy is schematized in *Fig.* 3.

Generality?

In the two transgenic models described above, autoreactive T cells thus have extremely different means to induce lesions in their target tissues. Can this dichotomy be generalized to other spontaneous disease states?

The first mode of destruction, that of the BDC2.5 T cells, is likely to be at play in insulin-dependent diabetes mellitus (IDDM) in murine models and in human patients: many of the characteristics of the BDC2.5 mice are also present in NOD mice, in which disease can also be transferred in the absence of B cells (47, 48); there is no evidence of a pathogenic effect of antibodies. On the other hand, introduction of the μM° mutation into NOD mice largely prevents diabetes (49–51), which would point to some role for B cells, perhaps in antigenic epitope spreading. By inference, IDDM in humans would also result from local and direct T-cell effects. A local action of T cells can also be invoked in experimental allergic encephalomyelitis, and by extention in multiple sclerosis. This is also the case in the several models of disease induced by immunization with tissue extracts or antigens (experimental thyroiditis, orchitis, prostatitis, myocarditis (see (9, 52–54) and references therein).

It is perhaps in the autoimmune diseases classically classified as 'B-cell autoimmunity' that one should look for homologues of the KRN mode of pathogenesis. In diseases such as myasthenia gravis, Grave's disease, pemphigus, or haemolytic anaemias, autoantibodies have a recognized role in provoking the pathological manifestations. The molecular targets of these effector antibodies, specific to each disease, are known (for reference, see (55)). Yet the primary dysregulation that provokes the synthesis of these antibodies is not. It is thus conceivable that a mechanism analogous to that of KRN mice is at play: pri-

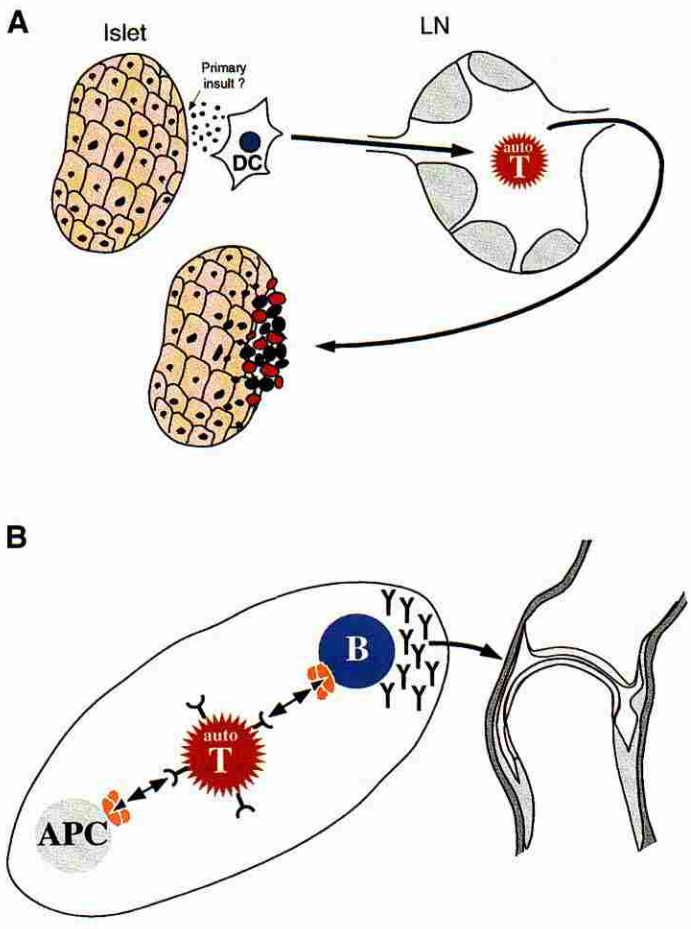

***Fig.* 3. Two fundamentally different modes of pathogenesis by autoreactive T cells.** A schematic representation of islet destruction in BDC2.5 mice and of arthritogenesis in K/BxN mice. **A.** In BDC2.5 mice, pancreatic antigen, perhaps released preferentially after a local insult, is picked up by dendritic cells, which ferry it to the draining pancreatic lymph node. There, they activate T cells expressing the BDC2.5 specificity, which then home back to the islet, creating the insulitic lesion which eventually destroys the insulin-producing β-cells. **B.** In K/BxN mice, the autoreactive T cells are stimulated by A^{g7}, their allo-specific target, presented by APCs in secondary lymphoid organs, and in turn stimulate B cells through the same molecule (and CD40:CD40L interactions). These B cells are enticed (through prevention of tolerance induction?) to produce pathogenic Igs. These Igs are responsible for the joint lesions, without any requirement for lymphoid cells at the effector stage.

mary amplification of an antigen-specific T cell, which secondarily activates and helps antigen-specific B cells. Of course, the notion that T cells must somehow be involved in these B-cell diseases, if only to provide help for IgG production, has long been obvious. What is striking in the present observations is that an Ig-mediated disease has, at its origin, a pure T-cell autoreactivity. The autoimmune manifestations of fas-deficient mice and humans could also fall into this category: is the production of pathogenic autoantibodies due to a deficiency of cell-death mechanisms in B cells, or does it result indirectly from the unchecked proliferation of double-negative T cells? And, last but not least, the mode of pathogenesis in KRN mice may be a model for human arthritis: autoreactive T cells trigger MHC class II targets on B cells, which then produce arthritogenic antibodies.

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