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Commentary

Cross-tolerance: A Pathway for Inducing Tolerance to Peripheral Tissue Antigens

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T lymphocytes develop within the thymus, where they are positively selected for self-restriction and purged of cells exhibiting strong reactivity to self-antigens presented within this microenvironment. Mature lymphocytes then enter the peripheral lymphoid pool, where they recirculate between the various secondary lymphoid organs, including the spleen and the lymph nodes that drain peripheral tissues (1). It is almost exclusively within these lymphoid tissues that T lymphocytes first encounter antigen. The rapid recirculation of the total lymphocyte repertoire within the relatively confined secondary lymphoid compartment, in combination with the effective movement of antigens from peripheral sites to draining lymph nodes, permits highly efficient surveillance for infection throughout the whole organism. Thus, the secondary lymphoid organs effectively bring together the key players required for immunity; notably the T cells, their target antigen, and, importantly, the APCs. It is the APCs that simultaneously provide a crucial scaffold for effective recognition of extralymphoid (peripheral) tissue–derived antigen and, potentially, directly participate in the movement of antigen from peripheral sites of expression to the central locations where effective T cell activation takes place. In this commentary, we will focus on the trafficking and presentation of peripherally derived antigens within the secondary lymphoid compartment, and discuss emerging evidence suggesting that this presentation is not only responsible for effective T cell priming, but may also function in the induction of T cell tolerance to self-antigens expressed exclusively by peripheral tissues.

Cross-tolerance: Tolerance Induced by Cellular Antigens Indirectly Presented by Bone Marrow–derived APCs. Evidence that cellular antigens can be transferred and indirectly presented by professional APCs can be traced to early experiments examining the MHC-restriction of responses to minor histocompatibility antigens (2–5). For example, Bevan primed (BALB/c × BALB/B)F1 mice ($H\text{-}2^d \times H\text{-}2^b$) with cells from C57BL/10 (B10) mice, which shared $H\text{-}2^b$ MHC molecules but differed in their expression of B10 minors (4). As expected, $H\text{-}2^b$–restricted CTLs specific for B10 minors were induced by this immunization, but, unexpectedly, so were $H\text{-}2^d$–restricted CTLs. Concluding that in order to induce an $H\text{-}2^d$–restricted response, minor antigens must have been transferred to APCs of host origin, Bevan coined the term "cross-priming", referring to the CTL priming associated with the capture and presentation of cell-derived antigens by host APCs. We have used this definition as the basis of the term "cross-presentation", which signifies the presentation event itself. By extension, tolerance that results from such cross-presentation has been called "cross-tolerance". Traditionally, these terms have referred to access of exogenous antigens (primarily cell-derived antigens) to the class I pathway, whereas indirect presentation has referred to the presentation of cell-derived antigens via the class II pathway. For simplicity, here we will use the term cross-presentation to encompass both class I– and class II–restricted pathways.

Cross-presentation Permits Recognition of Peripheral Antigens by Lymph Node T Cells. These early cross-priming experiments, which primarily focused on class I–restricted CTL responses, led to the suggestion that cross-presentation represented a mechanism whereby T cells could be primed to antigens expressed in peripheral sites, such as those resulting from tissue-tropic virus infection (6, 7). Furthermore, the subsequent realization that the cytosolic-based MHC class I–restricted antigen presentation pathway normally excluded presentation of exogenous antigen (8), strongly implied that either the form of the antigen, or the APCs themselves, possessed some special properties enabling access to the class I pathway (6, 9).

Although the identity of a specialized cross-presenting APC, explored below, remains contentious, the formal demonstration of cross-presentation of peripheral tissue–derived antigen has been achieved in recent years. This demonstration required the generation of transgenic animals expressing antigens exclusively within defined peripheral tissues, under the control of tissue-specific promoters. Lo et al. used bone marrow chimeras to show that hemagglutinin expressed by islet β cells could be cross-presented within the pancreas to $CD4^+$ T cells by a bone marrow–derived APC (10).

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Class I–restricted cross-presentation of peripheral tissue antigens was formally demonstrated using transgenic mice expressing ovalbumin (OVA) in the pancreas and kidney (11). When OVA-specific $CD8^+$ T cells were transferred into these OVA-expressing mice, they proliferated specifically in those nodes that drained sites of OVA expression, i.e., the pancreatic and renal lymph nodes. By manipulating the MHC haplotype of the bone marrow compartment, it was possible to show that the cell responsible for OVA presentation was derived from the bone marrow. Thus, under normal conditions, a specialized APC was able to constitutively capture OVA from the OVA-expressing tissues and present it to $CD8^+$ T cells in the draining lymph nodes.

Cross-tolerance as a Consequence of Bone Marrow–derived APC Presentation of Peripheral Antigen. Although the experiments of Kurts et al. showed that $CD8^+$ T cells were activated and proliferated in lymph nodes draining the sites of peripheral antigen expression (11), this did not represent effective T cell priming. Long-term examination of the survival of these $CD8^+$ T cells revealed their gradual deletion from the peripheral T cell pool (12). Such deletion appeared to be mediated by a mechanism related to activation-induced cell death, since it was preceded by an active proliferative response (12) and was recently shown to be dependent on signaling through CD95 (fas, Apo-1; 12a).

These studies revealed that cross-presentation of self-antigens by a bone marrow–derived APC provided a mechanism for induction of peripheral tolerance, at least for $CD8^+$ T cells. A somewhat similar mechanism of bone marrow–derived, APC-mediated $CD8^+$ T cell cross-tolerance had been observed previously within the thymus by von Boehmer and Hafen (13).

Like $CD8^+$ T cells, $CD4^+$ T cells specific for a model autoantigen, SV40 T antigen (14, 15), have been reported to be activated in the draining lymph nodes of those organs expressing this protein. In this case also, proliferation was followed by deletion, although some remaining cells exhibited properties of anergy (15). Adler et al. now extend these findings in mice expressing hemagglutinin in various parenchymal cells, by showing that $CD4^+$ T cell tolerance is mediated by cross-presentation of this antigen on a bone marrow–derived APC (16). Here, tolerance is induced only when the responding autoreactive $CD4^+$ T cell population is provided with bone marrow–derived cells expressing the correct MHC haplotype to present hemagglutinin. In this case, the tolerance induced is more consistent with anergy, although it is difficult to rule out contributions by a deletional mechanism.

In support of a role for professional APCs in tolerance induction, $CD4^+$ T cell tolerance to hen egg lysozyme expressed as a model self-antigen was fas-dependent and preceded by proliferation (17), indicating that the cell responsible for tolerance induction had the capacity to activate naive T cells, a property supposedly linked to professional APCs. Furthermore, CTLA-4 signaling by B7 (expressed primarily by B cells and professional APCs) was shown to be involved in the induction of peripheral tolerance to a soluble exogenous antigen capable of inducing T cell anergy (18).

Taken together, there is compelling evidence that in order to maintain self-tolerance a specialized APC is capable of capturing tissue antigens, transporting them to the lymphoid compartment, i.e., the draining lymph nodes, and presenting them to both naive $CD4^+$ and $CD8^+$ T cells. It should be emphasized that it is yet to be established whether the APC traffics with antigen or is resident in the lymphoid compartment and merely captures antigens draining to this site. Whatever the case, this APC appears to be capable of processing exogenous antigens into the class I and class II pathways. Moreover, although the conventional view is that "professional" APCs are constitutively involved in productive T cell activation (priming), the combined data clearly show that such APCs can also tolerize T cells under certain circumstances.

Ignorance Versus Tolerance? The above data argue for the existence of a "professional" APC that constitutively induces tolerance to antigens expressed in extralymphoid tissues. This is consistent with numerous reports of tolerance to peripheral antigens (12, 14–16, 19), but how then can we explain other reports of immunological ignorance (20–25), where naive $CD4^+$ or $CD8^+$ T cells neither respond to nor are tolerized by peripheral tissue antigens? Perhaps the answer to this apparent contradiction comes from the efficiency of transport and presentation of parenchymal antigens by the APCs responsible for tolerance induction. In studies using transgenic mice expressing different levels of OVA in the pancreas, we have recently found that antigen concentration is critical in determining whether such antigens are cross-presented in the draining lymph nodes.[1] In brief, although OVA expressed at high levels was cross-presented in these lymph nodes, and may induce tolerance, a lower level of OVA expression was ignored by naive T cells. However, this low dose could still sensitize islet β cells for recognition and destruction by activated CTLs, mimicking the ignored antigens reported by others (20, 21). Thus, the level of antigen expression appears to determine whether an antigen induces cross-tolerance or is ignored by naive T cells.

What Is the APC That Mediates Cross-tolerance? Whether the same APC is responsible for inducing both the $CD4^+$ T cell tolerance to hemagglutinin reported by Adler et al. (16) and the $CD8^+$ T cell tolerance to OVA seen in our own model (12) is unclear. More recently, we showed that provision of $CD4^+$ T cell help, in the form of large numbers of transgenic $CD4^+$ T cells specific for OVA, severely impairs the deletion of autoreactive $CD8^+$ T cells in mice expressing OVA in the pancreas and kidneys (26). Since $CD4^+$ help for CTL induction must be mediated through the same APC as seen by the $CD8^+$ cell (27–29), this finding is consistent with the idea that the same APC presents both class I– and class II–restricted determinants. However, it should be

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emphasized that class II–restricted presentation of exogenous antigens is a normal property of all class II–bearing bone marrow–derived populations, including dendritic cells (DCs), macrophages, and B cells, so more than one cell type may contribute to this process.

It is interesting to note that deletion of both $CD4^+$ (14, 15) and $CD8^+$ T cells (12) is preceded by a period of proliferation, suggesting that the APC responsible for tolerance induction must be capable of activating T cells into proliferative cycles. This supports the idea that the tolerogenic APC is of the professional class, expressing the costimulatory molecules necessary to push a naive T cell into cell cycle. It is perhaps not that unusual to find that antigens can induce tolerance when presented by bone marrow–derived cells, since several antigens including H-Y, superantigens, and soluble peptide appear to be tolerogenic when presented generally by this compartment (30–33). What is important is the implication that the tolerogenic APC is a cell capable of trafficking from peripheral tissues to draining lymph nodes and there initiating the proliferation of naive T cells. Even more importantly for $CD8^+$ T cell tolerance, this APC must be capable of capturing exogenous antigens and cross-presenting them in the class I pathway. Various cell types have been shown to have the capacity to cross-present exogenous antigens in vitro, including myeloid-derived DCs (34, 35), macrophages (36, 37), and B cells (38). If trafficking from peripheral tissues to draining lymph nodes is essential, then it is unlikely to be a B cell, which unless activated would remain in the secondary lymphoid compartment. Macrophages may migrate from tissues to draining lymph nodes, but usually require exposure to pathogen products or lymphokines for expression of class II molecules. These cells are therefore not likely to present captured tissue antigens to $CD4^+$ T cells under normal circumstances.

On the other hand, the myeloid DC constitutively expresses class II molecules and may traffic from peripheral tissues to draining lymph nodes, making this cell a potential candidate. In support of this view, myeloid DCs grown from human peripheral blood were shown to present exogenous antigen via the class I presentation pathway (35). Interestingly, this study demonstrated a preference for antigen derived from cells undergoing virally induced apoptosis, consistent with the original notion that this presentation pathway, at least for class I, represents a mechanism for peripheral immune surveillance against viral infection (6). In our own studies using whole animals, cross-presentation of islet antigens to $CD8^+$ T cells was dramatically enhanced when islet β cells were killed by activated CTL.[1] These results are consistent with the idea that apoptosis facilitates cross-presentation in vivo and suggest that this may play a role in tolerance and/or immunity to peripherally expressed antigens.

Another cell type that may fit the profile of the cross-tolerance APC is the recently described lymphoid DC (39). It is capable of activating both CD4 (40) and CD8 (41) cells in vitro, and has been speculated to have an immunoregulatory role (40). Interestingly, these lymphoid DCs have now been shown to occupy T cell areas of the spleen and lymph nodes, and to express high levels of self-antigens (42), raising the possibility of a role in the maintenance of self-tolerance. Preliminary findings from our laboratory indicate that fas signaling contributes to the deletion of $CD8^+$ T cells by cross-tolerance, leading to the conclusion that CD95-ligand expression, perhaps by the APC, is central to this form of peripheral tolerance (12a). Again, this property correlates with the described attributes of the lymphoid DC (40).

What Determines Cross-tolerance Versus Cross-priming? The lymphoid DC is a good candidate for cross-tolerance induction primarily because it is yet to be linked to a positive immune response. However, another possibility is that the traditional myeloid DC, or perhaps another member of the macrophage/DC family (43), may be immunogenic under some circumstances and tolerogenic under others. If this is the case, then what determines the direction of the immune response, and what is the difference between the signals that drive T cells into cycle in response to tolerogenic stimulation with self-antigens versus immunogenic stimulation with foreign antigens? As suggested by Matzinger, "danger" signals from environmental pathogens may be the key to positive immune responses (44). Because at least in our model the tolerogenic response is preceded by proliferation, it would appear that the ability to induce proliferation of T cells is not the key to whether immunity is induced, but rather it is a normal precursor to both tolerogenic and immunogenic outcomes. In a number of models (29, 45), $CD4^+$ T cell "help" has been shown to be important for induction of CTL immunity. Such "help" even impairs the deletion of autoreactive $CD8^+$ T cells in the cross-tolerance to tissue antigens (26). Thus, as proposed earlier (45), $CD4^+$ T cell help may determine the direction of responses by $CD8^+$ CTL. But what determines the direction of a CD4 response? This is probably one of the outstanding questions at the moment, for if qualitative expression of the costimulatory B7 molecules is not the deciding factor, as argued by the fact that B cells express these molecules but are tolerogenic to naive $CD4^+$ T cells (46–50), and by the observation that B7 may deliver signals necessary for induction of peripheral tolerance (18), then what molecular interactions provide the signals for immunity versus tolerance? Perhaps there are other as yet undefined costimulatory molecules that play a deciding role. Alternatively, the level of either of the B7 molecules and their competitive interactions with CD28 and CTLA4 may be critical (51, 52). Whatever the case, there has to be a signal(s) that regulates professional APCs such that in a resting state they are tolerogenic, and once activated they drive immunity. At present, we favor the concept that these signals are derived from pathogens or, perhaps, tissue damage.

In conclusion, there is emerging evidence that APCs of the "professional" class may be not only central to the trafficking and presentation of foreign antigens for induction of immunity, but they may also provide an important role

in the induction of cross-tolerance to peripheral tissue antigens. Defining the specific APCs involved, the mechanism of transport, and the molecular signals that determine whether responses are immunogenic or tolerogenic will, no doubt, provide us with a greater capacity to direct the immune response to our own benefit.

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