Commentary

Alpha E: No More Rejection?

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Integrin $\alpha E\beta 7$ (CD103) has been an enigmatic and tantalizing molecule (1). The history of experiments on its functional significance is a record of promise and disappointment in equal measure. CD103 has been considered to have a role mainly or exclusively in the mucosal immune system, but this supposition now needs to be reappraised. The molecule is expressed at high levels by mucosal T cells, especially the CD8$^+$ population in the epithelium of the gut, but is found on small subsets of T cells elsewhere. It is also present on mucosal mast cells and mucosal dendritic APCs. This eccentric pattern of expression has recently been extended to include splenic CD4$^+$ CD25$^+$ Treg cells, $\sim$30% of which are CD103$^+$ (2). A plausible explanation for the expression profile is that the αE subunit is transcriptionally regulated by transforming growth factor (TGF)-β. In fact, no other stimulus has consistently been shown to induce expression. Thus, CD103 is found on T cells residing in tissue microenvironments where bioactive TGF-β is abundant. This is often the case in the vicinity of epithelia and in situations in which chronic inflammation is taking place. The particular association of CD103$^+$ cells with epithelia is also explained by the fact that its principal ligand is E-cadherin, an epithelial homophilic adhesion molecule. The relationships between the integrins discussed here and their ligands are shown in Table I.

Studies on CD103 function have, until now, met with mixed fortunes. Like other integrins, when ligated it provides costimulation for T cell proliferation and effector function. Importantly, the interaction between CD103 and E-cadherin will substitute for that between lymphocyte function–associated antigen (LFA)-1 and intercellular adhesion molecule (ICAM)-1 in CD8$^+$-mediated CTL effector function (3). This could be especially significant for epithelial target cells, which often lack ICAM-1. It has been suggested that CD103 could function as a homing receptor encouraging T cells to extravasate to the gut. However, the balance of evidence more clearly favors a role in retention or microlocalization of T cells in the vicinity of epithelia rather than in mucosal-specific homing. In contrast, the sister integrin of CD103, $\alpha 4\beta 7$, is known to play an important role in the homing of leukocytes to mucosal sites. Initial studies on the CD103$^{-/-}$ mouse were somewhat disappointing in that the only noticeable change was a modest reduction in the numbers of mucosal T cells and a T cell–dependent dermatitis of unknown etiology (4–6).

An Unexpected Role for CD103 in Allograft Rejection. The paper by Feng et al. (7) in this issue is the first clear-cut demonstration that CD103 can have a pivotal role in T cell effector function in vivo, specifically in allograft rejection. The authors have shown that CD103$^{-/-}$ Balb/c mice cannot reject A/J strain islet allografts implanted under the kidney capsule. Adoptive transfer experiments indicated that the defect was in the CD8$^+$ T cell population. In other respects, CD8$^+$ CD103$^{-/-}$ cells were immunologically competent and responded normally in vitro to A/J cells by producing IFN-γ and generating CTL which lysed target lymphoblasts effectively. Moreover, CD8$^+$ CD103$^{-/-}$ cells could accumulate efficiently around islet grafts and so had no intrinsic defect in their capacity to exit the vasculature. Indeed, at the stage when rejection would normally be almost complete (day 14), the grafts were surrounded by a halo of activated T cells seemingly unable to enter the islets. Although one cannot entirely rule out the possibility that development of CD8$^+$ effector T cells was in some way abnormal in CD103$^{-/-}$ mice or that the cells were restrained by a regulatory population, there appeared to be no defect in sensitization. What then is the role of CD103 in rejection of islet grafts and is this study relevant to the broader context of allotransplantation and autoimmune disease?

Examination of the cell population infiltrating islet allografts undergoing rejection in control mice showed that about half of the cells expressed CD8 and only a minority were CD103$^+$. The finding that such a small proportion of CD103$^+$ cells, <10% of the total infiltrate, trigger the rejection mechanism at first sight seems surprising. The most straightforward explanation was that CD8$^+$ CD103$^+$ T cells have a 'pathfinder' role in promoting entry of effector cells into the islets. Thus, engagement of E-cadherin on islet cells, which are known to express this molecule (8), may directly or indirectly trigger local secretion of chemoattractants. This could occur through a costimulatory effect of the integrin acting in concert with recognition of cognate alloantigen by the TCR. CD8$^+$ cells are known to secrete chemokines of the CXC and CC family (9). In addition,

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Table I.

Integrin	Other names	Principal ligands
$\alpha E\beta 7$	CD103, αIEL, HML-1, αM290	E-cadherin
$\alpha 4\beta 7$	LPAM-1	MAdCAM-1
$\alpha 4\beta 1$	CD49d/CD29, VLA-4	VCAM-1, fibronectin
$\alpha L\beta 2$	CD11a/CD18, LFA-1	ICAM-1, -2, -3, -4, -5

IFN-γ derived from the CD8$^+$ T cells could induce chemokine secretion from islet β cells themselves (10). A more significant factor might be the induction of ICAM-1 on the islet cells. Other T cell populations, both CD8$^+$ and CD4$^+$, would then be drawn to the site and cause islet cell death through the concerted action of IFN-γ and perforin or Fas-mediated mechanisms. Alternatively, the primary event could be direct cytotoxic lysis of islet cells by a small cohort of CD103$^+$ CD8$^+$ cells that accumulate in the graft by adhesion to E-cadherin on islet cells. Infiltration of other T cells would then follow as a secondary phenomenon.

Are Islets a Special Case? Why should CD103 be so significant in the case of islet grafts? The importance of adhesion between immune effector cells and their targets is well known. The interaction between LFA-1 on the T cell and ICAM-1 on its target holds the cells in intimate apposition and provides crucial costimulatory signals for the organization of the immune synapse which focuses killing mechanisms (11, 12). Is the interaction between LFA-1 and ICAM-1 available in the case of islet allografts? One suspects not, at least not at first. Feng et al. demonstrated that LFA-1 was expressed by the activated CD8$^+$ cells surrounding the graft but did not examine the islet allografts for ICAM-1. Previous studies show that ICAM-1 can be induced on islet cells by inflammatory cytokines (13) but that it is normally absent, as are ICAM-2 and -3. ICAM-4 and -5 would not be expected to be involved here because of their known tissue specificity. Therefore, it is probable that an LFA-1–ICAM interaction is not available for effector CD8$^+$ T cells to initiate the rejection process but that ICAM-1 is induced after infiltration by the first cohort of CD103$^+$ cells (14). Thus, interaction between CD103 on CD8$^+$ T cells and E-cadherin on islet cells would provide an alternative, crucial, integrin/ligand pair for accumulation of CD8$^+$ cells and their costimulation within the graft. There is no evidence that CD103 has any unique signaling properties that cannot be provided by LFA-1. It should be noted that inhibition of LFA-1 and VLA-4 can also effectively prolong islet allograft survival (15). This can be partly explained by a role for these molecules in extravasation of inflammatory cells, which requires recognition of their respective endothelial ligands, ICAM-1 or -2 and vascular cell adhesion molecule (VCAM)-1, and also a function in a second wave of infiltration into the islets that is CD103 independent. Unlike the situation with CD103, initial sensitization to graft antigens may also be inhibited by blocking these other integrins.

In contrast to the acceptance of islet allografts by CD103$^{-/-}$ mice, Feng et al. (7) showed that skin allografts were rejected normally and that rejection occurred by T cell infiltration into the dermis and vascular bed, not the epithelium. Thus, CD103 would not be involved. In fact, it is possible that another reason Feng et al. observed such a dramatic effect of CD103 deficiency on pancreatic allograft rejection was their use of highly purified islet cell preparations free of vascular and ductal tissue. This, coupled with the use of an indicator of rejection (blood glucose levels) that depends on the function of the islet cells themselves, may have limited the potential to observe pathology involving CD103-independent mechanisms. One wonders if reduced purity of some transplanted islet preparations could account for the subset of CD103$^{-/-}$ mice that were able to reject the allografts.

Significance of TGF-β. Previous studies from G.A. Hadley's laboratory (16) have shown that TGF-β produced during allostimulation of T cells in vitro induces CD103 expression on a proportion of effector CD8$^+$ T cells. It should also be noted that TGF-β is important for the development and function of islet cells and is produced by them (17). So this local source of TGF-β may contribute to the induction or maintenance of CD103 expression on T cells in the vicinity of the graft.

Implications for Transplantation in a Broader Context and for Autoimmune Disease. Two groups have reported that T cells infiltrating the tubular epithelium of renal allografts undergoing late rejection crises express CD103 (18, 19). A positive correlation was reported between the severity of tubulitis, the prevalence of CD8$^+$ CD103$^+$ T cells and the local production of TGF-β by the epithelium. Similarly, in Sjogren's syndrome, an autoimmune disease affecting exocrine glands, CD8$^+$ CD103$^+$ T cells are found in close association with the acinar and ductal epithelia, the focus of tissue damage (20). It is enticing to speculate that blocking E-cadherin recognition by CD103 could reduce the epithelial pathology in these two situations. The feasibility depends on the availability of other costimulatory pathways between the T cell and the epithelium, especially LFA-1–ICAM-1, which in the case of Sjogren's syndrome may be minimal (20). The role of CD103 in inflammatory bowel disease is not yet properly resolved. In mouse colitis evoked by TNP, treatment with anti–CD103 antibodies ameliorates the disease (21) but $\beta 7$ integrins are not necessary for the development of colitis in IL-2$^{-/-}$ mice or after transfer of CD4$^+$ CD45RB^{high} T cells into SCID mice (22).

Is the study of Feng et al. relevant to the pathogenesis of type 1 diabetes? Evidence so far suggests that LFA-1 and $\alpha 4$ integrin play dominant roles in initial penetration of T cells into the islets in murine models of this disease. The histology of pancreata of ICAM-1$^{-/-}$ NOD/IL-10 transgenic mice and of NOD mice treated with blocking antibodies to $\alpha 4$, $\beta 2$, and $\beta 7$ integrins and their respective ligands, VCAM-1, ICAM-1, and MAdCAM-1, bears a striking resemblance to that of the healthy allografts in the study by Feng et al. T cells surround but do not penetrate the islets (23, 24). Few T cells infiltrating the pancreas in NOD mice express CD103 (25), consistent with a greater importance

of these other adhesion systems. However, given the present results, the potential contribution of CD103 at an early stage of disease warrants further attention.

The paper by Feng et al. serves as timely reminder that when T cells, TGF-β, and E-cadherin coexist in a tissue microenvironment, CD103 function deserves a close look. One can envisage several situations in which CD103 inhibitors could be of therapeutic value. The benefits will depend on the extent to which epithelial cell destruction is involved in rejection or loss of organ function. This type of intervention may be useful as an adjunct to other strategies.

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