Journal of Autoimmunity 32 (2009) 70–77

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

CD103 is dispensable for anti-viral immunity and autoimmunity in a mouse model of virally-induced autoimmune diabetes

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ARTICLE INFO

Article history:
Received 6 October 2008
Received in revised form
4 December 2008
Accepted 5 December 2008

Keywords:
Integrin CD103 (αEβ7)
Type 1 diabetes (T1D)
LCMV
Insulitis
$CD8^+$ effector/memory response

ABSTRACT

Recent studies suggest a beneficial role for blocking CD103 signaling in preventing islet allograft rejection and thus Type 1 diabetes (T1D) in non-obese diabetic (NOD) mice. However, antibody blockade approaches generally raise anti-microbial safety issues, necessitating additional studies to address the possible adverse effects of antibody therapy. Here we report that CD103 had no significant impact on the development of primary and memory $CD8^+$ or $CD4^+$ responses after acute lymphocytic choriomeningitis virus (LCMV) infection. In addition, CD103 was found to be dispensable for T1D progression in a rapid, CD8-mediated virally-induced T1D model (the rat insulin promoter [RIP]–LCMV), suggesting that its previous efficacy in the NOD mouse model may not be related to its effect on the generation, memory conversion and/or effector function of $CD8^+$ or $CD4^+$ T cells. While the data does not preclude a role for CD103 in T1D in its entirety, the current study does provide much evidence to suggest that CD103 blockade may prove to be a safe intervention for autoimmunity and allo-transplantation. While in cases of rapid microbial (CD8)-driven T1D CD103 antibody blockade may not limit disease progression or severity, in mucosally-driven cases of T1D anti-CD103 antibody treatment may provide a new and safe therapeutic avenue.

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1. Introduction

The integrin CD103 (αEβ7) has been found to be expressed by subsets of $CD4^+$ and $CD8^+$ T cells and some dendritic cells (DCs) and can bind to E-cadherin, which is expressed on a variety of cell types including intestinal epithelial cells (IECs) and Langerhans' cells [1–4]. While CD103 is not a homing receptor, the ability of CD103 to bind to E-cadherin-expressing epithelial cells is thought to retain lymphocytes at the epithelial surface, thus playing a role in T cell homing to the gut [5–7]. Increased CD103 expression has also been found in the lungs. While the precise role of CD103 on T cells is not fully understood, studies suggest a role for CD103 in $CD8^+$ T cell cytotoxicity through its ability to conjugate CTL (cytotoxic T-lymphocyte) effectors to E-cadherin-expressing epithelial cells in the lungs, thereby facilitating their destruction upon virus infection [8]. Similarly, CD103 was found to be expressed by tumor-infiltrating lymphocytes (TILs), playing a major role in effective tumor cell lysis [9]. In a graft-versus-host disease (GVHD) model, the destruction of the host intestinal epithelium was also dependent on CD103 [10].

Regarding the CD4 T cell compartment, reports have linked $CD103^-$ natural regulatory T cells (nTregs) to systemic regulation and $CD103^+$ nTregs to tissue-specific regulation according to the model systems analyzed [11–13]. For example, CD103 dependency was demonstrated in Leishmania-induced dermal inflammation but not in T cell-induced colitis [14–16]. These observations suggest that CD103 expression is not essential for the suppression of mucosal inflammation in general and moreover, the requirement for nTreg retention in the tissue can vary by organ. Interestingly, with respect to the skin, Treg cells are particularly prevalent, where they express a unique $CCR4^+CD103^{hi}$ phenotype. Mice with a complete loss of CCR4 in the Treg compartment developed lymphocytic infiltration and severe inflammatory disease in their skin and lungs, accompanied by peripheral lymphadenopathy [17]. Thus, selectively altering Treg cell distribution in vivo can lead to the development of tissue-specific inflammatory disease. In agreement with these observations, CD103-deficient mice develop cutaneous inflammatory disease [18].

The main cell type to express CD103, apart from T cells, is the dendritic cell (DC) [19]. CD103 is expressed on almost all lamina propria (LP) DCs, a subset of mesenteric lymph node (MLN) DCs, and only on a few splenic DCs. Gut-associated lymphoid tissue

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doi:10.1016/j.jaut.2008.12.001

(GALT) DCs possess a unique ability to generate $CCR9^+\alpha4\beta7^+$ gut-tropic $CD8^+$ T cells. $CD103^+$ and $CD103^-$ GALT–DCs represent functionally distinct subsets, in which CD103 expression on DCs is a prerequisite for the generation of gut-tropic $CCR9^+\alpha4\beta7^+$ $CD8^+$ T cells [19]. Overall, CD103 is thought to be important for intra-epithelial lymphocyte (IEL) localization and/or function. Furthermore, CD103 is involved in the expansion and recruitment of $TCR\alpha\beta^+$ $CD8^+$ IEL following microbial colonization [20]. Recently, a connection between CD103-expressing DCs and Tregs was made: $CD103^+$ MLN and LP DCs are responsible for inducing the development of $Foxp3^+$ Treg cells in the gut [21]. Importantly, this is dependent on TGF-β1 and the dietary metabolite, retinoic acid (RA), and influences the balance between effector and regulatory T cell activity in the intestine [22].

While little is known about the relationship between CD103 expression and Type 1 diabetes (T1D) pathogenesis, several studies suggest a possible link. Few T cells infiltrating the pancreas in NOD mice express CD103 [23]. Studies involving blocking antibodies to all integrins (α4, β2, and β7) and their respective ligands (Table 1) showed a defect in T cell penetrating the pancreatic islets [24]. Similar observations were made after pancreatic islet allo-transplantation, where allografts survived indefinitely in CD103-deficient hosts [25]. CD8 cells in CD103-deficient hosts exhibited normal effector responses to donor alloantigens in vitro and trafficked normally to the graft site in vivo, but strikingly failed to infiltrate the islet allograft itself.

The previous results suggested CD103 as a target for intervening with T1D development. In order to assess its influence on T1D progression in a virally-induced T1D model, CD103-deficient mice were crossed to rat insulin promoter–lymphocytic choriomeningitis virus (RIP–LCMV) transgenic mice. Interestingly, upon acute infection with LCMV Armstrong, CD103 deficiency revealed no significant effect on LCMV-specific effector and memory $CD8^+$ or $CD4^+$ responses or on T1D progression. Although these results suggest a minimal effect for CD103 blockade in preventing a solely CD8-mediated virally-induced T1D, they also provide evidence for CD103 blockade safety. This is the first report to demonstrate that CD103 does not adversely effect the development of either effector or memory $CD4^+$ or $CD8^+$ T cell populations after an acute viral infection and as such, CD103 blockade may be proven of therapeutic value in other immune-based disorders, in which a beneficial outcome can be anticipated.

2. Methods

2.1. Mice

Mice deficient in CD103 ($CD103^{-/-}$) was generated and back-crossed on C57BL/6 background and kindly provided by Dr. Bromberg [20]. $CD103^{-/-}$ mice were crossed to RIP–GP and RIP–NP to obtain $CD103^{+/-} \times$ RIP–GP mice. These mice were intercrossed to obtain $CD103^{+/+}$, $CD103^{+/-}$, and $CD103^{-/-} \times$ RIP–GP. In some experiments, non-transgenic $CD103^{-/-}$ or $^{+/-}$ and $^{+/+}$ littermate control mice were used. Mice were housed under specific pathogen-free conditions at La Jolla Institute for Allergy and Immunology.

Table 1
Integrin family members and their ligands.

Integrin	Other commonly used name	Principal ligands
αEβ7	CD103	E-cadherin
α4β7	LPAM-1	MAdCAM-1
α4β1	VLA-4	VCAM-1, fibronectin
αLβ2	LFA-1	ICAM-1, -2, -3, -4, -5

2.2. Viruses

LCMV Armstrong was used throughout all experiments. Eight to 14-week-old mice were infected with a single dose of 10^4 PFU i.p.

2.3. Blood glucose values

Blood glucose was monitored with OneTouch Ultra at weekly intervals. Diabetes was defined as blood glucose values (BGVs) over 300 mg/dl.

2.4. Peptides

Peptides used for viral studies were the dominant D^b-restricted LCMV epitopes GP33–41 and NP396–404 as well as an I-A^b-restricted epitope GP61–80 (all from Abgent).

2.5. Immunohistochemistry

Pancreata were immersed in Tissue-Tek OCT (Bayer) and quick-frozen on dry ice. Using cryomicrotome and Superfrost Plus slides (Fisher Scientific), 6 μm tissue sections were cut. Sections were fixed with 100% acetone for 15 min and dried for 1 h at room temperature, and after rehydrating in TBS, an avidin/biotin-blocking step was included (Vector Laboratories). To detect insulin and CD4 or CD8 expression in pancreatic sections, primary Abs (guinea pig anti-swine insulin from Dako [dilution 1:300], anti-CD4 (RM4.5) or anti-CD8a (Ly-2) IHC from BD–Pharmingen [dilution 1:50]) were applied to frozen tissue sections. Primary and biotinylated (Vector Laboratories) secondary antibodies were incubated with the sections for 60 min each, and color reaction was obtained by sequential incubation with avidin–peroxidase conjugate and AEC (3-amino-9-ethylcarbazole) or alkaline phosphatase conjugate and Vector Blue AP III (SK-5300) (Vector Laboratories).

2.6. Flow cytometry

For intracellular stains, single cell suspensions were restimulated for 3 h with 1 μg/ml MHC class I-restricted viral peptides, 2 μg/ml MHC class II-restricted viral peptides in the presence of brefeldin A (Sigma–Aldrich). Cells were stained for surface expression of CD4 and CD8, fixed, permeabilized, and stained for intracellular IFNγ and TNF. D^bGP33 and D^bNP396 MHC class I pentamers were purchased from Proimmune. Cells were acquired on an LSRII flow cytometer (BD Biosciences) and analyzed using FlowJo software.

2.7. Statistical analysis

Data are expressed as a mean ± SD. The statistical significance of the difference between means was determined using the two-tailed Student's *t*-test or the log-rank test. *, $p < 0.05$; **, $p < 0.01$; and ***, $p < 0.001$.

3. Results

3.1. Normal development of T1D in CD103-deficient mice

In order to examine the role for CD103 in T1D, $CD103^{-/-}$ mice were crossed to RIP–GP and RIP–NP transgenic mice. $CD103^{+/+}$, $CD103^{+/-}$ or $CD103^{-/-} \times$ RIP–GP or RIP–NP littermates were infected with 10^4 PFU LCMV Armstrong to induce diabetes. BGVs were measured weekly, and by 2 weeks post infection (p.i.), 80–100% of RIP–GP mice, irrespective of CD103 expression and gender,

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