Journal of Autoimmunity 71 (2016) 44–50

Contents lists available at ScienceDirect

Journal of Autoimmunity

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

Review article

Obstacles and opportunities for targeting the effector T cell response in type 1 diabetes

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ARTICLE INFO

Article history:
Received 11 February 2016
Accepted 23 February 2016
Available online 3 March 2016

Keywords:
CD4 T cell
Type 1 diabetes
Immunomodulation
Genetic susceptibility

ABSTRACT

Autoreactive lymphocytes display a programmed set of characteristic effector functions and phenotypic markers that, in combination with antigen-specific profiling, provide a detailed picture of the adaptive immune response in Type 1 diabetes (T1D). The CD4+ T cell effector compartment (referred to as "Teff" in this article) has been extensively analyzed, particularly because the HLA genes most strongly associated with T1D are MHC class II alleles that form restriction elements for CD4+ T cell recognition. This "guilt by association" can now be revisited in terms of specific immune mechanisms and specific forms of T cell recognition that are displayed by Teff found in subjects with T1D. In this review, we describe properties of Teff that correlate with T1D, and discuss several characteristics that advance our understanding of disease persistence and progression. Focusing on functional disease-associated immunological pathways within these Teff suggests a rationale for next-generation clinical trials with targeted interventions. Indeed, immune modulation therapies in T1D that do not address these properties of Teff are unlikely to achieve durable clinical response.

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1. T1D Teff display hallmarks of adaptive recognition and expansion

Properties of Teff in T1D closely parallel the types of T cell activation seen in normal immune responses, albeit with some features discussed below that serve to define the autoreactive population. The strong genetic association for T1D with HLA-DQB1*0302 and linked HLA-DRB1*04 genes corresponds to the presence of Teff populations in T1D with specificity for numerous islet-derived proteins and peptides bound and presented in the context of those class II molecules. Although Teff specific for GAD65 and for proinsulin have been the most extensively studied, similar cell populations specific for other islet antigens including ZnT8, IGRP and chromogranin, have also been described [1–5]. In general, there are several features commonly found in these Teff:

(i) There are multiple antigens, and a diverse set of islet-derived peptides, recognized by Teff within each individual subject with T1D. In other words, the response is polyclonal with respect to targets, and there is no single dominant antigen recognized by all T1D subjects [6–9].

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http://dx.doi.org/10.1016/j.jaut.2016.02.009
0896-8411/

(ii) Even within a single target specificity there is diverse T cell receptor utilization, indicating a polyclonal response with respect to repertoire selection. However, some particular TCR VB genes are found preferentially in GAD65-specific responses in T1D, indicating a bias in the antigen-driven response in many subjects [10,11].

(iii) HLA-matched normal subjects also have islet-responsive T cell repertoires, but the Teff from T1D subjects tend to display higher avidity for the peptide-MHC complex and carry memory (CD45RO) markers, consistent with in vivo activation and exposure to their specific antigens [12–14]. As a consequence of this chronic in vivo activation, T1D Teff also utilize a characteristic Teff potassium channel, Kv1.3 [15].

(iv) Consistent with this diversity of specificities, avidity, and repertoire, the cytokine profile for T1D Teff is also variable, with evidence of Th1-like (IL12, IFNγ), Th17-like (IL17, IL22), and Tfh-like (IL21) properties in both antigen-specific and antigen-nonspecific Teff derived from peripheral blood, although none of these phenotypes appear to be exclusively present or even always present [16–23]. Reconciling the diversity of this Teff response with the observations of oligoclonal expansion of particular specificities and TCR clonotypes led to the concept of "determinant focusing", in which an initial highly diverse T cell response is progressively narrowed by the selective expansion of particular sets of dominant Teff during disease progression [24]. The choice of which Teff become expanded may be a random event, or may be driven by factors that are also highly variable within T1D subjects, such as antigen density, antigen processing, additional HLA molecules present, etc. Recent descriptions of Teff that recognize post-translationally modified islet autoantigens also suggest the possibility that shifting repertoires occur over time, contributing to the variability of particular immunodominance patterns [25–27], as is the possibility that some islet antigens are displayed in more than one class II-binding register [28,29].

Although most T1D Teff studies have utilized cells derived from peripheral blood, there is also strong evidence for the presence of these cells in the islet lesions themselves. Immunohistochemistry identifies CD4 T cells within islets in pancreatic specimens from T1D subjects [30,31], and T cell clones derived from islets or lymph nodes mirror the properties of similar cells found in blood [32–35]. In a longitudinal study of pancreas organ transplantation in T1D, activated and expanded islet-specific Teff were identified in peripheral blood of subjects who had experienced a return of their hyperglycemia, consistent with a recurrence of T1D, correlating with staining for CD4 T cells in pancreatic biopsy specimens [36]. Interestingly, in some of these cases, tetramer and TCR repertoire studies documented the presence of the same T cell clonotypes in specimens collected years apart, indicating a persistent and dominant Teff memory response in association with disease. Indeed, simply transplanting islets into T1D recipients may be sufficient to boost Teff numbers, directly demonstrating the capacity for recalling memory responses [37].

The Teff properties summarized above in T1D indicate a major role for these cells in disease pathogenesis, consistent with an active immunological process of T cell recognition, activation, expansion, and effector function. While the overall framework for this immune response displays typical features of repertoire heterogeneity and avidity maturation, there are a number of distinct disease-promoting elements, which lead to a response that deviates from the homeostatic norm. These include properties that support unregulated Teff expansion, signals that favor the deviation of Teff toward proinflammatory lineages, and failure of effector functions to be controlled by other regulatory cell populations (Fig. 1). These are reviewed in the next section, followed by a discussion of the implications for immunotherapy in T1D.

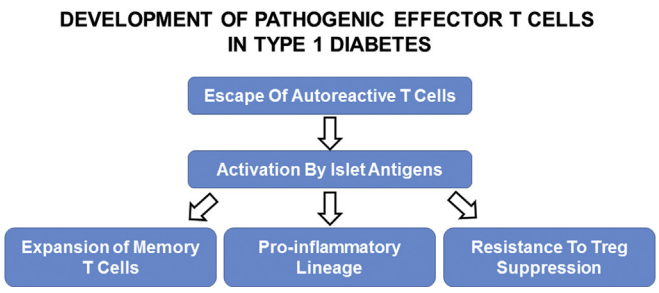

Fig. 1. Development of pathogenic effector T cells in type 1 diabetes.

2. CD4 effector T cells are programmed to be pathogenic in T1D

As noted in Section 1 the strong genetic association for T1D with HLA-DQB1*0302 and linked HLA-DRB1*04 genes support a role for islet specific CD4 T cells in disease that is further supported by identification of such cells in the peripheral blood and islets of individuals with T1D. However, additional studies support the concept that there are global alterations in CD4 T cell function in T1D, which promote the development of pathogenic T cell responses. These properties support unregulated Teff expansion, a skewing of lineage commitment, and failure of effector T cells to be controlled by other regulatory cell populations.

A disturbance in the CD4 T cell pool has been consistently observed in T1D subjects. This includes the observation that there is an expanded number of CD4 T cells in the peripheral blood [38], but more consistently investigators have shown that the CD4 memory compartment is expanded in T1D as compared to healthy subjects. In several of these studies the increase was seen among the recently activated T cells based on CD27 expression and the CD45RA + RO + subset of cells which are thought to be chronically activated [38–40]. This observation has been extended to the pancreatic draining lymph nodes (PLN) [33]. Further evidence of altered homeostasis within the CD4 memory compartment is the observation that in vivo the turnover of CD4 memory T cells is increased in T1D subjects as compared to healthy controls [41]. A recent study evaluated transition from central memory to effector memory in CD 4 T cells of T1D subjects and their relatives and found enhanced activation of central memory T cell in these individuals compared to healthy controls resulting in the transition to effector memory T cells that are relatively short lived [42]. These studies argue that the Teff cells of T1D subjects are influenced by factors including genetic, environmental or the immune milieu present in T1D that promotes CD4 T cells activation and expansion of memory T cells.

Among the CD4 T cells there is further evidence that cell fate decisions are altered in T1D. Studies of peripheral blood T cells have been done examining the function and lineage of effector T cells through assessment of cytokines and chemokine expression on CD4 T cells isolated from peripheral blood. This is an evolving area as the variety and plasticity of the CD4 T cell lineages has become better understood. Studies of murine models of diabetes have implicated Th1 (IFNγ producing) cells in disease, and studies in humans show an increase in INFγ expression by CD4 T cells in new onset T1D [43] and more recently it has been shown that the effector memory T cells of T1D subjects display an elevated cytokine signature that is predominantly IFNγ [42]. More recently