Autoimmunity Reviews 12 (2013) 633–637

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

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

Review

Is autoimmune diabetes caused by aberrant immune activity or defective suppression of physiological self-reactivity?

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ARTICLE INFO

Article history:
Received 15 November 2012
Accepted 4 December 2012
Available online 28 December 2012

Keywords:
Type 1 diabetes
Inflammatory insulitis
Diabetogenic cells
Regulatory T cells
Immune surveillance
Physiological autoimmunity
Activation induced cell death

ABSTRACT

Two competing hypotheses are proposed to cause autoimmunity: evasion of a sporadic self-reactive clone from immune surveillance and ineffective suppression of autoreactive clones that arise physiologically. We question the relevance of these hypotheses to the study of type 1 diabetes, where autoreactivity may accompany the cycles of physiological adjustment of β-cell mass to body weight and nutrition. Experimental evidence presents variable and conflicting data concerning the activities of both effector and regulatory T cells, arguing in favor and against: quantitative dominance and deficit, aberrant reactivity and expansion, sensitivity to negative regulation and apoptosis. The presence of autoantibodies in umbilical cord blood of healthy subjects and low incidence of the disease following early induction suggest that suppression of self-reactivity is the major determinant factor.

Contents

1. Introduction

Autoimmune disorders reflect a condition of disturbed immune homeostasis with dominant effector cell activity and insufficient suppressor cell function. Type 1 diabetes (T1D) represents a particular case: autoimmunity erupts early and an indolent course of disease extends over long periods of time before diagnosis. The clinical manifestations appear after irreversible damage causes loss of a major fraction (~80%) of β-cell mass. The etiology of this disease with peak appearance in childhood and adolescence has been the focus of intense research, however the initiating factors are not well defined. The eruption of autoimmunity is considered to be facilitated by genetic polymorphism that predisposes to inflammation [1,2]. Environmental factors [3] and possibly infectious agents [4] are thought to play important roles in T1D, though it is yet unknown whether they facilitate disease evolution in subjects with genetic predisposition, or affect healthy subjects. In recent decades we witness a persistent increase in incidence of this disease.

2. Initiation of autoimmunity

The basic conceptual model states that autoimmunity is a hyperactivity disorder of aberrant clones targeting self-antigens has evolved

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http://dx.doi.org/10.1016/j.autrev.2012.12.004

along characterization of the function of cytotoxic T cells. This concept has developed along identification of the mechanisms of antigen-specific T cell activation and induction of the humoral arm of immunity resulting in generation of antibodies [5–7]. Clonal selection is the pivotal homeostatic mechanisms in the immune system responsible for determination and selection of the antigenic targets. The first model attributes the onset of autoimmune insulitis to defective discrimination between self and non-self, allowing evasion from surveillance of pathogenic clones reactive against self-antigens. The principles of the effector model are currently widely accepted as the main axis of self-tolerance, however an alternative model of autoimmunity suggests a different scenario.

A competing model suggests that autoimmunity reflects primarily a problem of immune suppression. Reactivity against self or self-like epitopes may occur quite frequent as a consequence of the intrinsic mode of immune activation as described by the immunological homunculus hypothesis [8,9]. This model proposes that arise and effective resolution of sporadic aberrant reactions against multiple antigenic targets are physiological processes. The defective suppression hypothesis has been invigorated by the description of regulatory T cells (Treg) [10], and identification of numerous variants of suppressor cells in virtually all lymphoid and myeloid lineages. Among the multiple phenotypes, dominant activity is attributed to naturally occurring Treg (nTreg) that originate in the thymus and mediate local immune suppression at the site of inflammation. Therefore, in analogy to aberrant clonal deletion of pathogenic clones, genetic predisposition to autoimmunity might relate to defective development of suppressor cells.

The conceptual and factual debate on factors that initiate the autoimmune disorder is, besides the theoretical value, of outmost significance to the experimental and therapeutic approaches to T1D. Better definition of the deficit underlying the eruption of inflammatory insulitis is essential to promote the understanding of this autoimmune disorder. Most studies are designed and interpreted according to the effector hypothesis, however if the suppressor hypothesis is correct we often search for irrelevant mechanisms at the wrong time and place.

3. Is T1D caused by defects in effector or suppressor mechanisms?

Autoimmune insulitis is a reaction that starts at very early age, possibly in the pre-natal phase, and the tempo of disease progression is widely variable among individuals [2]. β-cells undergo multiple rounds of physiological adjustment to body mass and sources of nutrition during fetal and neonatal development, and repeated cycles of β-cell death might trigger an autoimmune reaction in early life. Transition from extraction of nutrients from maternal blood to intestinal degradation of milk at birth and food after weaning reduces insulin demand despite growth in body weight. Gradual reduction in β-cell mass by death of insulin producing cells might be responsible for repeated cycles of sensitization required to elicit an immune reaction (Fig. 1). According to this scenario immune reactivity against β-cells is physiological: healthy subjects successfully resolve anti-islet reactivity, and few individuals that fail to terminate this reaction will eventually become diabetic. The most convincing evidence for this scenario is the presence of autoantibodies in umbilical cord blood of individuals that will not develop autoimmune insulitis [11–13]. Autoantibodies are generally of poor predictive value at the time of diagnosis [11,13], possibly because the clones producing antibodies might be extinct in some individuals with new onset diabetes after a long course of the disease. We therefore must consider the possibility that the basic immune deregulation took place in fetal or neonatal life, and thereafter one can only find the consequences of this event.

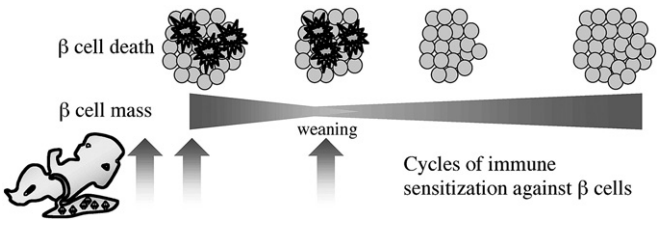

Fig. 1. Repeated cycles of β-cell death imposed by adjustment of β-cell mass to insulin demand might sensitize physiological anti-islet reactivity.

To test the hypothesis that anti-islet autoimmunity is an early event associated with weaning (3 weeks in mice), cyclophosphamide was administered to young NOD mice [14,15]. Autoimmunity erupts in this mouse strain both due to extreme sensitivity of Treg to this agent and dominant rebound recovery of cytotoxic cells under conditions of lymphopenia [16]. A series of calibration experiments showed that Cy administration to mice aged 4.5 weeks induces early disease. Importantly, most mice remained euglycemic long after the colony developed spontaneous diabetes (Fig. 2). These data argue in favor of the second model of defective regulation in two aspects. It demonstrates that diabetic autoreactivity evolves early after weaning in NOD mice predisposed to this disorder. Most important, successful resolution of the early reaction grants euglycemia in mice with genetic predisposition to inflammatory insulitis, which also explains the partial expression of spontaneous disease in this strain.

4. Propagation of inflammatory insulitis

Once the autoimmune reaction is initiated, inflammation is amplified in the pancreatic lymph nodes, which are related to the active mesenteric lymphatic trunk that provides an effective hideout for the evolving pathogenic cells [17]. It has been emphasized that the pancreatic lymph nodes are required for the evolution of autoimmune insulitis, providing an ambient environment for the development of diabetogenic clones [18]. The pancreas is frequently affected in systemic autoimmune disorders, some of which result in acute hyperglycemia [19,20]. Diabetes is not the only disorder with such pathogenesis: autoimmune thyroiditis is a prevalent inflammatory reaction in a tissue located in the vicinity of a hyperactive lymphoid trunk responsible for neutralization of inhaled and digested antigens [17]. Thus, irrespective of the initial insult that induces the autoimmune process, evasion of pathogenic clones from immune surveillance or inadequate suppression of physiological anti-islet reactivity, genetic, environmental and local predisposing factors amplify the immune reaction.

Appearance of overt hyperglycemia at an approximate threshold of ~20% of β cell mass follows a long state of inflammatory insulitis in the order or weeks in mice and years in humans. The chances to

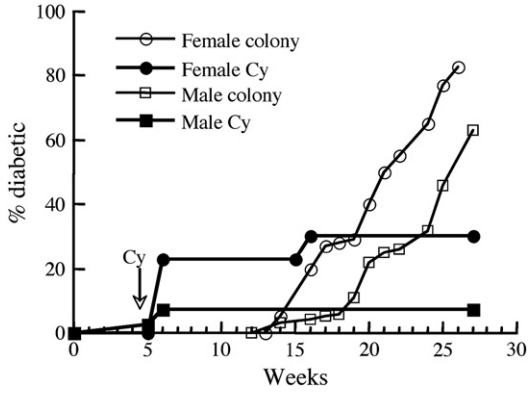

Fig. 2. NOD mice were infused with 200 mg Cyclophosphamide (Cy) at the age of 4.5 weeks after weaning at 3 weeks [15]. Diabetes was considered at blood glucose levels above 200 mg/dl in females (n=33) and males (n=38) as compared to incidence of spontaneous hyperglycemia in the female (n=312) and male (n=156) colonies.