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Review

Thymus and type 1 diabetes: An update

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ABSTRACT

Type 1 diabetes (T1D) is a chronic disease resulting from the selective autoimmune destruction of pancreatic islet β cells. The absence and/or breakdown of immune self-tolerance to islet β cells is now recognized as the essential cause for the development of the diabetogenic autoimmune response. For a long time, a failure in peripheral tolerogenic mechanisms was regarded as the main source of an inappropriate immune process directed against insulin-secreting β cells. While defective peripheral self-tolerance still deserves to be further investigated, the demonstration that all members of the insulin gene family are transcribed in thymic epithelial cells (TECs) of different species under the control of the AutoImmune REgulator (AIRE) gene/protein has highlighted the importance of central self-tolerance to insulin-secreting islet β cells. Moreover, there is now evidence that a primary or acquired failure in thymus-dependent central self-tolerance to β cells plays a primary role in T1D pathogenesis. This novel knowledge is currently translated into the development of innovative tolerogenic/regulatory approaches designed to reprogram the specific immune self-tolerance to islet β cells.

Contents

1. Introduction

Since the identification in 1965 of mononuclear cell infiltrates in Langerhans' islets of diabetic patients [1], research worldwide has definitively demonstrated that type 1 diabetes (T1D) results from a highly selective autoimmune process that generates first an inflammation (insulitis), then the death of insulin-secreting islet β cells in the pancreas. In the immune

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system, the absence or disruption of immune self-tolerance leads to the development of devastating chronic autoimmune diseases such as T1D. The establishment of immune self-tolerance includes, on the one hand, a central arm in the thymus with the negative selection of self-reactive T cells clones emerging during the random recombination of gene segments coding for the variable parts of the β and β chains of the T cell receptor for antigen (TCR), as well as the positive selection of self-antigen specific natural regulatory T (nTreg) cells [2–7]. On the other hand, the peripheral arm of self-tolerance includes different regulatory mechanisms that are able to inactivate in periphery self-reactive T cells having escaped central thymus-dependent self-tolerance or emerging from the failure of anergizing self-reactive T cells. So, the very fundamental question when trying to explain the origin of autoimmunity is to understand the origin of self-reactivity. There is now evidence that a defect in intrathymic T cell differentiation plays a crucial role in the generation of self-reactive T cells and the development of many autoimmune diseases. In this review, we will more specifically address the question of a thymus dysfunction as a primary event in T1D pathogenesis.

2. T1D-related autoantigens and autoantibodies

Islet β cells are the only cells of the organism that synthesize and secrete insulin according to the endocrine model. Thus, logically, insulin was long presumed to be the principal target of autoimmune T1D. This was first supported by the discovery of anti-insulin antibodies, then definitively demonstrated by two independent studies showing that insulin and its dominant epitope Ins B9-23 are playing a prime role in the development of diabetogenic autoimmunity both in NOD mice and in humans [8–10]. The other antigens solely expressed in islet β cells are the islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP) [11], and the islet-specific cation efflux transporter ZnT8 [12]. Other less specific autoantigens targeted in T1D are the 65-kDa isoform of glutamic acid decarboxylase (GAD65), the tyrosine phosphatase IA-2, and chromogranin A. Anti-insulin, anti-GAD65, and anti-IA-2 autoantibodies are very reliable markers of the autoimmune response against islet β cells. The serum of more than 90% of children with recent-onset T1D contains antibodies against one or several of these antigens. They also have a predictive value since these antibodies can be detected several years before the clinical signs of insulin deficiency, which appear when about 80% of the β-cell mass is destroyed. T1D prediction is increased when the detection of autoantibodies is associated with the presence of susceptible genetic alleles of the major histocompatibility complex (MHC) class II and class I loci [13,14]. However, the pathogenic significance of T1D-related antibodies is very low, if not absent [15], and the real effectors of β-cell autoimmune destruction are self-reactive CD4+ and CD8+ T lymphocytes [16]. A rationale question was therefore to investigate the question of an education of T-cell precursors to recognize and tolerate T1D-related antigens during their differentiation in the thymus.

3. The central role of the thymus in self-tolerance to neuroendocrine functions

Initiated in 1985, our studies have established that several neuroendocrine-related genes are transcribed in thymic epithelial cells (TECs) of animal and human species [17]. For each of these families, one member is predominantly expressed in thymus epithelium: oxytocin (OT) for the neurohypophysial family, neurotensin for neuromedins, neurokinin A for the tachykinins, and insulin-like growth factor 2 (IGF-2) for the insulin family. In the same time, this intrathymic expression of neuroendocrine peptides was proposed to be responsible for the induction of central self-tolerance to the functions mediated by these peptides outside the thymus [17]. Very importantly, the processing of thymic neuroendocrine-related precursors is not coupled to the classic neurosecretory model but leads to the presentation of neuroendocrine self-antigens by thymic MHC machinery [18,19]. The AutoImmune REgulator (AIRE) protein controls the transcription in TECs of most neuroendocrine-related genes. In *Aire*$^{-/-}$ mice, the decrease in the intrathymic level of tissue-specific gene expression (including genes encoding OT, Insulin 2, IGF-2 and neuropeptide Y) is associated with the appearance of autoimmunity directed toward several peripheral organs [20].

The expression of an insulin-related peptide in the thymus had already been suspected in 1965. On the basis that AKR female mice develop hypoglycaemia and thymic hyperplasia associated with lymphatic leukaemia, Pansky et al. reported the presence of an insulin-like peptide within the thymus of AKR strain mice, as well as in bovine and porcine species [21]. Immunohistochemistry then revealed that insulin-like growth factor 2 (IGF-2) is the member of the insulin family that is predominantly expressed in rodent and human TECs [22], and soon after Jolicœur et al. reported transcription of the insulin gene in the thymus [23]. Actually, all the members of the insulin gene family are expressed in the thymus network according to the following hierarchy: *IGF2* (TECs) > *IGF1* (TECs and macrophages) > > *INS* (rare subsets of medullary TECs) [24]. This hierarchy is meaningful since the level of tolerance to a given polypeptide is proportional to the degree of its intrathymic expression [25]. In addition, the blockade of IGF-mediated signaling between TECs and thymic T cells was shown to inhibit early T cell proliferation and differentiation, an effect that was not observed after blockade of (pro)insulin [26]. From an evolutionary point of view, this economical hierarchy in the organization of the thymic repertoire of neuroendocrine-related precursors also possesses very important selective advantages that were described in detail elsewhere [27]. In brief, the appearance of the thymus, concomitantly or shortly after the emergence of the adaptive immune response, was very helpful for further integrated evolution of the immune and neuroendocrine systems by preventing the inherent risk of auto-toxicity directed to the neuroendocrine polypeptide hormones that was inherent to the random generation of extreme TCR diversity catalyzed by recombination-activating genes.

In mice, where two genes code for (pro)insulin (*Ins1* and *Ins2*), *Ins2* is predominantly expressed in the thymus while *Ins1*