

A unifying model of self-tolerance and autoimmunity to the neuro-endocrine system

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Expression and presentation of neuroendocrine self-peptides by thymic epithelial cells (TECs) is the basic fundamental mechanism responsible for programming central immune self-tolerance to the neuroendocrine system. This mechanism ensured a harmonious and integrated coevolution of this system with adaptive immunity after its emergence in cartilaginous fishes (sharks and rays) some 450 millions years ago. It is noteworthy that the first unique thymus (with TEC differentiation controlled by *Foxn1*) appeared quite in the same time than the recombination-activating genes *Rag1* and *Rag2* responsible of adaptive immunity. Thus, the thymus emerged as the first rampart against the high risk of autoimmunity associated with the huge diversity of antigen receptors (TCRs and BCRs) generated within the adaptive immune system.

A genetic or acquired defect of this essential mechanism of self-presentation in the thymus is the earliest event implicated in the development of autoimmunity and this may occur already during fetal life. However, several types of environmental factors are also required for the clinical manifestation of an autoimmune disease.

With regard to autoimmune juvenile type 1 diabetes (T1D), insulin-like growth factor 2 (IGF-2) is the dominant member of the Insulin family expressed by cortical and medullary TECs in different species. Contrary to (pro)insulin, IGF-2 intervenes in the regulation of T-cell differentiation in the thymus. *Igf2* transcription is defective in the thymus of Bio-Breeding rats, an animal model of human T1D. IGF-2 expression is necessary for the establishment of a complete self-tolerance to Insulin, the primary antigen of islet β cells targeted by the diabetogenic autoimmune process. Contrary to Insulin B9-23, presentation of IGF-2 B11-25 to PBMCs isolated from DQ8+ diabetic adolescents elicits an immunosuppressive cytokine profile. Also in contrast with Insulin that is highly immunogenic, the tolerogenic properties of IGF-2 have been evidenced in different experimental conditions.

Based on this novel knowledge, our laboratory is currently working on the design of a completely novel type of vaccination, an IGF-2 based “tolerogenic inverse self-vaccine” for T1D prevention and cure.

Reference

Geenen V *et al.* The presentation of neuroendocrine self-peptides in the thymus: an essential event for individual life and vertebrate survival. *Annals of the New York Academy of Sciences* 2019; **1455**: 113-125, doi: 10.1111/nyas.14089.

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