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The thymus as an obligatory intersection between the immune and neuroendocrine systems: pharmacological implications

Editorial overview

Vincent Geenen

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Vincent Geenen

Center of Immunology, Institute of Pathology, University of Liège, Liège, Belgium
e-mail: vgeenen@ulg.ac.be

Vincent Geenen received the MD (1982) and PhD (1987) degrees from the University of Liege Medical School in Belgium. He is currently Research Director for the National Fund of Scientific Research of Belgium (NFSR), Chairman of the Center of Immunology at University of Liege, Professor of Developmental Biology at Liege Faculty of Sciences, Professor of History of Biomedical Research at Liege Medical School, and Clinical Head in Endocrinology at Liege University Hospital. The recipient of several research awards in Belgium and Europe, he has given more than 90 invited lectures worldwide, authored or coauthored more than 140 papers and several book chapters, and coedited the book *'Immunoendocrinology in Health and Disease'* (2004). He wrote the chapter 'Thymus and T cells' for the 2nd Edition of the *Encyclopedia of Neuroscience on CD-ROM* (Elsevier, 1998). His research focuses on thymus-dependent immunological self-tolerance, the role of a thymus dysfunction in the development of autoimmunity, the design of a thymus-based negative self-vaccine against type 1 diabetes, and immune-neuroendocrine interactions during embryo implantation and pregnancy. Dr. Vincent Geenen was the coordinator of the European FP6 Integrated Project **Eurothymaide** (2004–2008) entitled *'Novel approaches in pathogenesis, diagnosis, and treatment of autoimmune diseases based on new insights into thymus-dependent self-tolerance, with special attention to type 1 diabetes'*. Since 1995, his name is included in Who's Who in the World, Who's Who in Science and Engineering, and Who's Who in Medicine and Health Care. Dr. Vincent Geenen holds memberships in the Endocrine Society, the American Association of Immunologists, the American Association of Diabetes, the International Federation of Neuroendocrinology, the European Association for the Study of Diabetes, the International Society of NeuroImmunoModulation and the European Neuroendocrine Association, among many organizations.

Already in his famous side-chain theory (1900), P Ehrlich formulated the hypothesis that immune cells could express receptors susceptible to react against normal components of the body. In that case, however very improbable for him, he claimed that the organism should deploy specific mechanisms to escape from this difficulty (*horror autotoxicus*). In the second edition of *'The Production of Antibodies'* (1949), F Macfarlane Burnet and F Fenner proposed the principle of self/nonself discrimination as the cardinal point of immune physiology, as well as the concept of self-markers for antigens encountered by precursors of immunocytes during embryonic life, to which thenceforth immunological tolerance could never be broken later in life. Autoimmunity, if this should occur, would then depend on 'forbidden' immune clones that later arose through somatic mutation. Since that time, self-tolerance has become a cornerstone of immune physiology, together with diversity, specificity and memory of the immune response. The absence or breakdown of self-tolerance is responsible for the progressive development of autoimmune diseases, either systemic (such as lupus erythematosus) or organ-specific (such as autoimmune endocrine diseases). All endocrine glands without exception may become deficient because of an autoimmune response directed against one or a few endocrine tissue-specific autoantigens. A legitimate question then is to understand why autoimmune pathogenic processes so frequently aggress endocrine tissues. The discovery of the intrathymic mechanisms responsible for the installation of central self-tolerance has provided a number of answers to this important question. Among these answers, an important one concerns the true nature of *self* that is presented in the thymus to differentiating T cells during fetal life. Since its formulation some 60 years ago, *self* had been a seminal word coined in immunology's language first as a fecund metaphor with some equivocal correlations to philosophy, psychology, and neurocognitive sciences. For unknown reasons, there were no serious attempts to elucidate the biochemical identity of *self* before a number of essential consecutive studies in the late 1980s and in the 1990s.

In all living species, (neuro)endocrine and innate immune systems have coevolved until now without any apparent problem. Some 470 millions years ago, while the rudiments of an anticipatory immune response already existed in early jawless vertebrates (agnathes), recombinase-dependent adaptive immunity appeared for the first time in jawed fishes (gnathostomes). As demonstrated by S Tonegawa and M Davis, gene recombination in somatic lymphoid cells is responsible for the random generation of diverse immune receptors for antigens, B-cell ($\pm 5 \times 10^{13}$ BCR combinations) and T-cell receptors ($\pm 10^{18}$ TCR combinations). Because of its inherent risk of auto-toxicity, the emergence of this sophisticated type of immune response exerted a pressure so powerful that novel structures and mechanisms

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appeared for orchestrating the setting-up of immunological self-tolerance. The progressive rise in the level of immune diversity and complexity may explain why failures in self-tolerance (autoimmune diseases) are increasingly detected during evolution, with the maximum observed in the human species. Of note, the first thymus also appeared with cartilaginous fishes and, *a posteriori*, it can be legitimately stated that the emergence of this organ was required for a further 'pacific' coevolution of the immune and neuroendocrine systems. Two essential and closely associated mechanisms are responsible for the thymus-dependent central arm of self-tolerance: clonal deletion of self-reactive T cells stochastically generated by the recombinase-dependent generation of TCR diversity, and differentiation of self-specific natural regulatory T cells (Treg), which are able to inhibit in periphery self-reactive T cells having escaped thymic negative selection. As recalled several times by NA Mitchison, B-cell tolerance is primarily due to a lack of T-cell help and, therefore, the thymus and T lymphocytes play a predominant role in the establishment of immunological tolerance and development of autoimmunity. In addition, more and more experimental data are providing firm evidence that a disruption in the tolerogenic pathways operating during intrathymic T-cell differentiation constitutes a major event in the initiation of autoimmune diseases.

Immunoneuroendocrinology was recognized as a scientific field early in the 20th century, soon after immunology was identified as a specific domain of investigation. By the 1930s, H Selye introduced the concept of stress-induced, adrenal cortex-mediated thymus involution and secondary immunosuppression. In the 1940s, the discovery and chemical synthesis of glucocorticoids and their therapeutic usage in rheumatoid arthritis represented a major progress recognized by the 1950 Nobel Prize in medicine and physiology. Before the seminal work conducted in the 1960s by JFAP Miller, who established the thymus as the lymphoid organ ensuring T-cell generation (thymopoiesis), this organ was assumed to be a specific gland belonging to the endocrine system. However, as we have shown, the model of (neuro)endocrine cell-to-cell signaling failed to accurately describe the interactions between the thymic stromal network and developing T cells. Actually, the processing of neuroendocrine-related precursors synthesized in thymic epithelial cells is not coupled to classical (neuro)secretion, but to constitutive pathways involved in membrane targeting and self-presentation by the thymic proteins of the major histocompatibility complex. The dissection of the intricate cellular and molecular interactions between the major systems of cell-to-cell signaling — the neural, endocrine, and immune systems — was initiated in the 1980s and this scientific domain has received only gradual acceptance by the scientific community. Endocrinologists did not hesitate to widely open the door to this new field and

provided the first robust experimental arguments for its fundamental relevance to physiology. Recently, immunoneuroendocrinology has been expanded exponentially, and the immunological self-tolerance of neuroendocrine proteins was proved to be an obvious necessity for preserving general homeostasis. As it will be largely illustrated in this issue, many hormones and neuropeptides exert an important control upon the immune and inflammatory responses through binding to and activation of neuroendocrine receptors expressed by immunocompetent cells. If self-tolerance to neuroendocrine ligands and receptors were not firmly installed, then the risk of developing autoimmune phenomena would have been extremely high and species survival would have been severely compromised. The primary objective of this issue is to show the pharmacological importance of immunoneuroendocrinology for modulation of thymus functions and regeneration of immune defenses, as well as for the therapeutic approach of type 1 diabetes and other autoimmune endocrine diseases.

From a clinical point of view, aging of the immune system (immunosenescence) is characterized by a higher susceptibility to various infections, an increase in the incidence of cancer and autoimmune diseases, as well as a decrease in response to vaccinations. Since a long time, thymic adipose 'involution' is considered as the prominent feature of immunosenescence. It is associated with a marked decrease in the generation of diverse T cells (in particular naïve CD4+ T cells), an expansion of memory CD8+ T cells, and a diminished influence of thymus-dependent central self-tolerance. The involution of the thymus following hypophysectomy was the first evidence for the control of the immune system by a major endocrine gland (Smith, 1930). In 1932, the Swedish thymologist JA Hammar observed a positive relationship between the size of the hypophysis and the development of thymic medullary epithelium in young rabbits. The GH receptor belongs to the extended family of receptors to type I cytokines and pioneering studies by KW Kelley and colleagues unambiguously demonstrated that GH administration reverses age-dependent thymic atrophy. Today, thymus function can be clinically monitored through the sophisticated technology of signal-joint (sj) and β TCR excision circles (TRECs) that are generated during the intrathymic recombination of gene segments encoding the variable parts of the TCR α and β chains. Using this methodology, it is now possible to measure with precision the impact exerted *in vivo* by the endocrine system upon two important parameters of thymus physiology, the intrathymic proliferation of T-cell precursors (sj/ β TREC ratio) and the thymic output of naïve T cells (sjTRECs). Several chapters of this issue will further illustrate the importance of the somatotrope ghrelin/growth hormone (GH)/insulin-like growth factor 1 (IGF-1) in the regulation of thymus biology. The

restoration of thymus function is now a major objective in the elderly, in AIDS, and in a series of hematological diseases. From these in-depth studies, it is highly probable that GH, GH secretagogues (such as ghrelin), GH and ghrelin receptor agonists, or IGF-1

and thymus-specific growth factors will be used in the very near future to regenerate thymopoiesis and thymus tolerogenic function, as well as, secondarily, several immune functions including responses to vaccines in aged and other immunodeficient patients.