

# Historical introduction to the thymus and the concept of immune self-tolerance

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The name ‘thymus’ first appeared in Galen’s manuscripts (±160 AD) and was so named because of its morphological analogy with the leaf of *Thymus cunila*. For centuries however, this organ was considered only as a vestigial organ that served as a cushion between the sternum and basal blood vessels, and then involuted after puberty. In the late 50’s, JFAP Miller discovered that the thymus was the site for development of a special population of immune cells, the thymo-dependent T lymphocytes. In concordance with P Ehrlich’s early concept of ‘*horror autotoxicus*’, FM Burnet predicted in 1962 that the thymus should play a crucial role in the elimination of developing lymphocytes with potential reactivity against the ‘self’ (‘forbidden’ T cell clones). This theory of intrathymic negative selection of self-reactive T cells was finally demonstrated in late 80’s through the elegant studies in the laboratories of N Le Douarin (Nogent-sur-Marne), P Murrack and J Kappler (Denver), HR Mac Donald (Lausanne) and H von Boehmer (Basel).

In the same time, an important question raised about the biochemical nature of the ‘self’ expressed in thymic microenvironment. Our laboratory established that thymic epithelial cells (TECs) from different species transcribe dominant genes of many neuroendocrine families (OT for neurohypophysial family, NKA for tachykinins, NT for neuromedins and IGF-2 for insulin family). However, after transcription, neuroendocrine precursors are not linked to classic (neuro)secretion. Their processing is the source of neuroendocrine self-peptides that are presented by proteins of the major histocompatibility complex (MHC) expressed by TECs and thymic dendritic cells. Through this unique process, already during fetal development, the thymus programs central self-tolerance of the adaptive immune system to neuroendocrine functions and this was an absolute necessity after emergence of this novel form of immunity generating the diversity of antigen recognition some 470 millions years ago. The laboratory of the late B Kyewski further demonstrated the central role of the thymus in central immune tolerance to almost all peripheral tissues.

Several laboratories then addressed the logical hypothesis that a defect in the tolerogenic function of the thymus could be a primary event promoting the development of autoimmunity. Several experimental data argued for this assumption and the question was definitively solved with the identification of the AutoImmuneREgulator gene. *AIRE* controls the level of transcription of many (but not all) tissue specific self-peptides in medullary TECs and *AIRE* mutations (or *Aire* ablation) is associated with the development of autoimmunity tackling many peripheral organs. More recently, the *Fezf2* gene, already known to be involved in neuronal development, was shown to be expressed in TECs and to regulate the transcription level of *Aire*-independent genes also coding for tissue specific self-antigens.

As stated by several authors, the discovery of the central tolerogenic of the thymus revolutionized the whole field of immunology. Undoubtedly, this novel knowledge will pave the way for innovative tolerogenic therapies aiming to prevent and treat autoimmunity, the so heavy tribute paid by all mankind for the extreme diversity and efficiency of adaptive immunity.

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## References

1. Martens H, Goxe B and Geenen V. The thymic repertoire of neuroendocrine self-antigens: physiological implications in, T cell life and death. *Immunol Today* 1996; **17**:312-7.
2. Geenen V *et al.* Programming of neuroendocrine self in the thymus and its defect in the development of neuroendocrine autoimmunity. *Front Neurosci* 2013; **7**: article 187 - doi: 10.3389/fnins.2013.00187.
3. Geenen V. Histoire du thymus : d’un organe vestigial à la programmation de la tolérance immunitaire. *Med Sci* 2017; **33**:653-63.