**The presentation of neuroendocrine self in the thymus: a necessity for an integrated evolution of the neuroendocrine and adaptive immune systems**

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The immune system is a sensory organ able to respond to danger signals that are not detected by nervous cells. The immune response is not autonomous but also regulated by central and peripheral nervous system, as well as by neuropeptides, vitamin D and neuroendocrine axes such as the corticotrope, somatotrope, thyrotrope and gonadotrope axes. During evolution, the thymus emerged concomitantly with recombinase-dependent adaptive immunity as an ‘immune brain’ or a ‘master class’ highly specialized in the orchestration of central immunological self-tolerance. In compliance with Paul Ehrlich’ concept and prediction of “*horror autotoxicus*”, this was an absolute requirement for survival of species because of the high risk of autotoxicity inherent to the stochastic generation of extreme diversity characterizing this novel adaptive type of immune defenses against non-self. The thymus now appears to be an obligatory intersection for the integrated evolution of the major systems of cell-to-cell signaling, the nervous, endocrine and immune systems. The presentation of most self-peptides in the thymus is controlled by the autoimmune regulator (AIRE) gene/protein and is responsible for the clonal deletion of self-reactive T cells. In the same time, the presentation of thymic self-peptides also promotes quite paradoxically the generation of self-specific FOXP3+ CD4+CD25+ natural regulatory T cells that are able to inhibit in periphery self-reactive CD4+ and CD8+ T cells having escaped the thymus censorship. Moreover, there is now evidence that a thymus dysfunction is a crucial event driving the development of organ-specific autoimmunity, which is the tribute paid, mainly by mankind, for the preservation of self against non-self. This novel knowledge about thymus physiology and physiopathology now serves as the basis for the development of innovative and efficient immunomodulating strategies in pharmacology.

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