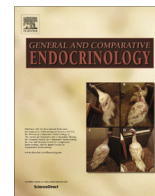




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Review article

## Thymus: Conservation in evolution

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### ABSTRACT

From an evolutionary point of view, the thymus is a new organ observed for the first time in fish concomitantly with the appearance of adaptive clonotypical immunity. Hormone and neuropeptide expression was demonstrated in different species suggesting a conserved role of these molecules. An integrated evolution of immune and neuroendocrine responses appears to have been realized by means of the re-use of ancestral material, such as neuroendocrine cells and mediators, to create a thymic microenvironment for the maturation and differentiation of T cells.

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### 1. Introduction

The immune-neuroendocrine effector system of invertebrates is centered on the phagocytic cell (immunocyte) and characterized by primitive and highly promiscuous recognition units (Ottaviani and Franceschi, 1997; Ottaviani et al., 2007; Ottaviani, 2011; Malagoli et al., 2015). In vertebrates, the increasing complexity of the internal circuitry, enlargement and refinement of recognition units are concomitant with the appearance of a new organ, the thymus, in order to copy with new problems of self/not-self recognition (Ottaviani et al., 1998). This primary lymphoid organ for functional T cell development is present in all jawed vertebrates, despite differences among species. These include the number of thymic glands per animal, anatomical location, developmental origin and processes (Zapata and Cooper, 1990; Rodewald, 2008). Thymus anlage arises from the endoderm located in different position along the pharyngeal area and the organogenesis does not always involve complete separation of the primordium from the pharynx (Grevellec and Tucker, 2010; Gordon and Manley, 2011). Although it is assumed that a true thymus is absent in Agnatha, primitive lympho-epithelial structures scattered in the gill basket were described in lampreys. They were termed thymoids and indicated as the site of development of T-like cells (Bajoghli et al., 2011). It should be underlined that the appearance of these ancestor anatomically distinct tissue aggregates occurs in coincidence with the emergence of the dual nature of the adaptive immune

system (Guo et al., 2009). Indeed, two separate lineage of lymphocytes that express specific somatically diversified antigen receptors (the leucine-rich-repeat-containing variable lymphocyte receptors, VLR) and cytosine deaminase to initiate the assembly of VLRs by gene conversion, were identified in lampreys (Rogozin et al., 2007; Guo et al., 2009). Comparative studies performed in basal groups of vertebrates to investigate the emergence of thymus, suggest that changes in genetic networks and cellular mechanisms that control the organogenesis may be correlated to its evolution (Bajoghli et al., 2009; Ge and Zhao, 2013). Foxn1 (forkhead family transcription factor) is one of the earliest specific marker of proliferation and differentiation of thymic epithelial cells in jawed vertebrates (Vaidya et al., 2016). It has been indicated as a key regulatory gene essential to establish a functional microenvironment by controlling the expression of delta-like and chemokine genes requested for specification to the T cell lineage and lymphoid progenitor attraction (Bajoghli et al., 2009; Vaidya et al., 2016). Foxn1- and delta-like genes appeared in the cephalochordate amphioxus and were identified in lamprey thymoids suggesting an ancient evolutionary specification to thymic epithelial cell fate (Bajoghli et al., 2009, 2011). The emergence of thymus also overlaps with that of thymopoietic chemokines, i.e., ccl25 and its receptor, ccr9. This molecule pair, first demonstrated in cartilaginous fish, was not found in lamprey genomes, even if T-like lymphocytes express a partial sequence which is closely related to ccr9 (Guo et al., 2009). However, other chemokine receptor genes, such as cxcr4, were detected in jawless fish T-like cells (Bajoghli et al., 2009; Bajoghli, 2013). Findings in chicken and mice embryos demonstrated that inductive interactions between mesenchymal cells of neural crest origin and thymic epithelial cells contribute

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to initial thymus morphogenesis, although this dependence is somewhat controversial (Bockman and Kirby, 1984; Suniara et al., 2000; Anderson et al., 2006; Griffith et al., 2009; Nelms et al., 2011; Lee et al., 2013). Interestingly, the co-evolution of neural crest and thymus has been suggested in lampreys (Ge and Zhao, 2013).

The basic morphology of thymus from different vertebrates is largely constant (Zapata and Cooper, 1990). The maturation and phenotypical differentiation of T cells occur in an “inductive” microenvironment, consisting primarily of organized epithelial networks, influenced by the neuroendocrine system through a bi-directional circuit (Savino and Dardenne, 2000). The *in situ* production of hormones and neuropeptides as well as the expression of respective receptors on thymic cells were also demonstrated in mammals (human, rodent) and non-mammals (avian, amphibian and fish), suggesting an evolutionary conservation of these molecules (Dardenne and Savino, 1994; Silva et al., 2006; Silva and Palmer, 2011). The findings also highlight that paracrine and autocrine signaling could control the organ physiology (Dardenne and Savino, 1994).

In this review, we discuss the intrathymic immune and neuroendocrine interactions in an evolutive perspective, with particular focus on pro-opiomelanocortin (POMC)-derived peptides.

## 2. Presence of POMC-derived peptides in thymus from fish to mammals

The thymic morphology is variable within teleosts (Bowden et al., 2005). In *Carassius c. auratus*, it is a paired, bean-shaped organ located in the branchial cavity at an angle between the operculum and head wall (Ottaviani et al., 1995a). The histological observations demonstrated a thin capsule surrounding a parenchyma with easily recognizable, although not clearly separated, medulla and cortex regions. This transition area has been defined intermediate region. No evident cortico-medullary differentiation, as normally seen in higher vertebrates (Fig. 1), was found in other fish species (Bowden et al., 2005). Immunohistochemical reactions demonstrated the presence of POMC-derived peptides (ACTH,  $\beta$ -endorphin,  $\alpha$ -MSH) in few scattered, differently shaped cells, that were mainly located in medulla and the intermediate region (Fig. 2A) (Ottaviani et al., 1995a). These cells reacted positively to anti-cytokeratin monoclonal antibody (mAb), while negatively to anti-vimentin mAb, suggesting that they belong to the epithelial lineage (Lazarides, 1980). To our knowledge, the only other evidence of POMC-products in fish thymus was found in *Dicentrarchus labrax*. In particular, ACTH- and the related receptor-like molecules were observed in parenchyma cells in the course of post-hatching development, suggesting an early role for this peptide during organ maturation (Mola et al., 2005).

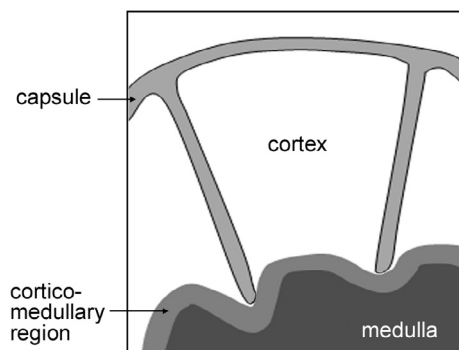


Fig. 1. Schematic representation of the structural thymic regions.

The thymus of *Rana esculenta*, located posterior to the middle ear, is characterized by clear demarcation between cortical and medullary regions (Franchini et al., 1995). Immunoreactive POMC-products were also detected in the epithelial cells and they were located in distinct thymic locations. The cells positive to anti-ACTH and  $\alpha$ -MSH were found in the subcapsular and inner cortex, while  $\beta$ -endorphin in inner cortex and medulla (Fig. 2B).

It should be underlined that both fish and amphibian thymic lymphocytes were negative to anti-ACTH antibody, while peripheral blood lymphocytes were immunoreactive in anurans (Ottaviani et al., 1992). Analogously, human thymic lymphocytes were negative for the presence of ACTH (Batanero et al., 1992) and peripheral blood lymphocytes were positive (Smith and Blalock, 1981).

The thymus of *Gallus domesticus* is generally constituted by seven lobes located on each side of the neck. Scattered cells located in the medullary region were immunoreactive to POMC-product antibodies. These cells showed the structural characteristics of epithelial cells (positive to anti-cytokeratin) and/or interdigitating cells (positive to anti-vimentin) (Ottaviani et al., 1997a). Changes in the presence of these molecules were also analyzed during the age-dependent development and involutive stages of the thymus (Franchini and Ottaviani, 1999). The POMC products were early (from 4-days-old chicken) and similarly detected in epithelial cells and interdigitating cells located both in the medulla and cortico-medullary region and the number of the immunoreactive cells increased with aging. Concomitantly with progression of the morphological modifications, positive interdigitating cells, showing cytological features of an active phagocytizing functional phase, were seen associated with the connective islets invading thymic parenchyma. These cells decreased in number in 6-month-old chicken. The findings indicate a physiological role of these molecules in the course of organ growth and involution (Franchini and Ottaviani, 1999).

As regards mammals, the study of thymus of the Sprague-Dawley rat (*Rattus norvegicus*) (Ottaviani et al., 1997a) revealed the presence of POMC-products in epithelial cells located in cortex and in few cortical cells, morphologically similar to macrophages and positive to anti-vimentin (Fig. 2C). ACTH immunoreactivity was also demonstrated in epithelial cells from human thymic cortex (Batanero et al., 1992).

## 3. Role of POMC-products in thymus

POMC-derived peptides were detected in thymus of all the examined species, from fish to mammals. The immunoreactive cells, located with species-specificity, were a population of epithelial cells, in addition to interdigitating cells in chicken and macrophages in rat. Thymic lymphocytes resulted always negative for the presence of these peptides. As regards the possible functional role of these molecules, it has been proposed that ACTH exerts an indirect function on lymphocytes by favoring the release of thymic hormones, such as thymulin. Millington and Buckingham (1992) demonstrated that ACTH rapidly released thymulin from thymic fragments *in vitro* or after its injection in rats. Moreover, the thymulin production was found to be modulated by endogenous opioids such as  $\beta$ -endorphin (Dardenne and Savino, 1994). ACTH was also shown to directly stimulate thymus growth in mice and the regulation of thymocyte expansion and maturation was independent of the glucocorticoid effect on thymocyte apoptosis (Talaber et al., 2015). The mammalian thymic stromal nurse cells, a subset of epithelial cells located in subcapsular cortex involved in T lymphocyte development, maturation, and selection, contain both neurohypophysial peptides and interleukin-1 (Robert et al., 1991; Guyden and Pezzano, 2003). In the thymus of different

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