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Review article

Cross-talk among immune and neuroendocrine systems in molluscs and other invertebrate models

Davide Malagoli, Enzo Ottaviani *

Department of Life Sciences, University of Modena and Reggio Emilia, Via Campi 213/D, 41125 Modena, Italy

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ABSTRACT

The comparison between immune and neuroendocrine systems in vertebrates and invertebrates suggest an ancient origin and a high degree of conservation for the mechanisms underlying the integration between immune and stress responses. This suggests that in both vertebrates and invertebrates the stress response involves the integrated network of soluble mediators (*e.g.*, neurotransmitters, hormones and cytokines) and cell functions (*e.g.*, chemotaxis and phagocytosis), that interact with a common objective, *i.e.*, the maintenance of body homeostasis. During evolution, several changes observed in the stress response of more complex taxa could be the result of new roles of ancestral molecules, such as ancient immune mediators may have been recruited as neurotransmitters and hormones, or *vice versa*. We review older and recent evidence suggesting that immune and neuro-endocrine functions during the stress response were deeply intertwined already at the dawn of multicellular organisms. These observations found relevant reflections in the demonstration that immune cells can transdifferentiate in olfactory neurons in crayfish and the recently re-proposed neural transdifferentiation in humans.

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1. Introduction

The functional and the molecular basis of the relationship between immune and the neuroendocrine response have started to be studied already in the 20th century. Systematic experiments have been performed in human lymphocytes and demonstrated that the same molecules can work as neurotransmitter, hormones or immune signal as well (Blalock, 1999). During the 80′s and 90′s, studies performed in human and mammalian models showed the existence of an interaction between the immune and the neuroendocrine systems (Smith et al., 1987; Smith and Blalock, 1988). Thanks to this interaction hormones and neurotransmitters are able to bind specific immunocyte receptors and modulate their activities. The same holds true for cytokines that may be produced by, and influence the activity of, immune cells, but they also may intervene as mediators in the nervous system (see Cohen and Kinney, 2001). This commonalty of mediators makes in some cases hard to distinguish between environmental stressor and immune (Ottaviani et al., 1997).

The complexity of human immune and neuroendocrine components have prompted studies in simpler models. Among these, molluscs are valuable systems for analyzing the basis of the immune and neuroendocrine interaction (Malagoli et al., 2015) and numerous experiments

* Corresponding author at: Department of Life Sciences, University of Modena and Reggio Emilia, Via Campi 213/D, 41125 Modena, Italy.
E-mail address: enzo.ottaviani@unimore.it (E. Ottaviani).

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were performed by a restricted number of pioneer researchers (Cohen and Kinney, 2001).

This review summarizes the main findings collected in molluscs that set the basis of comparative immune-neuroendocrinology. We will cover functional, immunocytochemical and molecular evidence that in the last three decades have documented the tight relationship between immune and neural cells in molluscs and other invertebrate models.

2. Immune-neuroendocrine response in molluscs

Molluscs are a wide represented animal group, that consists of numerous families. Among these, the most intensively studied are the bivalves and the gastropods. The interests on these models roots in their economical relevance, since mussels, clams and oysters are currently cultivated in several countries and used as a food worldwide, whereas gastropods have proven to be important also for neurophysiologists and parasitologists (Smith et al., 2016).

The main pillars of molluscan immune system are the circulating hemocytes (Smith et al., 2016) that, in consideration of their principally immune-related role, may also be labeled as immunocytes (Ottaviani, 2011). A comprehensive review on the hemocyte classification and their origin have been published recently (Smith et al., 2016) and this topic will not represent the focus of the present review.

In mammals, the hypothalamic-derived CRH stimulates the release of ACTH by pituitary. ACTH, on its turn, promote many physiological responses, including the release of glucocorticoids from the surrenal gland. Though molluscs lack all of the organs that in mammals constitute the anatomical basis of the stress-response axis, the molecular mediators, or molecule alike them, are present. This suggests an ancient origin of the intertwine between immune and neuroendocrine response (Malagoli et al., 2015).

In both bivalves and gastropods, the exogenous administration of mammalian purified ACTH (1-24) and CRH chemotactically stimulated the hemocytes and prompted their activation in *in vitro* experiments (Sassi et al., 1998; Malagoli et al., 2000). Notably, the human-derived CRH and ACTH also stimulated the release of neuro-mediators like epinephrine and noradrenaline by molluscan hemocytes. More precisely, it has been observed that by incubating the molluscan hemolymph with ACTH and CRH a rapid and marked release of biogenic amines took place in the hemolymph. The greatest release occurred after 15 min of the administration of CRH and or ACTH, while after 45 min the values of the biogenic amines were again similar to those of the controls. Concomitantly to the increase in catecholamine concentration in the fluid component of the hemolymph, it was observed a decrease of biogenic amines in hemocytes (Ottaviani et al., 1993).

Immunocytochemical experiments demonstrated the presence in hemocytes of mediators of the response to stressful events. In the freshwater snail *Planorbarius corneus* and in the Mediterranean mussel *Mytilus gallorpovincialis* CRH- and ACTH-like material have been evidenced (Ottaviani et al., 1990; Franchini et al., 1994; Malagoli et al., 2000). The reliability of the reported immunocytochemical evidence obviously suffers from the necessity to utilize heterologous antibody and the bias that this approach might introduce (Baker, 2015; Weller, 2016). It is worth mentioning that immunocytochemical evidence led to the erroneous conclusion that CRH was secreted by mononuclear immune cells in mammals, while RT-PCR experiments demonstrated that the secreted factor was urocortin (Bamberger et al., 1998).

This notwithstanding, molecular data were collected in molluscs and supported the immunocytochemical observations. Fragments of ACTH-like proteins have been sequenced in the blue mussel *Mytilus edulis*, providing further sustain at the morphological evidence (Stefano et al., 1999). The presence of these ligands have also been associated to the presence of the relative receptors. In *M. galloprovincialis in situ* hybridization experiments indicated the presence of two forms of CRH-R, namely CRH-R1 and CRH-R2 (Malagoli et al., 2000).

Altogether, these observations suggest that the circulating immunocyte of molluscs presents characteristics similar to human macrophage and lymphocyte as well. By the one hand the immunocyte patrols the organism phagocytizing non-self particles, similarly to macrophages. On the other hand, the immunocyte also seems able to react to stressful situations by producing CRH- and ACTH-like material, which, in its turn, may act in autocrine or paracrine fashion and stimulate both neural and immune functions (Fig. 1). In these respects, the evolutionary conservation of the immune-neuroendocrine role of mammalian macrophage has been proposed (Ottaviani and Franceschi, 1997), and the possible evolution of vertebrate lymphocyte lineages from invertebrate immunocytes have been advanced (Scapigliati, 2013).

The overlap between immune and stress response in molluscs was also demonstrated by numerous other experiments, that used immune-related challenges or environmental stress as cues that promoted or inhibited immunocyte functions. For instance, the administration of human IL-2 interfered with the effects of CRH, suggesting a sharing of receptors or signaling pathway subsets for these two molecules (Ottaviani et al., 1994). The exposure of whole mussels to extremely-low frequency magnetic fields (ELF-MF) interfered with immune-related signaling pathways and modified the response to the bacterial tripeptide fMLP (Malagoli et al., 2003). Moreover, western blot experiments evidenced that immunocytes promote the synthesis of HSP70 and HSP90 in proportion to the intensity of the ELF-MF applied, indicating that hemocyte may autonomously respond to stressful events in order to maintain their immune functions under stressful conditions (Malagoli et al., 2004). In these respects, a tight connection between stressful conditions and immune reactivity has been observed in the hemocytes of the mussel, where the duration and the intensity of the stress proven to be critical in determining the maintenance of the phagocytic activity (Malagoli et al., 2007).

The experiments reported above provide relevant descriptions of the relationships between environmental or experimental stress and the immune response. However, evidence has also been provided about the possibility that immune response may interfere with higher order nervous system functions. In the freshwater snail *Lymnaea stagnalis*, injections of β-glucan laminarin has no direct effect on neuronal basal activity. Conversely, laminarin injections blocked the long term memory formation while it did not affect intermediate term memory (Hermann et al., 2013). In another gastropod model, the apple snail *Pomacea canaliculata*, the injection of *Escherichia coli*-derived LPS *was* sufficient to promote the phospho-acetylation of histone H3 in the central nervous system, in absence of other stress (Ottaviani et al., 2013). Among the numerous epigenetic modifications observed so far, the phosphorylation on serine residues in histone tails is considered to stimulate gene expression and the phosphorylation of histone H3 at Ser 10 [P(Ser10)-H3] has been proposed to be involved in transcriptional activation (Cheung et al., 2000). Our experiments thus demonstrated that the injection of a bacterial extract, *i.e.*, a typical immunological stimulus, activates transcription in snail ganglia central nervous system (Ottaviani et al., 2013).

3. Immune-neuroendocrine overlaps outside molluscs

One important drawback of molluscs as experimental system, was the relatively low availability of molecular databases to use as a reference for postgenomic approaches. While this gap is conceivably going to be filled by the recent techniques of high-resolution sequencing, convincing evidence of a deep interconnection between immune and neuroendocrine system have been provided outside molluscs.

In annelids, the importance of the immune functions and the neuro-immune cross-talk during the regeneration of experimentally damaged neurons have been demonstrated (Rodet et al., 2015).

In crustaceans and insects, models evolutionary far distant that diverged from molluscs and annelids more than 500 million years ago

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