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Editorial

Immunity and Neuroimmune Interactions at the Mucosal Barriers in Fish

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Immune and neuronal cells are often colocalized at defined anatomical sites, forming neuronal cell units, where both cells coordinate their responses. Neuronal cells are able to receive signals from immune cells and provide signals to these cells. As such, a neuronal regulation of immunity is found across multiple organs, and neuroimmune interactions emerged as the important regulators of the physiology and biology of certain tissues in fish.

Fish gills are essential for gas exchange, and they are vulnerable to waterborne microorganisms. They have a diffuse presence of immune cells, some of which (mast cells) are co-localized with neuroepithelial cells that are present in the mucosal linings covering the gills. Moreover, the air-breathing organs (ABOs) and the skin harbor a variety of immune cells, showing the co-localization of immune cell types and the interaction of immune cells with nerve terminals [1–4]. Gill-associated lymphoid tissues (GIALT) are also defined as one of the main mucosal compartments found in teleost fish. The skin-associated lymphoid tissue (SALT) and nasal-associated lymphoid tissue (NALT) in addition to gut-associated lymphoid tissue (GALT) were also identified in teleosts. Teleost NALT consists of abundant leucocytes that are scattered both intraepithelially as well as in the lamina propria of the fish's olfactory lamellae and readily respond to pathogens and vaccines [5,6].

The gut is an important organ with digestive and immune regulatory functions that harbor the microbiome ecosystem. The brain–gut axis has been the subject of the research over the past several years. A crosstalk between the brain and the gut occurs through multiple biological networks, including the neural network, the neuroendocrine system, immune system, and metabolic pathways, which enable bidirectional communications.

The gut microbiome influences the epithelial barrier's integrity by controlling the transit of signaling molecules from the lumen of the gut to the lamina propria, which contains various immune cells and neurons, or by controlling blood circulation. Macrophages and mast cells are regarded as the key regulators of the gut's physiological functions. Markers for macrophage subtypes are slowly but definitively emerging in fish species [7].

More recently, Graves et al. provided a preliminary structural study on the organization, distribution, and diversity of the zebrafish's gut macrophages during development and in adults [8]. The imaging analysis showed the presence of diverse intestinal macrophage subsets, namely muscularis and mucosal macrophages, similarly to mammalian counterparts, and it revealed the intimate contact between the macrophages and enteric neuronal processes.

Zaccone et al. (this issue) reported specific immune cell markers, such as CD14, Acetylcholine, alpha 7 acetylcholine nicotinic receptor (nAChR), the inducible nitric oxidase synthase (iNOS), and antimicrobial peptide piscidin 1 in the intestinal macrophages of two fish teleost species. These results are in agreement with those found in diverse animal taxa where the macrophages are a heterogeneous mix of diversified and functionally specialized cell subtypes, including the co-localization of enteric neurons with macrophages and neuron-associated macrophages, both providing the survival and homeostasis of enteric neurons that show a dynamic balance between neuronal apoptosis and neurogenesis. Although no available data exist in the literature regarding the regulatory mechanisms of

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the acetylcholine in fish gut, the above paper is the first contribution to the occurrence of a cholinergic system in the immune cells (macrophages and mast cells) in fish gut and of the non-neuronal acetylcholine in the epithelial mucous cells of the intestine. In line with above papers, the readers are referred to the studies on cellular mechanisms relative to mucosal immunology and neuroimmunology [9,10].

The intestinal barrier is liable to pathogen invasion. Both bacteria and virus induce intestinal immune responses, activating several cytokine signaling pathways (see for review [11]. To control the infection of intestinal pathogens, mucosal vaccines were explored, and their different effects were analyzed in mucosal and non-mucosal fish organs [11]. Regarding the crosstalk between the gut and other organs in the gastrointestinal immunity of fish, many data in the literature reflected the participation of the liver, kidney, and spleen [11]. Recently, Sayed et al. reported the presence of a rich variety of immune cells in the spleen of the Molly Fish *Poecilia sphenops* and the strong immunoreactivity of the cell constituents for APG-5, IL-beta, NF-kB, and TGF-beta, thus demonstrating that the spleen is at the frontline of innate immune responses [12].

Advances in the research of gastrointestinal immunity and its associated inter-organ crosstalk as well as the important aspects of the NALT mucosal immunity [5] and its application for mucosal vaccination in aquaculture will provide novel findings for improving our understanding of mucosal barrier functions in teleost fish.

We expect that aquaculture researchers will find the above articles within the subject of fish neuroimmunology inspiring and informative. For more detailed information, the readers are also referred to the Special Issue on gastrointestinal immune responses that are consequences of food, pathogen, or vaccination stimulation.

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