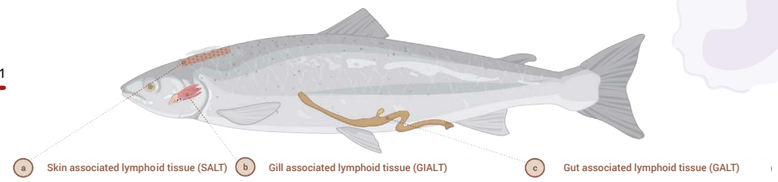
Cellular innate immune response

The fish immune system is made up of two subsystems: innate and adaptive. The innate immune system is the first one to respond again pathogens and does not retain memory of previous responses. If the pathogen persists, the adaptive immune system is activated and with a specific remembered response. Activation of immune response is called "immunostimulation" or "immunomodulation", but the term "trained innate immunity" has begun to be used to explain the stimulation of the innate immune defense that can confer greater nonspecific resistance to pathogen infections. Innate immune system considers three defense mechanisms: (1) physical barriers (**Figure 1**), (2) cellular components (**Figures 2**, **3**, **4** y **5**) y (3) humoral responses (**next data sheet**).

Physical barriers

Innate immune system first line defenses are physical barriers that prevent the entry of pathogens: skin, gills and gastrointestinal tract (**Figure 1**).

Figure 1



Skin: Teleost skin contains skin-associated lymphoid tissue (SALT) that consists of multiple cell types, including mucosal cells, B and T lymphocytes, granulocytes, macrophages, and a dendritic cell type called Langerhans-like cells. Skin has the ability to secrete mucus that acts as a physical and chemical barrier to trap and neutralize pathogens; it contains lectins, lysozymes, complement proteins and antimicrobial peptides.

Gills: Participate in osmotic balance and gas exchange. In addition, gills are also an important physical barrier composed of a layer of epithelial cells, a layer of glycocalyx, and a layer of mucus. Macrophages, neutrophils, eosinophilic granulocytes, and B and T cells are some of the cells that are in the gills (GIALT).

Gastrointestinal Tract (GI): GI tract facilitates the absorption of nutrients and through its epithelium prevents invasion of pathogens. Gut associated lymphoid tissue (GALT) is found in teleosts as a diffuse network of myeloid and lymphoid cells without major organization. Macrophages, eosinophilic granule cells, dendritic cells, B and T cells are seen in the posterior segment of the intestine.

Cell components

If the pathogen manages to cross physical barriers, it will encounter the cellular and humoral components of the innate immune system. Cellular components include: eosinophilic and neutrophil granule cells, monocytes/macrophages, dendritic cells (DC), and natural killer (NK) cells (**Figure 2**). When an innate cell encounters a pathogen, it will recognize a pathogen-associated molecular pattern (PAMP) and will be activated to participate in various responses such as: pathogen phagocytosis and destruction, cytosines production and adaptive immune system activation through antigen presentation (**Figure 2**).

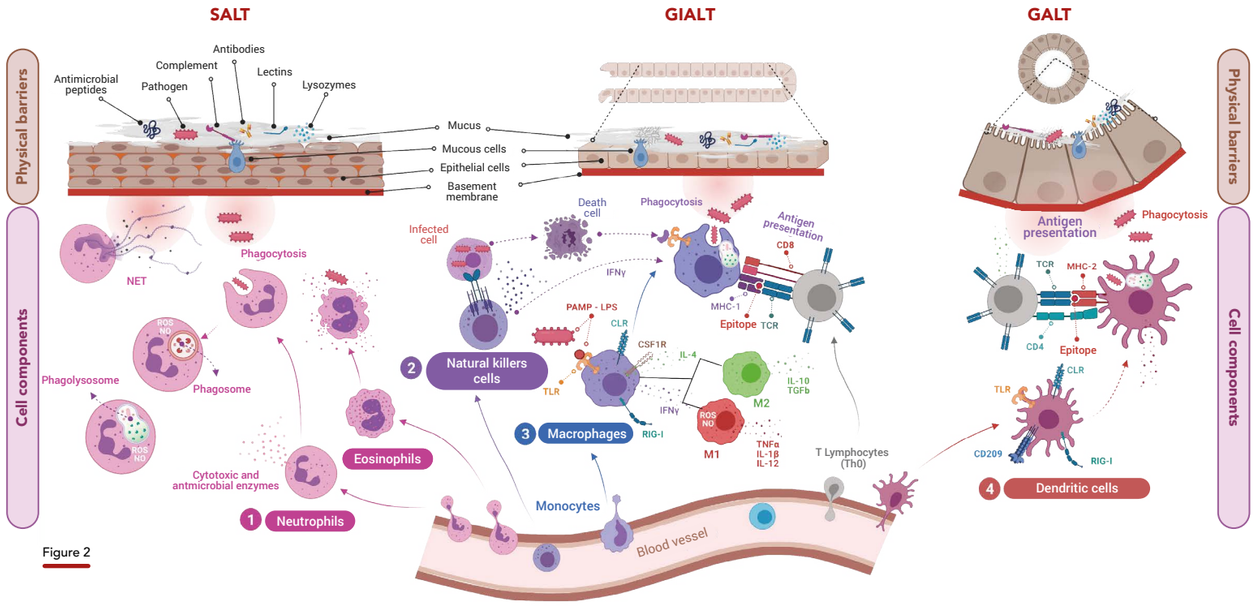
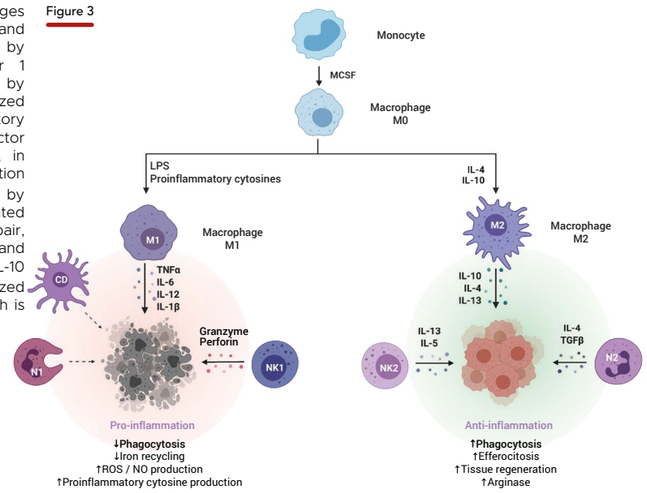


Figure 2

Neutrophils: Along with monocytes/macrophages, these are the firsts cells to arrive and respond to infection. Neutrophils show antimicrobial response through intracellular and extracellular mechanisms, including cytotoxic and antimicrobial enzymes granule release, neutrophil extracellular traps (NET) release, phagocytosis, and reactive oxygen species (ROS) and nitric oxide (NO) production (**Figure 2**).

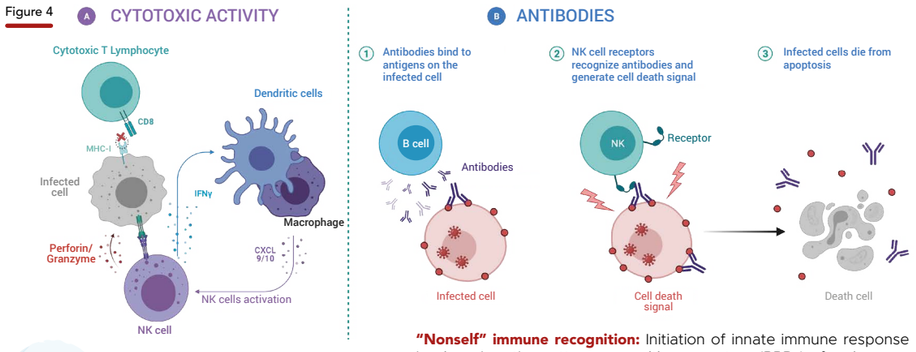
Monocytes/Macrophages: Macrophages derive from circulating monocytes and their differentiation is controlled by colony stimulating factor receptor 1 (CSF1R). Macrophages activated by classical pathway (M1) are characterized by production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin 1 beta (IL-1), in addition to ROS and NO production (**Figure 3**). Macrophages activated by alternative pathway (M2) are associated with immunosuppression, tissue repair, and elevated levels of arginase and anti-inflammatory cytokines such as IL-10 (**Figure 3**). The best characterized macrophage phenotype in teleost fish is found in M1 macrophages.

Figure 3



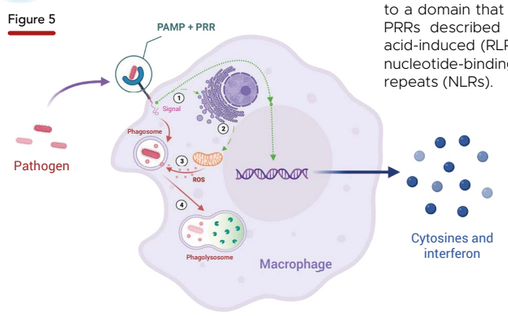
Natural Killer (NK): A third type of lymphocytes (plus B and T lymphocytes). Belonging to innate and adaptive branches of the immune system, main cytotoxic cells in fish are NK and cytotoxic T lymphocytes (CTL), respectively. NK cells can innately recognize infected cells and become activated to destroy them (**Figure 4A**), whereas CTLs require MHC class I-mediated induction. NKs also recognize and kill cells coated by antibodies or marked as infected to be attacked (**Figure 4B**). Active NKs secrete TNF-α interferon gamma (IFNγ), and/or granulocyte-monocyte colony-stimulating factor (GM-CSF), all important cytosines in the proliferation, differentiation, and activation of other immune cells.

Figure 4



"Nonself" immune recognition: Initiation of innate immune response begins when the pattern recognition receptors (PRRs) of an immune cell bind to PAMP of a pathogen (LPS, viral RNA, bacterial DNA, etc.) or damage-associated molecular pattern (DAMP) of proteins and other biomolecules that are released from stressed or injured cells (**Figure 5**). All PRRs have a domain to recognize PAMP that is coupled to a domain that interacts with signaling molecules. Among the main PRRs described in teleosts are Toll-like receptors (TLR), retinoic acid-induced (RLR) gene I-like receptors (RIG-I), C-type lectins (CLR), nucleotide-binding domains, and proteins that contain leucine-rich repeats (NLRs).

Figure 5



Phagocytosis: PRR pathogen binding triggers phagocytosis by phagocyte cells known as : macrophages, neutrophils, dendritic cells, and phagocytic B cells. After ingestion, phagosome, which contains the pathogen, binds to lysosome, forming a phagolysosome, where the pathogen is killed by various pathways, including ROS and NO production (**Figure 5**).

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