Humoral Innate Immune Response

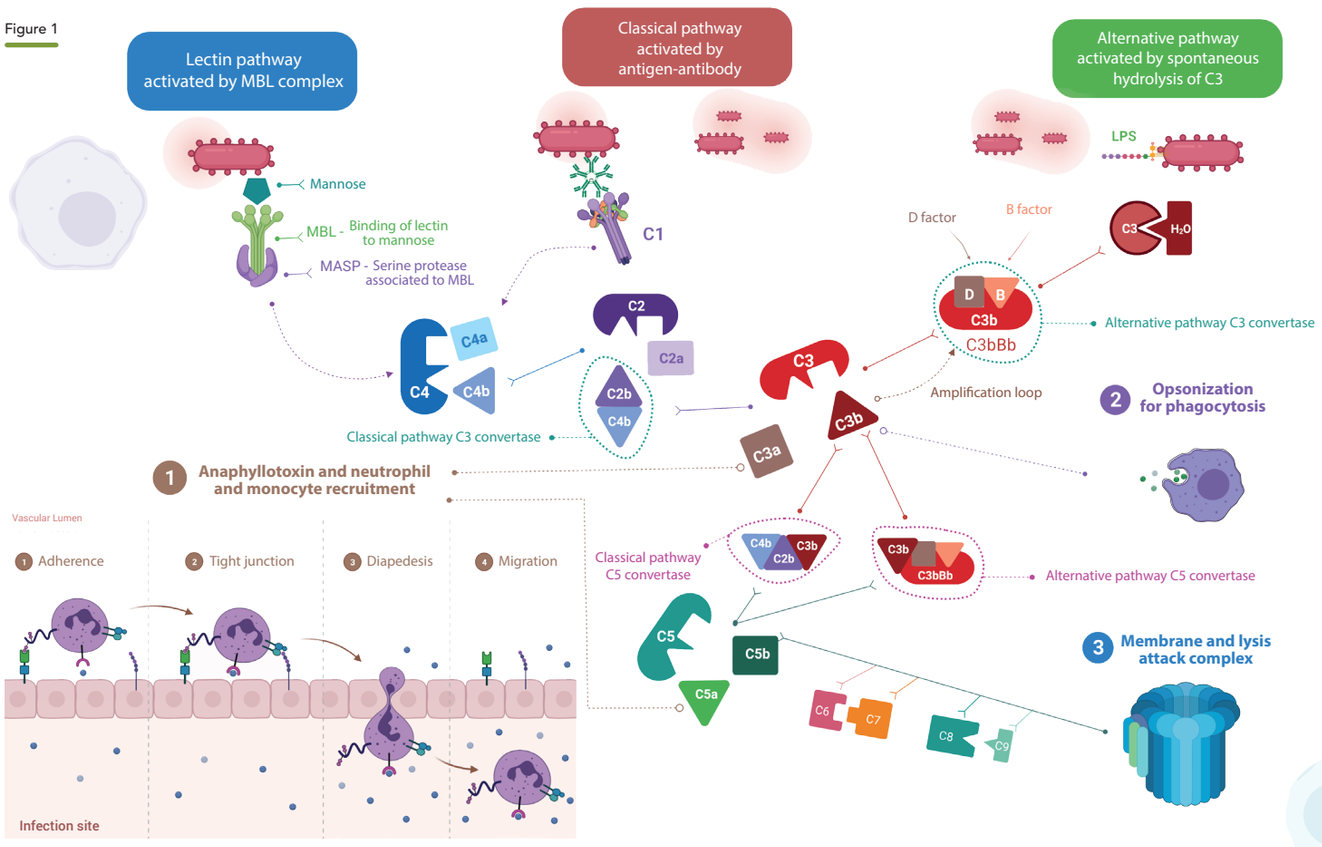
The innate immune system considers three defense mechanisms: (1) physical barriers, (2) cellular components, and (3) humoral responses. Humoral responses are mediated by macromolecules produced by cells and released into extracellular fluids after infection by a pathogen. Some of the most studied humoral components in fish include the complement system, antimicrobial peptides, and acute phase proteins, including lysozyme. These components have many different functions, including promoting inflammation, phagocytosis, and direct bactericidal effects.

Complement system

The complement system is a cascade of serum proteins that act cooperatively to mediate defense mechanisms, including the elimination of pathogens by opsonization and phagocytosis, and the promotion of the inflammatory response.

The teleost complement system basically corresponds to its mammalian counterpart: (1) classical pathway, activated by antigen-antibody complexes and, therefore, a bridge between innate and adaptive immunity; (2) alternative pathway, it is independent of antibodies and is directly activated by pathogens; (3) lectin pathway, activated by the binding of lectin to mannose (MBL) or ficolin to mannose residues (or other sugars) present on the surface of the pathogen. These pathways ultimately induce the activation of C3 convertase, which cleaves inactive C3 into C3a, an anaphylatoxin that acts as a chemotactic factor and aids in inflammation, and C3b, which acts as an opsonin, as well as a complement protein activator (C5 convertase) that lead to the formation of the membrane attack complex (MAC) (**Figure 1**).

Figure 1



Antimicrobial peptides (AMPs)

AMPs are oligopeptides with a variable number of amino acids that are generally positively charged and play an important role in the innate immune system of fish. AMPs protect against a variety of pathogens through direct disruptive or pore-forming actions on bacterial membranes, pro-inflammatory effects, and anti-inflammatory effects (**Figure 2**).

More than 90 fish AMPs have been identified and are characterized as ß-defensins, cathelicidins, hepcidins, histone-derived peptides, and piscidins. These AMPs show antiviral and antibacterial activities against a variety of pathogens, demonstrating that teleost AMPs exhibit many, if not all, of the characteristics of other vertebrate AMPs. Thus, cathelicidin has been shown to have antimicrobial activity against Vibrio anguillarum in rainbow trout and Atlantic salmon.

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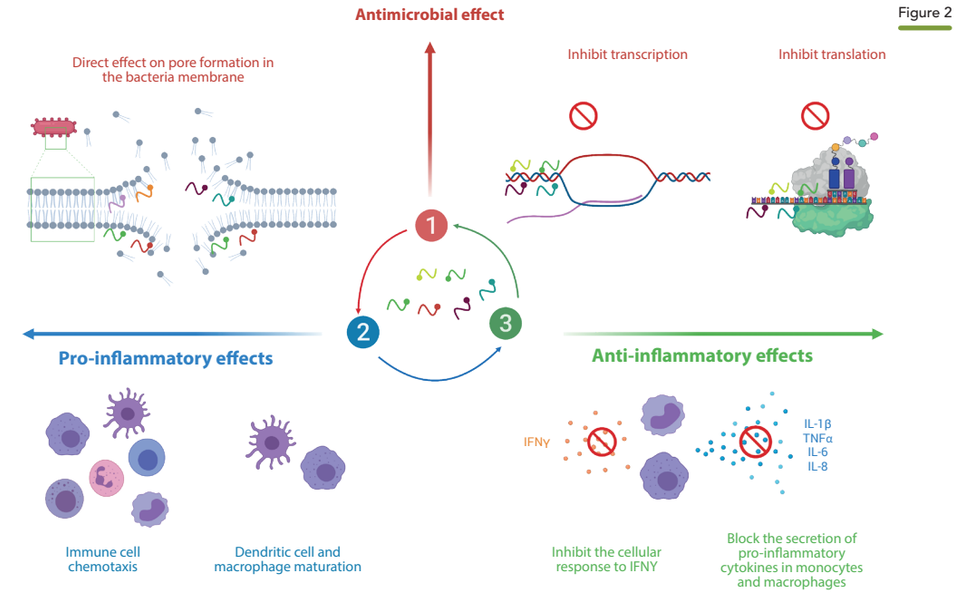
Figure 2



Acute phase proteins (APP)

Tissue injury, infection, and inflammation induce immune cells, such as macrophages, to secrete various cytokines into the bloodstream, which stimulate hepatocytes to produce and release acute phase proteins (APPs). They are involved in a variety of defense activities and include clotting factors, transport proteins, complement components, C-reactive protein (CRP), and serum amyloid proteins (SAP).

CRP and SAP are the most important and studied in fish and their serum concentrations increase up to 1000 times in response to various stimuli that induce inflammation. In addition, CRP and SAP have been shown to activate complement pathways and play a role in the elimination of apoptotic cells. The expression of CRP and SAP in Atlantic salmon head kidney leukocytes is upregulated in response to IL-1β and IFNγ.

Lysozyme is a lytic enzyme that acts on the peptidoglycan layer of cell walls resulting in bacterial lysis. It also participates in other defensive strategies such as opsonization, phagocytosis, and complement activation (**Figure 3**).

Figure 3