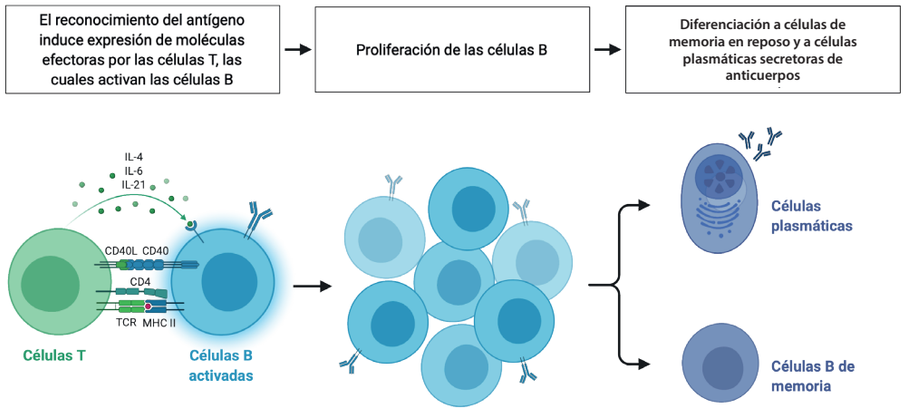
Humoral Adaptive Immune Response

Fish have an adaptive immune system based on B and T cells, antibodies (Abs) or immunoglobulins (Igs), B (BCR) and T (TCR) cell receptors, and major histocompatibility complex (MHC). Like the innate immune system, the adaptive immune system includes both humoral and cellular components.

B cell-based immunity

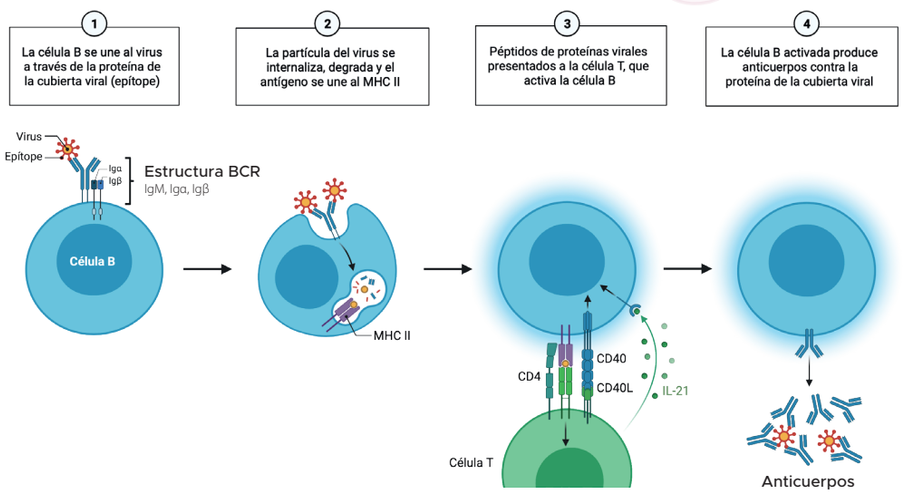
B cells are key elements of the humoral adaptive immune response. Bony fish lack bone marrow, the main site of hematopoiesis in mammals, and germinal centers, specialized sites where mature B cells proliferate, differentiate, and are selected for high-affinity BCRs. In fish it is proposed that mature B cells are released from the head kidney into the blood, where they encounter with antigen and mature into plasma cells. Plasma cells migrate back to the head kidney and become long-lived plasma cells, while B cells become resting memory cells (**Figure 1**).

Figura 1



The main function of B cells is to produce high affinity Igs and act as an antigen presenting cell (APC) to activate T cells. Abs occur in a soluble form (sAbs) that is secreted, and a membrane bound form (mAbs) that, in combination with Ig-α/Ig-β signaling molecules (CD79a/b), make up the BCR (**Figure 2**). IgM, IgD and IgT have also been identified in teleost fish.

Figura 2



1. IgM: it is the oldest and most prevalent Ab in teleost plasma and can be found in both secreted and transmembrane forms. It shares a similar function in all vertebrates: mediation of opsonization, activation-dependent cell-mediated cytotoxicity, and complement activation, contributing to the innate and adaptive immune response. Teleost fish have tetrameric and monomeric IgM, and two subisotypes have been identified in Atlantic salmon.

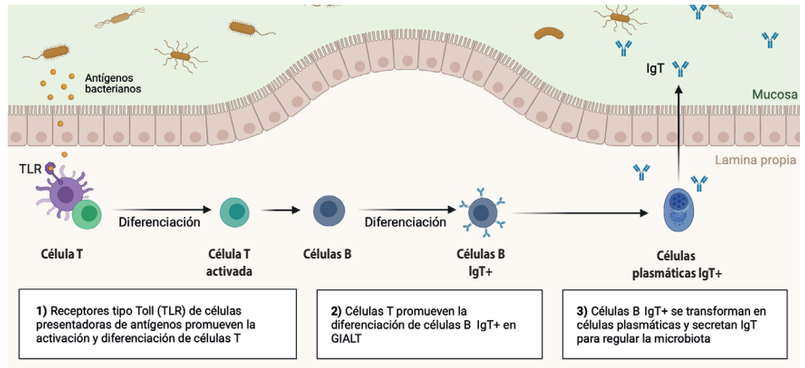
2. IgD: its function is not yet well understood. This Ig has only been found in transmembrane form, with the exception of channel catfish and Japanese globe, which contain both forms. In rainbow trout, the ratio of IgD to IgM in the gills is much higher than in other tissues and a subset of IgM-/IgD+ B cells expressed mainly in the gills has also been found, indicating a relevant IgD in the mucosal immunity.

3. IgT: evidence indicates that this Ig is specialized for mucosal immunity, since the IgT concentration in rainbow trout serum is lower than that of IgM and the IgT:IgM ratio is 63 times higher in the intestine than in serum. IgT is expressed by a unique subset of IgT+ B cells that does not express IgD or IgM. The number of IgT+ B cells increases in the intestine after infection, but the number of IgM+ B cells does not change. IgT+ B cells are also found in teleost skin-associated lymphoid tissue where they secrete IgT into mucus. SIgT is the predominant Ig isotype that covers a large part of the microbiota of fish, so sIgT is necessary for the control of mucosal pathogens and for the preservation of microbiota homeostasis (**Figure 3**).

Immunological memory and affinity maturation

Bony fish develop immunological memory, that is, the ability to implement a faster and larger response to a pathogen (secondary response) than previously encountered (primary response). The response time of teleost IgM is slower than in mammals, taking 3 to 4 weeks after immunization before specific titers are detected.

Figura 3

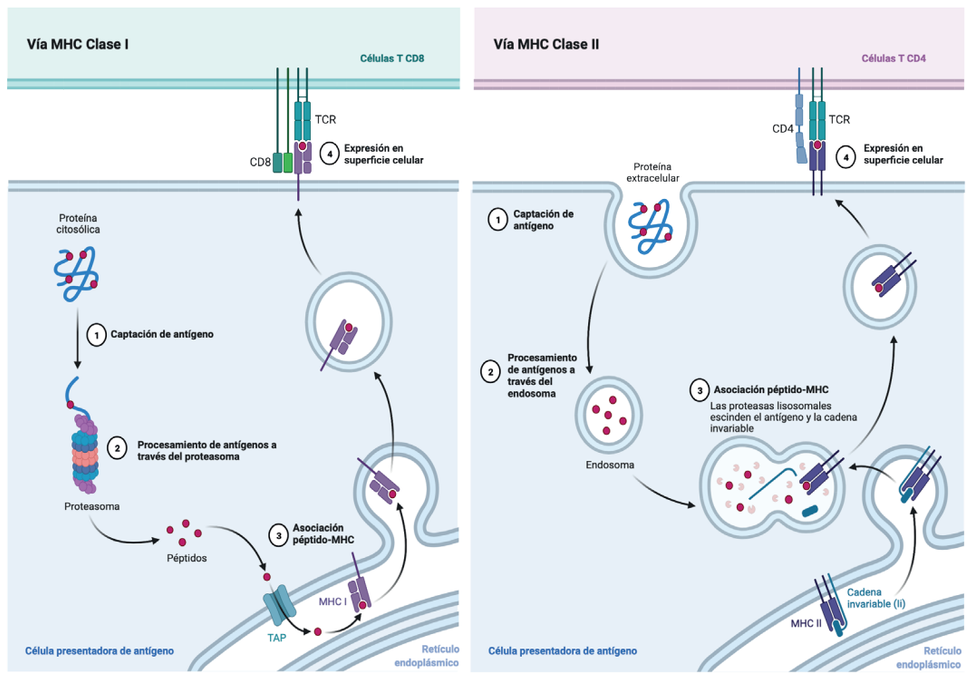


Affinity maturation is a process by which B cells produce antibodies with increasing affinity during the course of an immune response. With repeated exposures to the same antigen, the host produces successively higher affinity antibodies. However, this response in fish is less efficient than in mammals, probably due to the absence of germinal centers. Affinity maturation would imply a biological process mediated by activation-induced cytidine deaminase (AID), a process that refines Ig, increasing its affinity. The spleen is considered the only secondary lymphoid organ in teleosts where AID expression has been observed, suggesting that the spleen is the site for antigen stimulation.

Major histocompatibility complex (MHC) and antigen presentation

A primary function of B cells is to process and present antigen to activate T cells. However, T cells will only recognize antigen fragments that are bound to MHC I or MHC II on APCs. The antigens presented by MHC I are processed through the proteasome and transferred to the endoplasmic reticulum by a transporter associated with antigen processing (TAP), where they associate with MHC I and are eventually transported to the cell membrane. The antigens presented by MHC II are incorporated into cells by endocytosis, digested in lysosomes, and loaded on to MHC II molecules prior to their migration to the cell surface (**Figure 4**).

Figura 4



Autor:
Dr. Marco Rozas Serri

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