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Review

Functional aspects of fish lymphocytes

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ABSTRACT

After almost 40 years of studies in comparative immunology, some light has been shed on the evolutive immunobiology of vertebrates, and experimental evidences have shown that acquired immunity, defined by somatic recombination of antigen-binding molecules and memory, is an achievement as ancient as jawless vertebrates. However, the molecular processes generating antigen receptors evolved independently between jawless and jawed fishes, and produced lymphocytic cells with similar functions but employing different sets of genes. In recent years, data have been provided describing some *in vitro* and *in vivo* functional responses of fish lymphocytes. After a long gap, the number of specific markers for fish lymphocytes is increasing, thus allowing a first characterisation of lymphocyte subsets. Overall, in the near future it will be possible to open a new chapter in fish immunology and investigate functional immunity of lymphocyte responses by combining the extensive knowledge on immune gene products with markers for molecules and cells. The present review summarizes current knowledge on functional features of fish lymphocytes.

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1. Introduction

Immunocytes are present in all *Bilateria* species investigated and have probably originated by convergent, or polyphyletic, evolution in order to ensure best protection in every environment. In this respect, ancient and efficient antigen-clearing mechanisms (e.g. phagocytosis, proteases cascades, perforin-type killing, TLRs, antibiotic peptides) have been maintained by natural selection thoughout animal phyla and have acquired peculiar specialization in animal lineages.

The immunocytes of vertebrates have maintained these mechanisms, with the additional specialization of novel immunocytes, known as lymphocytes, having the capability of performing

Abbreviations: CMC, cell-mediated cytotoxicity; CDR, complementarity-determining region; ConA, concanavalin A; CTL, cytotoxic T lymphocytes; HEL, hen egg lysozyme; Ig, immunoglobulin; ISH, *in situ* hybridization; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibition motif; LPS, lipopolysaccharide; mAb, monoclonal antibody; MHC, major histocompatibility complex; MIF, macrophage-inhibitory factor; MLR, mixed leucocyte reaction; NCC, natural cytotoxic cells; NKT, natural killer T cells; PBL, peripheral blood leukocytes; PHA, phytohemoagglutinin (generally from beans); Poly I:C, polyinosine–cytidine; RAG, recombination-activating gene; TLR, toll-like receptor; TR, T cell receptor; 5-HT3, 5-hydroxytriptamine.

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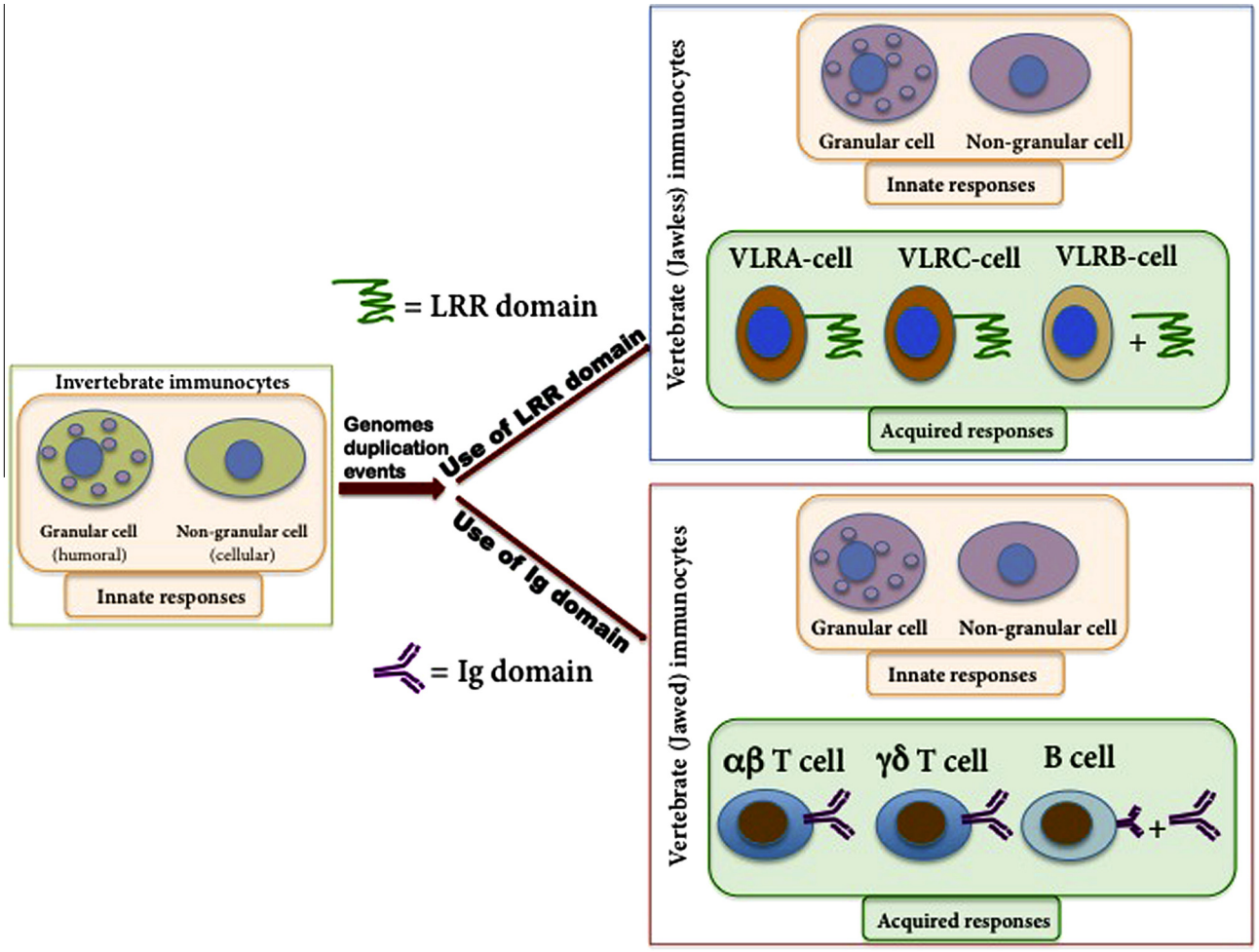

Fig. 1. A concept is represented illustrating the origin of vertebrate immunocytes from invertebrates. Invertebrate immunocytes perform innate activities and can be grouped in granular and smooth cells. By genome duplication events additional classes of immunocytes emerged employing for antigen recognition LRR-derived molecules in jawless fish (cell-bound LRR for T-like lymphocytes with VLRA analogous to αβ-T cells, VLRC analogous to γδ-T cells, and VLRB analogous to B cells), or Ig-derived molecules in jawed fish with classical Ig-based receptors for antigen recognition.

somatic recombination and exposing on their surface the recombined gene products, or antigen-binding receptor molecules. The origin of lymphocytes are obviously linked to the origin of vertebrates, but the evolutionary steps that produced lymphocytes from invertebrate immunocytes are still matter of debate (Litman et al., 2010). Each lymphocytic cell carries one type of Ig domain-containing receptor and thus originates a clone of cells upon induction. The Ig domain is as old as unicellular Metazoans (Gauthier et al., 2010), and has been rearranged during evolution as a recognition mechanism in multicellular species. In Fig. 1 a schematic view of possible evolutionary steps that originated lymphocytes is represented.

Lymphocytes can be functionally grouped in two classes, cells that permanently retain the antigen receptor in the membrane and thus must act through a direct cell-to-cell contact, and cells that secrete soluble antigen receptors and ship these receptors to the whole animal body. These two classes are called T cells and B cells, respectively, and for the fundamental roles they play in health-related arguments, main features of their immunobiology in mammals can be easily found in immunology textbooks.

To our knowledge, oldest living representatives of vertebrates are the hagfishes, originated ca. 550 My ago (around 70 extant species), cartilaginous fish (ca. 300 My, around 1000 species), and bony fish (ca. 230 My, around 28,000 species). Together, fishes represent around 43% of extant vertebrates (for a review on the origin and diversification of fishes see Santini et al., 2009). Therefore, the importance of investigating immune defences in fish in an evolutionary context it is evident. This is particularly true for bony fish (teleosts) because of the high similarity of their body plan with that of following vertebrates, including mammals. Indeed, teleost fish represent a widely employed animal model for studies of mammalian physiology and for biotechnology applications.

Interestingly, the presence of an anticipatory immune responses and thus of an acquired immune system is known for vertebrates only, raising the hypothesis that this feature can be associated with genetic events that have driven fish origin and diversification, like genome duplications (Kasahara et al., 1997) and novel usage of ancient genes (Litman et al., 2010).

Lymphoid organs and lymphocytes show three distinct functional roles: to provide suitable microenvironments for the development of immune effector cells, mediate quality control (positive and negative selection), and regulate the efficacy of the immune response (memory and suppression).

In the last decade an impressive amount of data has been obtained in fish on the cloning of genes coding for immunoregulatory peptides, showing that the great majority of genes known in mammals are present in fish. However, despite this molecular knowledge, functional aspects of lymphocye functions in fish have been investigated only partially, and this review summarizes the current knowledge and the important advancements achieved in recent years.