Heritage

Evolution of Innate Immune System from Invertebrates to Vertebrates

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Abstract:
A very highly specialized immune system is present almost in all vertebrates which is multitasking and specialized from the point of view of the type of antigen and mode of action against the antigen. The system shows a cascade of interactions to eliminate almost all the antigens that enters the host body. While there is a high degree of interconnectivity between its components, the sum of the immune system can be divided into two subsystems, the innate immune system and the adaptive immune systems. The innate immunity is non-specific, short lived, immediate and inducible response to pathogens.

In this review, the origin of innate immune system has been discussed keeping in mind that the innate immune system is the more ancient of the two systems, with roots deep in the deuterostome branch of the bilaterians, roughly one billion years ago. Conversely, the adaptive immune system appeared more recently and quite suddenly, around 450 million years ago with the emergence of the gnathostomes, more commonly called the jawed vertebrates. Because of its high degree of complexity and interconnectivity, the mammalian immune system has been labelled as "irreducibly complex".

Keywords: Cytolysis, anti-microbial peptides, cytokines, complement system, evolution

Introduction: Preface to the understanding of evolution of immunity

To understand the evolutionary twists and turns taken by immune systems over hundreds of millions of years, it is necessary to understand how they work. There are some basic requirements of any immune system.

Firstly, it should be able to distinguish the cells, tissues and organs that are a legitimate part of the host body from foreign things, called "nonself," that might be present.

Secondly, immune system should have the activity to eliminate those nonself invaders, which are often dangerous bacteria or viruses or pathogenic protozoans.

In addition, the immune system can recognize, and usually eliminate, "altered self"—cells or tissues that have been changed by injury or disease such as cancer.

It is evident that the immune systems of mammals and other higher vertebrates have the most sophisticated mechanisms both for recognizing and for eliminating non-self invaders.

Immune system contains certain components and cells co-ordinating each other by either a complex cascade pathway or a interactive pathways resulting in the elimination of the foreign or altered self components (1,2).

Evolution of innate immune system

Innate immunity is seen throughout the animal kingdom -— from bacteria to humans. To eliminate non-self invaders, the immune system of both invertebrates & vertebrates has some strategies —

Phagocytic or cytolytic cells

Phagocytosis is a common and simple mechanism seen in many animals. This phenomen on involves the engulfment or eating of a foreign pathogen and breaking down the pathogen and its pathogenicity. But surprisingly, this phenomenon is one of the very ancient method of multicellular host defence. Host defense systems began with the protozoans- the simplest of all living organisms. Protozoans, which evolved about 2.5 billion years ago, are single-cell life-forms accomplishing every physiological function in a single cell. In protozoans, basic physiological activities like respiration, digestion, defense and other functions are performed at least in part, by phagocytosis. In its defensive function, protozoan phagocytosis is similar to that of the mammals or humans. In triploblastic multicellular animals, phagocytic cells travel through a circulatory system or coelom. In multicellular animals such as sea sponges lacking a body cavity and circulatory system (such as sea sponges), the wandering phagocytic cells patrol the tissues and surrounding spaces.

The beauty of the discovery of such a cellular system is also not less. In December 1882, a Russian zoologist, Élie Metchnikoff, while examining a starfish pierced by rose throne, saw that the injured place is covered by some special cells around the throne and the cells are attempting to engulf it (3).

This observation was later recognized and established as the phenomenon of phagocytosis- a process in which the cells attempt to defend the larva by ingesting the invader. Phagocytosis was already known to occur in human cells and other vertebrates, but Metchnikoff's observation extended the dimension of the phenomenon. It was being considered as a fundamental mechanism by which creatures throughout the animal kingdom defend themselves against infection. In this domain of research, Metchnikoff created the discipline of cellular immunology and later, he shared the 1908 Nobel Prize in medicine with Paul Ehrlich. The starfish was an animal that remained virtually unchanged since its appearance at least 600 million years ago, thousands of years before the first vertebrate evolved (3,4, 5).

Antimicrobial peptides

Nature seems to be an unlimited source of peptides with antimicrobial activity by antimicrobial peptides (AMP), and AMPs have been discovered in genomes of both prokaryotes and eukaryotes.Peptides with antimicrobial activity has been isolated from sources as diverse as humans, frogs, flies, nematodes & several plant species. The early evolution & retention of this strategy coupled with the identification of more than 800 types of such different peptides testifies to their effectiveness. AMPs range from 6 to 59 amino acid long peptide sequences, mostly cationic in nanture, kill a wide variety of bacterial invaders like *Staphylococcus, Eschericia, Hemophilus* etc. Neutrophils, paneth cells, epithelial cells of pancreas & kidney secrete AMP like defensin, which can kill bacteria within a very short period of time (6,7).

However, as plants also biosynthesize protective secondary metabolites, AMPs may not be as crucial for the first line of defense as in animals.

Presence of similar type of AMPs from plants to mammals clearly tells about its origin from ancient life forms that are surely invertebrate. It is remained and selected by the nature for its efficiency in non-specific host defence mechanism. AMPs are undoubtedly attractive sources for the development of new antibiotics. These peptides are diverse in sequence and in structure but show a functional similarity in killing antigens (8).

Complement system

Complement system is another feature of the vertebrate immune system. Complements are missing from invertebrates. However, evidences state that there is an invertebrate analogue present for this system. In place of complement, several invertebrates exhibit a similar system known as the prophenoloxidase (proPO) system. Complement system is a cascade based pathway in vertebrate host body. Like this system, proPO system is also controlled and activated by a series of enzymes. A cascade of reactions ends with the conversion of proPO to the fully active enzyme phenoloxidase, which plays a role in encapsulation of foreign components in the host body. Kenneth Söderhäll of the University of Uppsala in Sweden and Valerie J. Smith of Gatty Marine Laboratory in Scotland have shown that the system serves other purposes as well, including blood coagulation and the killing of microbes.

α_2 macroglobulin (α_2M) is a protease inhibitor and serves as a target for bacterial proteases. C_3 is not a serine protease but a key molecule in the complement system. It is questioned how such a non-familiar molecule became associated with serine proteases. C3's strong sequence similarity to α_2M, which is not part of the complement system and presumably more ancient, clearly suggests a possible origin. Proposed model for the origin of the complement system suggests the evolution of an α_2M-like gene into a C_3-like gene of complement system. It can interact with as many as 25 other proteins, and is the point of junction for all three activation pathways. The fact that α_2M is a protease inhibitor and serves as a target for bacterial proteases also suggests how this may have come about (9).

It should also be mentioned that this model contains many loopholes that need to be filled by experiments or other evidence. However, the model also makes predictions, some of which can lead to future research, may disprove this model, and allow us to generate a new model that will fit the new evidence. This new model will make further, more specific predictions, and the cycle will continue until all remaining holes have been filled. We're at the beginning of the genomic era, and the comparison of sequences will allow us to test and refine this model in ways that would have previously been impossible (10,11).

Precursor of Immune Regulation by cytokines

Evolution seems to have conserved not only many aspects of host defence mechanisms found in invertebrates but also many of the control signals for these mechanisms. Cytokines are the key component which acts as a communicator in the vertebrate immune system. However, isolation of cytokine-similar molecules in invertebrates has been done. Cytokines include the interferon (IFN) family, the interleukin (IL) family (such as IL-1 and IL-6) and tumor necrosis factor (TNF) family. These molecules are important regulators of vertebrate immunological aspects (12).

The interpretation of invertebrate cytokine like communicator molecules were evidenced from starfishes. The presence of such molecules in primitive organisms was presumed for many reasons. Firstly, these molecules regulate some of the primitive vertebrate immune-defence mechanisms; secondly, the structure and defensive functions of IL-1 like cytokines are similar in many different vertebrates suggesting common origin. Finally, macrophage like white blood cells are ubiquitous throughout the animal kingdom which produce IL-1. Later, IL-1 like molecule was isolated from the coelomic fluid of the common Atlantic starfish *Asterias forbesi,* the molecule behaved like IL-1 in its physical, chemical, biological as well as immunological properties. Subsequently, many invertebrates were found to possess molecules similar to vertebrate cytokines. Worms and tunicates (sea squirts) carry substances similar to IL-1 and TNF. Beck 1996 found molecules resembling IL-1 and IL- 6 in the tobacco hornworm. Thus, invertebrates possess analogues of some major vertebrate cytokines. The invertebrate cytokines perform functions similar to those in vertebrates. In the experiments of Edwin L. Cooper and David A. Raftos, it was showed that IL-1 stimulated macrophage-like cells to destroy invaders by engulfing antigens and pathogens. Invertebrate cytokines therefore appear to co-ordinate the host defensive response like the vertebrates (12,13).

Evidences show that immune system has originated from a very primitive common ancestral phenomenon that was meant to provide the basic defence mechanism to the host. However, the sophistication came in the later part where much genetics were engaged to bring out the beauty of antibody diversity, T-cell receptor, B-cell receptor complexes and other phenomena. But the study of the root of immunity gives us a clear picture about the structural complexity of invertebrates and vertebrates as well. Complexity and sophistication of immune system of an organism directly correlates the complexity of origin and recent chance of origin in the evolutionary time scale.

CONCLUSION:

The complex immune system of vertebrates is to be studied in detail for a better picture of origin of gene regulated sophisticated immunity (14). However, the function of generalized immune system of invertebrates and sophisticated vertebrate immunity can be compared by considering general light camera and tech-developed digital SLR cameras. In both the cases, photos are captured, but in SLR cameras (which represent the vertebrate immune defence), different mechanisms are present to capture super special photographs for different light exposure and environments.

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