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A mini review on immune role of chemokines and its receptors in snakehead murrel *Channa striatus*

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ABSTRACT

Chemokines are ubiquitous cytokine molecules involved in migration of cells during inflammation and normal physiological processes. Though the study on chemokines in mammalian species like humans have been extensively studied, characterization of chemokines in teleost fishes is still in the early stage. The present review provides an overview of chemokines and its receptors in a teleost fish, *Channa striatus*. *C. striatus* is an air breathing freshwater carnivore, which has enormous economic importance. This species is affected by an oomycete fungus, *Aphanomyces invadans* and a Gram negative bacteria *Aeromonas hydrophila* is known to cause secondary infection. These pathogens impose immune changes in the host organism, which in turn mounts several immune responses. Of these, the role of cytokines in the immune response is immense, due to their involvement in several activities of inflammation such as cell trafficking to the site of inflammation and antigen presentation. Given that importance, chemokines in fishes do have significant role in the immunological and other physiological functions of the organism, hence there is a need to understand the characteristics, activities and performace of these small molecules in details.

1. Introduction

Chemokines are small cytokine proteins that are involved in various immunological and physiological functions and its name is derived from its characteristic as a chemoattractant in nature: CHEMOattractant cytoKINES [1]. During homeostasis and inflammation these chemokines were found to be involved in cell migration and localization and are known as chemotactic cytokines. A wide range of homeostatic chemokines were found to be expressed in specific tissues and cells, whereas the inflammatory stimuli exclusively triggers the expression of inflammatory chemokines and their functions also found to be limited in comparison with the homeostatic chemokines.

Both the chemokines are secreted through the pathogen recognition receptor signaling after the microbial infection. Moreover, chemokines play an important role in diverse immune functions including, being involved in immune system development to effector responses and regulation. They are particularly important for acting as a bridge between the innate and adaptive immune system [2]. Investigations on the immune functions of chemokines provided the understanding of their functions in activation of T lymphocytes and macrophages. Specifically, in the T lymphocytes activation the intermediate complex is generated through the polarization of T lymphocytes to chemokines. Further, the differentiation of T lymphocytes was also identified to be influenced by the chemokines [3].

Apart from playing a key role in immune responses, chemokines are involved in normal physiological processes like angiogenesis [4], neurological development, neuroinflammatory diseases [5,6], germ cell migration and organogenesis [7]. The mode of action chemokines in immune system is given in Fig. 1.

The aquaculture industry has been facing problems due to pathogenic infection caused by various bacteria, fungi and viruses. Several techniques currently employed as treatment strategy are inadequate and acute misuse of the chemicals has resulted in the development of resistant pathogens. In order to improve the disease management

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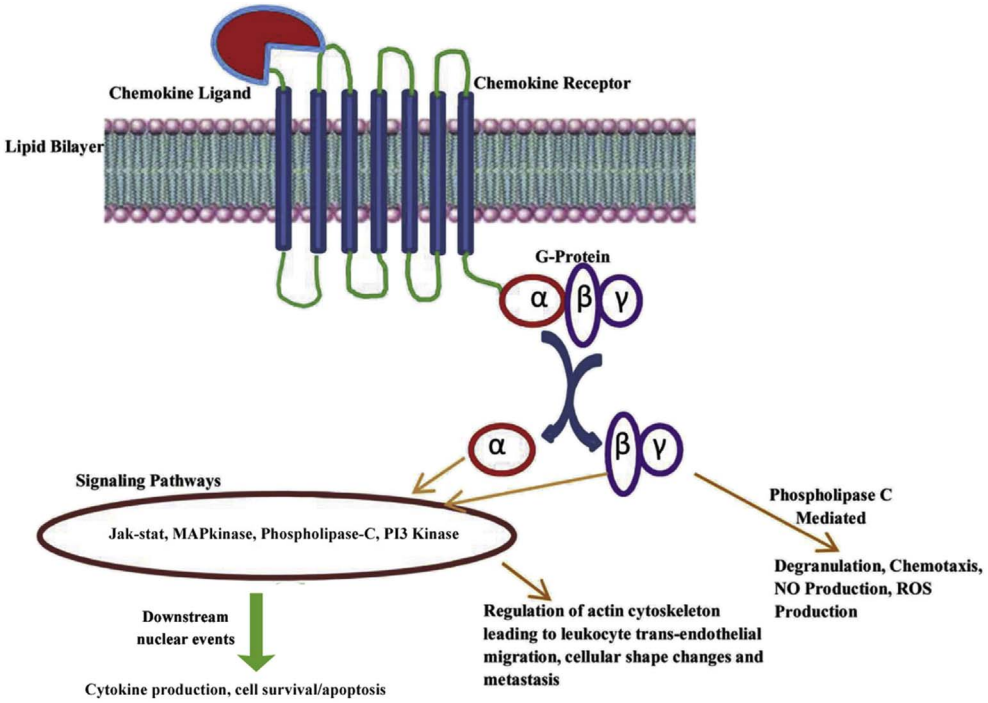

Fig. 1. Mechanism of chemokines action in a physiological system. The binding of chemokine ligand to the receptor results in the dissociation of G-protein into Gα and Gβγ. These components act on the signaling pathways leading various modulations of gene expression in nucleus.

tactics, novel avenues were explored in early part of this century with the focus on molecular characterization of immune genes involved during infection. A study based on genomics or proteomics of immune molecules provide information on the pattern of differentially regulated proteins or genes that are involved in the immune process [8]. Henceforth, understanding the innate immune system consisting of molecules such as cytokines, enzymes, antioxidants, caspases and chaperones received a greater interest. Of these molecules, the cytokines play a major role in immune regulation of fishes, thus studying its functions would provide a greater understanding of its role in immune mechanisms [9]. Perhaps, chemokines being the bridging entities of innate and adaptive immunities in fishes, a genomic analysis on these molecules could lead to the development of efficient strategies in their disease management.

2. Classification of chemokines

Chemokines are broadly classified on the basis of structure and function. Structurally, chemokines are divided into five classes based on the arrangement of cysteine residues in the N-terminal region, namely CXC, CC, CX3C, XC and CX [10]. Of these five classes, the subfamilies CXC and CC are known to have large number of members in human. Similarly, in fish high number of CC chemokines with seven diverse class were reported. Recently, one hundred and eleven chemokine genes were found and nearly sixty three CC and CXC genes were identified in the zebrafish. The CX family is reported to be unique to zebrafish, from the evolutionary and genomic analysis suggested that these family is the result of continuous tandem gene duplication events [11]. Functionally, chemokines are classified into two classes, namely proinflammatory and homeostatic chemokines [12,13].

3. Evolutionary features of chemokines

In general, chemokine super family exists as gene clusters on the chromosomes, which was attributed to the increase in gene numbers due to duplication events [14,15]. Large gene clusters have been identified in humans, but clustering of chemokines has not been observed in birds and teleosts [7,14,16]. The occurrence of whole genome duplication (WGD) events in teleosts is one of the major reasons for the existence of a large number of chemokines [11,17]. Besides, there is a lacuna in identifying the orthologs between teleost and mammalian chemokines. As a typical example of this anamoly, a recombinant CC chemokine molecule GmSCYA123 of teleost was found to be inducible in nature, but it was identified to be clustered with a human homeostatic chemokine CXCL19 [18]. Thus, a detailed and comprehensive compilation of all the teleost chemokines based on their structural and functional features are necessary for development of therapeutics from these molecules.

4. Important structural features in biological activity of chemokine

4.1. Cysteine residues

Various structural features have been identified in chemokines, which render the molecules to have proper structural orientation and functional activity. The primary structural significance can be attributed to the presence of cysteine residues at the N- terminal region. In spite of being a motif for classification of chemokines, these cysteine residues are also involved in the disulphide bonds with the third and fourth cysteine residues of the molecule. These cysteine residues when substituted with serine residues showed a marked decrease in the activity of the chemokine molecule, *Cs*CCK1 of *Cynoglossus semilaevis* [19]. Also, the presence of ELR motif at the N-terminal is an important factor for the classification of CXC chemokines but this motif is usually replaced by DLR in fish. Still the chemoattractant functions of these chemokines were preserved even in lack of DLR motif [20]. Thus, it can be reiterated that the four conserved cysteine residues are involved primarily in maintaining the structural propensity of the chemokine molecules and thereby complementing in retaining the functional property of the chemokine.

4.2. 3^{10} helix

Structural analysis of most chemokines has revealed the presence of a 3^{10} helix in the region between the N-loop and the first β-pleated sheet of the chemokine molecule. The 3^{10} helix, a conserved motif among most of the chemokine molecules, in the presence of a dipeptide

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