International Scholars Journals

African Journal of Immunology Research ISSN 2756-3375 Vol. 9 (3), pp. 001-002, September, 2022. Available online at www.internationalscholarsjournals.com © International Scholars Journals

Commentary

Functional and structural characteristics of chemokines

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Received: 01-Sep-2022, Manuscript No. AJIROA -22-74385; Editor assigned: 05-Sep-2022, PreQC No. AJIROA -22-74385 (PQ); Reviewed: 19-Sep-2022, QC No. AJIROA-22-74385; Revised: 26-Sep-2022, Manuscript No. AJIROA-22-74385 (R); Published: 03-Oct-2022

DESCRIPTION

Chemokines or chemotactic cytokines are a family of small cytokines or signaling proteins secreted by cells that induce the directional movement of leukocytes as well as other cell types, including endothelial and epithelial cells. In addition to playing an important role in the activation of host immune responses, chemokines are important for biological processes including morphogenesis and wound healing, and in the pathogenesis of diseases such as cancer.

Cytokine proteins are classified as chemokines according to behavior and structural characteristics. In addition to being known as mediators of chemotaxis, chemokines all have a mass of approximately 8-10 kilodaltons and have four cysteine residues at conserved sites that are key to their three-dimensional shape.

These proteins have historically been known by several other names, including the SIS cytokine family, SIG cytokine family, SCY cytokine family, platelet factor-4 superfamily, or intercrine. Some chemokines are considered proinflammatory and can be induced during the immune response to recruit cells of the immune system to the site of infection, while others are considered homeostatic and involved in the control of cell migration during normal processes of tissue maintenance or development. Chemokines are found in all vertebrates, some viruses and some bacteria, but were absent from other invertebrates.

Chemokines have been classified into four main subfamilies: CXC, CC, CX3C, and C. All of these proteins exert their biological effects by interacting with transmembrane G protein-coupled receptors, called chemokine receptors, that are selectively located on the surface of target cells.

Function

The main role of chemokines is to act as chemoattractants to direct cell migration. Chemokine-attracted cells follow the signal of increased chemokine concentration to the chemokine source. Some chemokines control cells of the immune system during immune control processes, such as directing lymphocytes to lymph nodes so that they can detect invading pathogens by interacting with antigen-presenting cells present in these tissues. They are known as homeostatic chemokines and are produced and secreted without the need to stimulate their parent cells. Some chemokines are involved in development; they promote angiogenesis (the growth of new blood vessels) or direct cells to tissues that provide specific signals important for cell maturation. Other chemokines cause inflammation and are released from a wide variety of cells in response to bacterial infection, viruses, and agents that cause physical damage, such as silica or the urate crystals that occur in gout. Their release is often stimulated by proinflammatory cytokines such as interleukin 1. Inflammatory chemokines act primarily as chemoattractants for leukocytes, attracting monocytes, neutrophils, and other effector cells from the blood to sites of infection or tissue damage. Some inflammatory chemokines activate cells to initiate an immune response or promote wound healing. They are secreted by different cell types and serve to target cells of both the innate immune system and the adaptive immune system.

STRUCTURAL CHARACTERISTICS

Proteins are classified into the chemokine family based on their structural characteristics, not just their ability to attract cells. All chemokines are small, with a molecular weight of 8 to 10 kDa. They are about 20%-50% identical to each other; that is, they share gene sequence and homologous amino acid sequences. They also all have conserved amino acids that are important for creating their three-dimensional or tertiary structure, such as (in most cases) four cysteines that interact with each other in pairs, creating the Greek key shape characteristic of chemokines. Intramolecular disulfide bonds typically connect cysteine residues one through three and two through four, numbered as they appear in the chemokine protein sequence. Typical chemokine proteins are produced as propeptides, starting with a signal peptide of about 20 amino acids that is cleaved from the active (mature) part of the molecule during its secretion from the cell. The first two cysteines in the chemokine are located near the N-terminal end of the mature protein, the third

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cysteine is in the center of the molecule, and the fourth is close to the C-terminal end. A loop of approximately ten amino acids follows the first two cysteines and is known as the N-loop. This is followed by a single-stranded helix called the 310-helix, three β-strands, and a C-terminal α-helix. These spirals and threads are connected in turn, called loops 30, 40 and 50; the third and fourth cysteines are located in the 30-loops and 50-loops.