

Chemokines: Brief review and its Role in Cancer Cell Biology



Medical Science

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ABSTRACT

The immensely complex immune system has various components in it to defend the human body against invaders. One among the components is a group of proteins called Chemokines. Chemokines are a super family of small, secreted proteins that play a critical role in many normal & pathological states. The role of these chemokines needs to be studied to help in treating various ailments some of which may be fatal. When the physiological role of chemokines is subverted or chronically amplified, disease often follows.

Introduction

In order to deal with the vast array of microorganisms which cause frequent diseases, the body has a very intricate defence system known as the immune system. Among the various vital component of the host defence system is a family of proteins known as the chemokines. Chemokines are secreted proteins that chemoattract and activate immune and non-immune cells both in vivo and in vitro. They have a variety of functions. These proteins are small molecules that bind to G-protein coupled receptors (GPCRs) and initiate the chemotaxis and direct migration of immune cells from the blood and lymph into the tissues where they seek out and destroy the foreign invaders. This hunt and raze method is tremendously well-organized and has evolved over many centuries.¹

Chemokines are distinct from other cytokines in their structure, cell surface receptors and unique pattern of activities. Chemokines are the largest family of chemotactic cytokines in human immunophysiology. Chemokines are small, with molecular weights in the range of 8 to 12 KD but there are exceptions which involve proteins comprised of multiple domains, one of which looks like a chemokine.^{2,3,4,5}

To date, 44 human chemokines have been described, many of which bind to several of the 21 described human chemokine receptors.⁶ Chemokine domains are defined by the presence of four cysteines in highly conserved positions. One major chemokine subfamily is called "CXC" because the two amino acids nearest the N-termini of these proteins are separated by a single amino acid. This family of chemokines have both angiogenic & angiostatic actions depending on the presence or absence of particular triplet of amino acids. The other major subfamily is called "CC" because the two cysteine are adjacent. Chemokine receptors bind several different chemokines, and chemokines bind several different receptors. The three-dimensional structure of each monomer is virtually identical, but the quaternary structure of chemokines is different for each subfamily. Chemokines share a common basic structure consisting of three anti-parallel β -strands and an overlying α -helix. ^{2,3,4,7.}

Chemokines are produced by a variety of cell types. Chemokines can be broadly divided into homeostatic and inflammatory categories based on their expression pattern and function in the immune system. These homeostatic proteins serve a variety of functions. The homeostatic chemokines are generally those that are "constitutively" expressed. They are mainly involved in

homeostatic lymphocyte and dendritic cell trafficking and lymphoid tissue organogenesis. They are also involved in immune surveillance and function to localize T or B cells with antigen (on the surface of antigen-presenting cells) in the lymphatic system.^{2,4,5}

Other chemokines are considered inflammatory and are only produced by cells during infection or a pro-inflammatory stimulus. The "inflammatory" chemokines are upregulated by pro-inflammatory stimuli and help coordinate innate and adaptive immune responses. The role of inflammatory chemokines is to induce the migration of leukocytes to the injured or infected site. In addition, inflammatory chemokines activate the cells to mount an immune response and initiate wound healing.^{2,4,5}

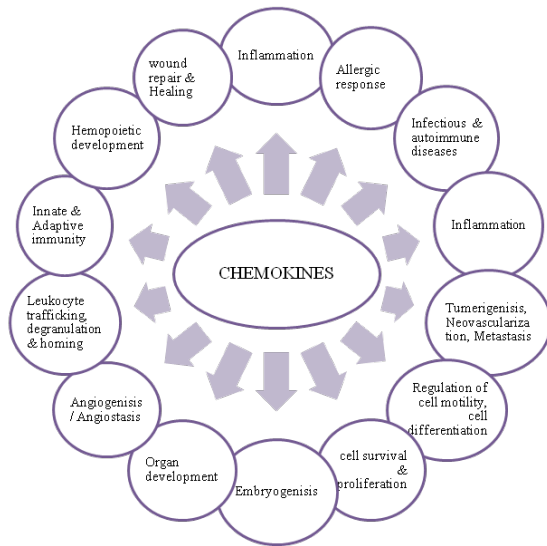
Function

Chemokine activity is initiated by the chemokine agonist binding to a specific G protein-coupled receptor. For activation of the receptor, the main body of the chemokine agonist specifically recognizes and binds the receptor leading to conformational change in the chemokines. The conformational change allows the N terminus to make the necessary interactions with the receptor that leads to receptor activation. Activation of the chemokine receptor is followed by exchange of bound GDP for GTP in the subunit of the G proteins. The G proteins disassociate from the receptor and activate several effector molecules downstream, which results in a cascade of signalling events within the cytoplasm of the cell. This sequence of events results in diverse physiological and pathological processes.⁴

Chemokines were originally discovered as mediators of directional migration of immune cells to sites of inflammation and injury. In recent years, it has become clear that the function of chemokines extends well beyond the role in leukocyte chemotaxis. Chemokines are important for the organization of tissues during development and regulate cell motility and localization both during development and in the adult life. They can also influence cell survival and proliferation. They participate in embryogenesis, organ development, angiogenesis/angiostasis, cell differentiation, leukocyte trafficking, degranulation & homing, innate immunity & adaptive immunity, hematopoietic development among other biological processes. They also play a role in wound repair & healing. Improper functioning of the chemokine-mediated signalling system can lead to pathophysiological processes such as inflammation, allergic responses, infectious and autoimmune diseases, inflammation, tumorigen-

esis, neovascularization & metastasis. Therefore, chemokines and their receptors are important targets for modulation of host responses in pathophysiological conditions and for therapeutic intervention of human diseases.^{2,4,7}

Figure 1: The role of chemokines in physiological & pathological conditions.



Cancer Cell Biology

Chemokines play a paramount role in physiology and homeostasis as well as in pathogenesis of tumors and their metastasis. In cancer biology, chemokines have been shown to be involved in all stages of cancer development including neoplastic transformation, tumor growth, immune evasion, metastasis and angiogenesis. Chemokines modulate tumour behaviour by three important mechanisms:

- Regulation of tumour-associated angiogenesis
- Activation of a host tumour-specific immunological response
- Direct stimulation of tumour cell proliferation in an auto-crine fashion.

Chemokines are responsible for activating, regulating and deactivating the immune response. One of the principal functions of chemokines is to regulate the trafficking of immune cells throughout the body, directing them to sites of infection. Improper initiation, or maintenance of immune system can lead

to defective inflammatory responses and result in the various diseases. The exact composition of the immune cell infiltrate is dependent on the specific disease and is influenced by the chemokine production in the particular tissue.^{7,8}

A major hurdle in tumour immunology has been the lack of immunogenicity of cancer cells. The ability of tumours to escape the immune system involves active and passive processes. Tumours actively secrete immunosuppressive molecules that outwit the immune system. Added to this difficulty is the low immunogenicity of tumour associated antigens. Tumours may evade the immune system's attempt to destroy tumour cells by directly or indirectly modulating the normal activation and signalling cascades of immune cells through a variety of stealth tactics, from secretion of immunosuppressive cytokines, to outright destruction of immune cells which prevents detection and destruction.^{9,10}

The tumor progression is influenced by the production of chemokines by tumor and stromal cells. Chemokines and their receptors provide directional cues for leukocytes or tumor cells for migration and metastasis, entry into the circulation, homing and colonization to specific tissues. Many cancer types have up-regulated expression of chemokines and chemokine receptors leading to aberrant chemokine receptor signaling and expression.⁸

Detecting the role of chemokines in pathogenesis is heralding a new era in cancer immunotherapy because of the ability to triumph over obstacles. As a result there has been great interest in understanding how chemokines and their receptors influence cancer cell behaviour, with the aim of developing new therapeutic strategies. Chemokines are particularly promising molecules because they have proved useful as both anti-angiogenic agents and critical determinants for successful tumour vaccine development in preclinical animal models. Antagonists for a number of chemokine receptor have been developed, raising the possibility of interfering with chemokine function as a therapeutic tool.^{4,5,7}

Conclusion

Chemokines clearly play significant roles in both normal physiology and pathology of a number of diseases. This provides an excellent prospect in the development of new therapeutic strategies in the treatment of such diseases. However the complex role of chemokines in various disease pathophysiology represents a major challenge. The role of chemokines in each disease needs to be studied so that specific pathomechanisms of the disease process is better understood thereby treatment mechanisms targeting these chemokines can be achieved.

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