CHEMOKINE SYSTEM - THERAPEUTIC TARGET FOR MANY DISEASES

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ABSTRACT

Chemokines are named so because they induce chemotaxis. Chemokines are proteins that are involved in directed migration of various leucocytes. Chemokines are known to play an important role in normal physiological and pathological diseases. Apart from cell trafficking, they are involved in inflammatory, autoimmune diseases and tumorigenesis. Based on this, many chemokine receptor antagonists have been developed the foremost being CCR5 inhibitor Maraviroc which is contributing a lot to control HIV epidemic. Hence, this chemokine system can provide new, exciting and useful targets for developing new drugs for the treatment of various diseases. In this review chemokine structure, their receptors and their role in various diseases are highlighted along with strategies to inhibit chemokines. Medline, medscape, EMBASE, Cochrane database, Scopus and clinicaltrials.gov were searched using terms like “chemokine”, “chemokine receptors” and “chemokine blockers”. Journal articles describing chemokine system were screened.

Keywords: Chemokines, Chemokine blockers, Chemokine receptors.

INTRODUCTION

Chemokines are chemotactic cytokines which are small (8-14 kD) heparin binding proteins involved in the leucocytes migration both in health (protective responses to invading pathogens) and disease (inflammation) 1. Apart from chemotaxis, chemokines are now known to play a role in angiogenesis, embryonic development and cell homeostasis as well 2. With the FDA approval of certain molecules like Maraviroc for AIDS and Plerixafor for aiding stem cell mobilization, chemokines are emerging as a new player in the treatment of various
diseases. In this review we discuss chemokines, their structure, receptors and functions in normal and pathological diseases.

**Chemokine terminology**
Structurally, chemokines contain at least four cysteine residues that form two disulphide bonds. Chemokines are subdivided into four subfamilies i.e. CC, CXC, CX3C and C subfamilies based on the pattern of cysteine residues near the N-terminus. C donates cysteine and X/X3 donates one or three noncysteine amino acids. Hence, CXC represents one amino acid separation between the first two cysteines while in CX3C chemokines, three amino acids separates two cysteines. In CC chemokines, the first two of the four cysteine residues are adjacent to each other and in C subfamily first and third cysteines are missing. Nowadays, structural classification is seldom used and new nomenclature of chemokines based on functional criteria is preferred. According to it, they can be of three types: inflammatory or inducible chemokines, Homeostatic or constitutive chemokines and Dual-function chemokines. Inflammatory chemokines are upregulated only under inflammatory conditions and are responsible for both innate and adaptive immunity whereas Homeostatic chemokines are expressed constitutively which helps in mediating homeostatic migration and homing of various cells. Chemokines whose function overlaps in both the fields are included under dual-function chemokines. However, this classification is not exclusive and some inflammatory chemokines may behave as homeostatic chemokines under some circumstances and vice-versa. Inflammatory chemokines are clustered in 4 and 17 chromosome while homeostatic chemokines are located singly or in mini-clusters in different chromosomes.

**Chemokine receptors**
Chemokine receptors are G-protein coupled receptors with seven transmembrane regions. They are grouped into four subfamilies according to their specificity for the chemokine ligands i.e. CXC chemokine receptors, CC chemokine receptors, CX3C chemokine receptors and C chemokine receptors. Many chemokine receptors are known, out of which seven CXC (CXCR1-CXCR7), ten CC (CCR1-CCR10), one C and one CX3CR1 have been identified and cloned. Furthermore, five nonsignalling atypical scavenger chemokine receptors are reported. They lack DRY motif in the second intracellular loop which is important for coupling with G-proteins. Classical e.g. of this atypical receptor is DARC (Duffy antigen chemokine receptor) which binds large number of inflammatory chemokines. Most chemokine receptors are stimulated by multiple chemokines and on the other hand
one ligand might stimulate more than one receptor. So chemokine receptors interactions are promiscuous but sometimes it can be exclusive also. Like their counterpart ligands, chemokine receptors are constitutively expressed while others are inducible. In addition, expression of some receptors is restricted to state of cell differentiation or activation. Chemokine receptor genes form clusters like their ligands and a large cluster is present in chromosome 3. Chemokine GPCRs have interesting ability to undergo constitutive homo and hetero-dimerization which can lead to varied functional consequences. Apart from this, chemokine binding to GAGs is essential for leucocyte migration and presentation of chemokines on endothelial cells. Chemokine receptors are present on many immune cells which depend on chemokines for their migration.

Table 1: Chemokine receptors and inflammatory cells

<table>
<thead>
<tr>
<th>Chemokines</th>
<th>Attractants for immune cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXC chemokines</td>
<td>Neutrophils, basophils and T-lymphocytes</td>
</tr>
<tr>
<td>CC chemokines</td>
<td>Monocytes, basophils, dendritic cells, macrophages, Natural killer cells, T cells</td>
</tr>
<tr>
<td>C chemokines</td>
<td>T cells to thymus</td>
</tr>
<tr>
<td>CX3C chemokines</td>
<td>Infiltration of T cells, NK cells and monocytes</td>
</tr>
</tbody>
</table>

Role of chemokines in various diseases
Chemokines are involved in various infectious diseases like HIV, Autoimmune diseases like SLE, sjogren syndrome, kawasaki disease, psoriasis, arthritis, Allergic diseases like asthma, various Cancers like lung cancer, leukemia, Glioblastoma, colorectal cancer, Cardiovascular diseases like hypertension and Nervous system diseases like alzheimer disease or Age related macular degeneration. Role of chemokines in some of these diseases is discussed below.

Chemokines in inflammatory lung disease
In Chronic Obstructive Pulmonary Disease (COPD), CCL2 and corresponding receptor CCR2 are responsible for migration of monocytes into bronchial epithelium. CXCL2 binds to CXCR1 and CXCR2 chemokine receptor which are predominant on neutrophils. It has been found that expression of CXCR1 is increased in circulating neutrophils of COPD patients as compared to healthy controls. Small molecule inhibitors against CXCR2 reduce neutrophilic infiltration in lung. CXCR3 are also involved in airway inflammation and development of COPD by activation by CXCL9, CXCL10 and CXCL11. Even CCR5 might have an additional role along with CXCR3 in the recruitment of T cells into the lungs.
Chemokines in asthma
Lung mast cells express CCR1, CCR3, CXCR1, CXCR3 and CXCR4 which through activation by respective ligands migrate to bronchial smooth muscles leading to hyper-responsiveness in asthmatic patients. CXCR3 is highly expressed in lung mast cells and hence its ligand CXCL10 is found in increased amount in bronchial biopsies of asthmatic patients. CCR4 and CCR8 are expressed in majority of the T cells infiltrating the lungs of asthmatics. CXCR4 expressed on Th2 cells is suggested to be a potential target for the treatment of asthma 18.

Chemokines in Inflammatory bowel disease
CXCR1 and CXCR2 receptors are increased in intestinal mucosa of IBD patients with corresponding chemokines like CXC8. CXCR2 antagonists have the potential to prevent neutrophil mediated inflammatory disease 19. Antibodies against these receptors are found to be effective in mouse IBD models. AntiCXCL10 antibodies lead to decrease in intestinal inflammation and various clinical trials are being taken up to establish it 18. CCR9+ T cells in mucosa of intestine have also shown to play a role in IBD. CCX282-B, also called vercirnon(CCR9 antagonist) has entered phase 3 trial for chron disease 20.

Chemokines in Rheumatoid arthritis
Chemokines are responsible for underlying pathology in the disease. The CXC- and CC-chemokines are involved in attraction of leucocytes that are involved in invasion of the synovium. Out of these CXCL8, CXCL5 and CXCL1 are predominantly expressed in serum and synovial fluid. B cells are also migrated into the RA synovium under the influence of CXCL13 7. Even T cell associated CXCR3 ligands, are perceived as biomarkers of rheumatoid activity 18. Recently, MDX-1100, a fully humanized anti-CXCL10 monoclonal antibody is found to be clinically efficacious in RA patients showing inadequate response to methotrexate 21.

Chemokines in Atherosclerosis
As chemokines are involved in leucocyte trafficking, they are responsible for their infiltration at the sites of vascular inflammation. Many of the chemokines like CXCL9,-10,-11 or CCL2, CX3CL1, CCL5,CCL20, CCL17,CCL5 are important chemokines involved in atherosclerosis 3. CCL2 has been found in macrophage rich atherosclerotic plaques. It is the link between the oxidized lipoproteins and recruitment of foam cells 22.
Chemokines in Cancer

There is upregulation of chemokines and chemokine receptors in many cancer types. Tumor microenvironment consists of CC and CXC chemokines which are involved in leukocyte trafficking. CXCR4 chemokine receptor is frequently found to be over-expressed on tumor cells. Muller et al have demonstrated that in breast cancer cells CXCR4 expression leads to metastasis in other organs. CXCR4 is also implicated in metastasis of ovarian, prostate and lung cancer.

Strategies for inhibiting chemokines

Non-signalling chemokine ligands with modified chemical structures can be used as antagonists. But these are generally proteins which can be degraded by proteolysis. Another approach is the use of antibodies against chemokine receptors or GAG-binding deficient chemokines. However, small molecule receptor antagonists are most widely studied and are undergoing clinical investigation.

CXCR2 antagonist like 2-hydroxyphenylureas have entered clinical trial for treatment of COPD. CXCR2 antibodies like SB-656933 have shown promising results in Cystic fibrosis and trials are undergoing to establish their role in such patients. Reparixin- an allosteric CXCR1 receptor inhibitor is under clinical trial for cell dysfunction in type 1 diabetes patient after islet transplantation. GW-766994 is CCR3 antagonist for treatment in asthma and allergic rhinitis is currently under clinical trial.

AMD3100 (Plerixafor) CXCR4 antagonist is approved for stem cell mobilization in combination with granulocyte-colony stimulating factor for non-Hodgkin's lymphoma and multiple myeloma. Fusion between viral and host membrane in HIV involves CXCR4 and CCR5 chemokine receptors. Hence, CCR5 is essential for the entry of T-tropic strains of HIV. In this regard, Maraviroc was approved in 2007 as a part of combination therapy in HIV-1. A study by Gulick et al carried in around 900 HIV infected patients showed that it is generally safe.

CONCLUSION

There has been considerable effort in elucidating the role of chemokines and chemokine receptors as drug targets. Previous years have seen rapid progress in the development of various chemokine receptor antagonists and many of them are now undergoing clinical trials. Hence this system can definitely provide new avenues to develop potential drugs for...
conquering various diseases.

REFERENCES


