Chemokines and Chemokine Receptors

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Based in part on the previous version of this Encyclopedia of Life Sciences (ELS) article, Chemokines by Richard Horuk.

Advanced article

Article Contents

Online posting date: 15th December 2009

Chemokines (CKs) are a family of small proteins secreted by a great variety of cell types. Their name (derived from *chemo*attractant cyto*kines*) is due to their ability to induce directed chemotaxis in nearby responsive cells. Some CKs are considered pro-inflammatory and can be induced during an immune response to promote cells of the immune system to a site of infection, whereas others are considered homeostatic and are involved in controlling the migration of cells during normal processes of tissue maintenance or development. CKs are found in all vertebrates, some viruses and some bacteria. These proteins exert their biological effects by interacting with G protein-linked transmembrane receptors called chemokine receptors (CKRs) that are selectively found on the surfaces of their target cells. CKs play roles in cell maturation and differentiation, infection, autoimmunity, cancer and, in general, in any situation where immune components are involved. Their role in human immunodeficiency virus (HIV) infection is of special relevance.

Introduction

To accomplish an efficient immune function, dispersion and clonality of the immune components force immune cells to recirculate with precision and fine coordination around all body tissues, selecting continuously specific anatomic sites to develop each step of immune responses. This efficiency in immune response is obtained in part by the coordinated synthesis and function of the small cytokines called chemokines (CKs) and their action on their counterparts, the chemokine receptors (CKRs); in fact, CKRs define the subpopulation that will be localized in each step of the immune responses. **See also**: Chemoattraction: Basic Concepts and Role in the Immune Response

CKs include over 50 small (6–14 kDa) chemotactic (attracts cells on behalf of their gradient of concentration) cytokines. They are structurally related, being their four well-conserved cysteine (C) residues the key aspect that allows classifying them. Four groups are defined on the basis of the first two Cs: CC, CXC, CX_3C and C CKs (**Figure 1** and **Table 1**). These four CK families define also a nomenclature that tries to standardize the names of CKs with the following codes: CCL*n*, CXCL*n*, CX_3CL*n* or XCL*n*, where '*n*' is a correlative number that individualizes each molecule, and 'L' is an abbreviation of 'ligand' which is used to distinguish CKs from their receptors (CCR*n*, CXCR*n*, CX_3CR*n* and XCR*n*) which use 'R' (an abbreviation of 'receptor'). In fact CKs develop their functions due to their surface cell receptors, and therefore CKs and CKRs act as a functional unit, making it necessary to understand in whole the function of this system of cell localization, to describe in parallel both elements. Actually, there are 18 CXC CKs from CXCL1 to CXCL17 (including the paralogous CXCL4L1), 29 CC CKs from CCL1 to CCL28 (including CCL3L1, CCL4L1 and CCL4L2, but excluding the numbers 6 and 9 from this family), 2 C CKs, called XCL1 and XCL2, and 1 CX_3C CK, named CX_3CL1.

Although CKs were originally described by their chemoattracting capability which allows regulation of immune cell trafficking (Schall and Bacon, 1994), their functions include growth regulation and haematopoiesis, tissue and cell development, modulation of specific immune recognition and participation in several

ELS subject area: Immunology

How to cite:
Juan, Manel; and, Colobran, Roger (December 2009) Chemokines and Chemokine Receptors. In: Encyclopedia of Life Sciences (ELS). John Wiley & Sons, Ltd: Chichester.
DOI: 10.1002/9780470015902.a0000933.pub2

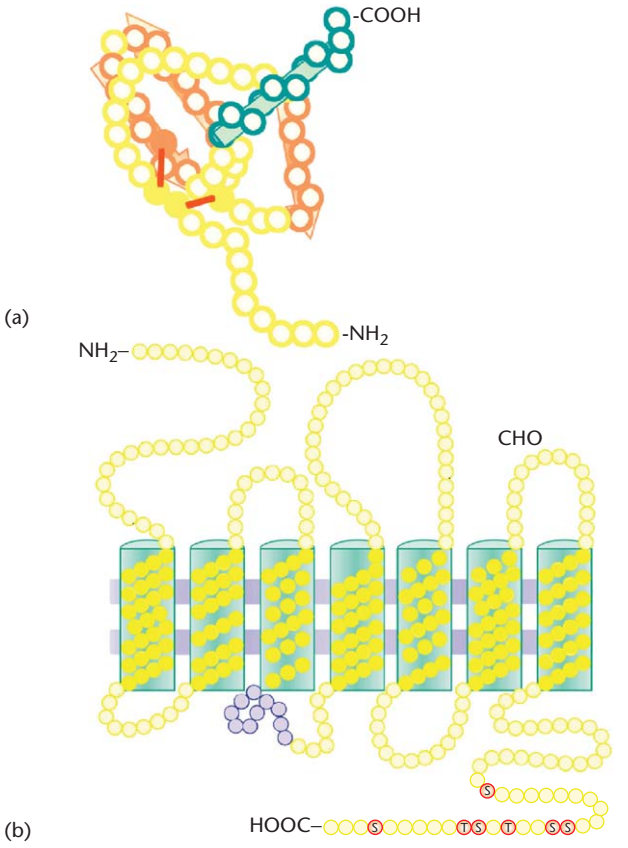

Figure 1 Chemokine – chemokine receptor structure and interaction. (a) Proposed general topography of the CCL4 CK. Amino acids forming the three β sheets and the α helix are depicted in orange and green, respectively. The two disulfide bridges that stabilize the tertiary structure are shown as red lines connecting the four Cs. (b) Proposed membrane topography of the human CCR5 receptor. Membrane-spanning α helices are defined on the basis of hydropathy analysis. CHO represents potential *N*-linked glycosylation sites. Residues shown in blue represent the DRYLAVHA sequence motif characteristic of CKRs. Residues in red represent Ser and Thr residues that are potential phosphorylation sites for specific receptor kinases during desensitization. Note that the CCL4 *N*-terminus interact with the extracellular part of CCR5 receptor.

pathophysiologic situations, with viral infection being one of the most complex and intriguing aspects that involves CKs and CKRs (Melchjorsen *et al*., 2003); in fact a major role in human immunodeficiency virus (HIV) infection has been clearly defined for some CKs and CKRs (see section on Role of chemokines in disease; Lusso, 2006).

On the basis of their pattern of expression, CKs can be classified as inflammatory or homeostatic. Inflammatory CKs are induced in productive cells by their injury; their basal expression, which is very low or absent increases when cells are damaged, defining inflammatory responses. Homeostatic CKs are basally expressed, and although they can be induced sometimes, their major role is to guarantee constant recirculation of leucocytes during physiology.

Because of the role of CKRs determining the localization of cells that express them (and consequently defining that 'the *correct* cells are sited in the *correct* place, for a *correct* function'), the patterns of CKs are also directly associated with specific functions of their cells [i.e. it is possible to define the major expression of some CKRs in T-helper 1 (T_H1) (CCR5) and T_H2 cells types (CXCR3)] (D'Ambrosio and Sinigaglia, 2000). **See also**: T Lymphocytes: Helpers

Next to the 20 CKRs (the conventional CKRs that define the signalling inside cells), there are also some 'extracellular nonconventional receptors' and some more 'conventional but nontransducing receptors'.

The 'extracellular nonconventional receptors' are named glycosaminoglycans (GAGs). GAGs are extracellular molecules that bind CKs and stabilize their concentration gradient, determining therefore the most effective chemotaxis in tissues. Although most CKs are secreted molecules, they are probably only functional for leucocytes *in vivo* when they are bound to these extracellular matrix molecules or to cell-surface proteoglycans (Proudfoot *et al*., 2003). Although *N*-terminal residues of CKRs interact with *N*-terminus of CKs, GAGs prevent dispersion of CKs by interacting with other regions (mainly basic amino acid motifs). In fact, *in vivo* the interaction with GAGs modulates the stimulatory interaction of CK–CKR, defining an effect which seems to be different from that showed by soluble CKs *in vitro*; GAGs are very relevant for CK function, probably as much relevant as CKRs (Proudfoot, 2006). **See also**: Glycosaminoglycans: Structure and Biological Functions

The 'conventional but nontransducing receptors' are also important molecules; usually named 'decoy receptors' (and also CK scavengers or interceptors), this group of molecules includes DARC (Duffy antigen receptor for chemokines), D_6 and CCX–CKR. Decoys bind and internalize CKs (through constitutive cycling from plasma membrane to endosomal compartments) without inducing cellular responses, which is important for the clearance of CKs, especially at inflammatory sites (Comerford and Nibbs, 2005).

Structure

Three-dimensional (3D) analysis [by nuclear magnetic resonance (NMR) and X-ray studies) revealed that all CKs are structurally related: a flexible *N*-terminal region (the residues that interact with CKRs) followed by three antiparallel ß strands (chained by short loops of residues, some of them important for GAG-binding in some CKs) and a *C*-terminal α helix (that can define dimerization or GAG-binding) (**Figure 1a**). Next to the distinctive CC, CXC, C or CX_3C residues that in their *N*-terminal position define the important intrachain S–S bridges, major differences between the CK families are found in regions that define dimerization and GAG-binding (*C*-terminal or inter-ß sheet loops). In fact although several studies revealed that the monomeric form can be apparently fully functional; most of CKs form homodimers (and also oligomers and multimers) and heterodimers (coupling between two different CKs) that apparently are the quaternary structures that, *in vivo*, really define the functional capabilities of CKs

Table 1 Overview of human chemokines and chemokine receptors

Name	Gene symbol	Alternative names	Location	Type	Receptor	Main source
CXCL1	CXCL1	GROα, MGSAα, NAP-3, SCYB1	4q13.3	I	CXCR2, 1	Mo, Ma, EnC, EpC
CXCL2	CXCL2	GROβ, MGSAβ, MIP-2α, SCYB2	4q13.3	I	CXCR2	Mo, Ma, EnC, EpC
CXCL3	CXCL3	GROγ, MGSAg, MIP-2β, SCYB3	4q21	I	CXCR2	Mo, Ma, EnC, EpC
CXCL4	PF4	PF4, SCYB4	4q12-q21	I	CXCR3-B	Platelets
CXCL4L1	PF4V1	PF4V1, CXCL4V1, SCYB4V1	4q12-q21	I	Unknown	Platelets
CXCL5	CXCL5	ENA-78, SCYB5	4q13.3	I	CXCR2	EpC, EnC, Mo, Ma, N
CXCL6	CXCL6	GCP-2, CKA-3, SCYB6	4q13.3	I	CXCR1, 2	EpC at mucosal tissues
CXCL7	PPBP	NAP-2, CTAP-III, βTG, SCYB7	4q12-q13	I	CXCR2	Platelets, Mo
CXCL8	IL8	IL8, NAP-1, NAF, SCYB8	4q13-q21	I	CXCR1, 2	Mo, T, EnC, EpC
CXCL9	CXCL9	MIG, CMK, SCYB9	4q21	I	CXCR3	Mo, Ma, EnC, N, SC
CXCL10	CXCL10	IP-10, crg-2, INP10, SCYB10	4q21	I	CXCR3	Mo, T, EnC, K
CXCL11	CXCL11	I-TAC, IP-9, SCYB9B, SCYB10	4q21	I	CXCR3	Mo, astrocytes
CXCL12	CXCL12	SDF1α, SDF1β, PBSF, SCYB12	10q11.1	H	CXCR4	Widely expressed
CXCL13	CXCL13	BLC, BCA-1, BLR1L, SCYB13	4q21	H	CXCR5	SLO
CXCL14	CXCL14	BRAK, bolekine, MIP-2γ, SCYB14	5q31	H/I	Unknown	Widely expressed
CXCL16	CXCL16	CXCLG16, SR-PSOX	17p13	I	CXCR6	Ma, DC, T
CXCL17	CXCL17	VCC1, DMC, Dcip1, UNQ473	19q13.2	I	Unknown	Lung, skeletal muscle
CCL1	CCL1	I-309, TCA3, P500, SISe, SCYA1	17q11.2	I	CCR8	T, Mo,
CCL2	CCL2	MCP-1, MCAF, SMC-CF, SCYA2	17q11.2–q21.1	I	CCR2	F, EnC, EpC, N, Eo
CCL3	CCL3	MIP-1α, LD78α, SCYA3	17q12	I	CCR1, 5	Mo, Ma, T, B, N, DC
CCL3L1	CCL3L1	LD78β, SCYA3L, SCYA3L1	17q12	I	CCR1, 5	Mo, Ma, T, B, N, DC
CCL4	CCL4	MIP-1β, Act-2, AT744.1, SCYA4	17q21–q23	I	CCR5	Mo, Ma, T, B, N, DC
CCL4L1	CCL4L1	LAG-1, SCYA4L1	17q12	I	CCR5	Mo, Ma, T, B, N, DC
CCL4L2	CCL4L2	SCYA4L2	17q12	I	CCR5	Mo, Ma, T, B, N, DC
CCL5	CCL5	RANTES, SISδ, TCP228, SCYA5	17q11.2–q12	I	CCR1, 3, 5	Ma, EpC, EnC, T, E
CCL7	CCL7	MCP-3, NC28, FIC, MARC, SCYA7	17q11.2–q12	I	CCR1, 2, 3	Mo, Ma, F, platelets
CCL8	CCL8	MCP-2, HC14, SCYA8	17q11.2	I	CCR2, 3, 5	F, N, multiple organs

(*Continued*)

Table 1 Continued

Name	Gene symbol	Alternative names	Location	Type	Receptor	Main source
CCL11	CCL11	Eotaxin, MGC22554, SCYA11	17q21.1–q21.2	I	CCR3	EpC, EnC, Mo
CCL13	CCL13	MCP-4, NCC-1, CKβ10, SCYA13	17q11.2	I	CCR2, 3	Ma, EnC
CCL14	CCL14	HCC-1, NCC-2, CKβ1, SCYA14	17q11.2	H/I	CCR1, 5	Widely expressed
CCL15	CCL15	HCC-2, NCC-3, MIP-5, SCYA15	17q11.2	I	CCR1, 3	Mo, multiple organs
CCL16	CCL16	NCC-4, LEC, HCC-4, SCYA16	17q11.2	H/I	CCR1, 3, 5, 8	Mo, liver, spleen
CCL17	CCL17	TARC, ABCD-2, SCYA17	16q13	H	CCR4	Thymus, lung, colon
CCL18	CCL18	PARC, DC-CK1, AMAC-1, SCYA18	17q11.2	H/I	Unknown	Ma, DC, lung, placenta
CCL19	CCL19	ELC, MIP-3β, exodus-3, SCYA19	9p13	H	CCR7	Lymphoid tissues
CCL20	CCL20	LARC, MIP-3α, exodus-1, SCYA20	2q33–q37	H/I	CCR6	LN, PBL, liver
CCL21	CCL21	SLC, 6Ckine, exodus-2, SCYA21	9p13	H	CCR7	LN, spleen, appendix
CCL22	CCL22	MDC, STCP-1, ABCD-1, SCYA22	16q13	H	CCR4	LN, thymus, Ma
CCL23	CCL23	Ckβ-8, MPIF-1, MIP-3, SCYA23	17q11.2	I	CCR1	Pancreas, lung, Mo
CCL24	CCL24	Eotaxin-2, Ckβ-6, MPIF-2, SCYA24	7q11.23	I	CCR3	Mo, Ma, EnC, T
CCL25	CCL25	TECK, Ckβ15, SCYA25	19p13.2	H	CCR9	Thymus, small intestine
CCL26	CCL26	Eotaxin-3, MIP-4β, IMAC, SCYA26	7q11.2	I	CCR3	Heart, lung, ovary, EnC
CCL27	CCL27	ALP, ILC, CTACK, SCYA27	9p13	H	CCR10	K
CCL28	CCL28	MEC, CCK1, SCYA28	5p12	H/I	CCR3, 10	Mucosal EpC
XCL1	XCL1	Lymphotactin, ATAC, SCYC1	1q24.2	I	XCR1	CD8, NK, mast cells
XCL2	XCL2	SCM-1β	1q24.2	I	XCR1	CD8, NK, mast cells
CX3CL1	CX3CL1	Fractalkine, neurotactin, SCYD1	16q13	I	CX3CR1	EnC, microglia

Mo, monocytes; Ma, macrophages; EnC, endothelial cells, EpC, epithelial cells, N, neutrophils; T, T lymphocytes; SC, stromal cells; K, keratinocytes; SLO, secondary lymphoid organs; F, fibroblasts; Eo, eosinophils; B, B lymphocytes; E, eosinophils; LN, lymph nodes; PBL, peripheral blood lymphocytes; NK, natural killer cells, CD8, CD8 T cells.

(Nesmelova *et al*., 2008). Additionally, a similar phenomenon happens with CKRs: most, if not all, CKRs are able to form dimers or higher order oligomers (Springael *et al*., 2005). **See also**: Nuclear Magnetic Resonance (NMR) Spectroscopy: Structural Analysis of Proteins and Nucleic Acids

Nomenclature from proteins and genes

Although since 2000, in general the standardization of CCL–CXCL nomenclature (Zlotnik and Yoshie, 2000) has been adopted by most scientists, some classical names of CKs are still in use. The third column in **Table 1** shows some of these most frequent synonymous, as fractalkine for CX_3CL1, lymphotactin for XCL1, interleukin 8 (IL-8) for CXCL8, stromal cell–derived factor-1 (SDF-1) for CXCL12 or RANTES (regulated on activation normal T cell expressed and secreted) for CCL5.

Although also an equivalent gene symbol has been introduced for naming gene loci [except for IL-8, pro-platelet basic protein (PPBP), platelet factor 4 (PF4) and platelet factor 4 variant 1 (PF4V1) loci] years, the codifying

genes for CKs have been also named as *SCYA1-28*, *SCYB1-17*, *SCYC1-2* and *SCYD1* (for *CCL1-28*, *CCL1-17*, *XCL1-2* and *CX_3CL1* loci, respectively; abbreviation '*SCY*' comes from '*small cytokine*'). **See also**: Human Gene Nomenclature

Chemokine Receptors

CKRs are surface molecules that belong to the superfamily of GPCRs, also known as seven transmembrane domain receptors (**Figure 1b**); CKRs are defined by their ability to bind CKs in a specific and saturable manner and to transduce a cellular response. Although leucocytes are the major site of expression of CKRs, several studies have recently demonstrated CKR expression in other cells (such as neurons in the central nervous system). Similarly beyond their roles in leucocyte trafficking, CKRs have multiple additional functions, including regulation of development of the cardiovascular, gastrointestinal, immune and central nervous systems. Until now, over 20 different CKRs have been cloned. The amino acid sequences of CKRs have 25–80% identity, indicating a common ancestry. The conserved binding pocket of most of GPCRs, located in the extracellularly oriented half of the seven transmembrane segments, is fitted by the amino terminus of CKs during the trigger of CKRs (**Figure 1**). It is accepted that a CK interacts with only one receptor molecule. Consequently dimeric CKs act over CKR dimers or induce their multimerization; this is a relevant process that seems to explain some of the differential effects of dimers/multimers versus monomers (Springael *et al*., 2005).

Aspects of signalling common to all known mammalian CKRs include induction of calcium flux and chemotaxis, and marked inhibition of both by *Bordetella pertussis* toxin. The latter reflects coupling of receptors in primary cells to G_i-type heterotrimeric G proteins. The first step in the complex signalling process is the ligation of the receptor by its high-affinity ligand. This induces a conformational change that leads to a dissociation of the receptor-associated heterotrimeric G proteins into α and $\beta\gamma$ subunits. These G protein subunits can then activate various effector enzymes, including phospholipases and protein kinases. This signal transduction cascade leads to the activation not only of chemotaxis by modulating actin-dependent cellular processes and upregulating adhesion proteins, but also of a wide range of functions in different leucocytes such as an increase in the respiratory burst, degranulation, adhesivity, phagocytosis and lipid mediator synthesis. Activation of CKRs ultimately results in desensitization, which has been associated with phosphorylation of serines (Ser) and threonines (Thr) in the C tail, and clathrin-mediated endocytosis. **See also**: G Proteins; G Protein-coupled Receptors

In addition several virus-encoded proteins that have sequence homology and share the serpentine structure of the cloned CKRs have been identified. These viral proteins have been termed viroceptors and appear, sometimes, to function as CKRs (Vischer *et al*., 2006). **See also**: Virus Host Cell Receptors

Next to GAGs (which can be considered extracellular CKRs, as previously commented), the third kind of receptors that bind CKs but do not signal inside the cells, are 'decoys CK receptors' (Comerford and Nibbs, 2005); the first one identified was DARC in human erythrocytes as a CXCL8-binding protein. But at present, DARC (the well-known Duffy blood group antigen, receptor for the malarial parasite *Plasmodium vivax*) is identified as the only promiscuous decoy receptor that binds both CC and CXC CKs with medium-high affinity. DARC share this 'decoy' function with D_6 and CCX–CKR (also named CCRL1 and originally CCR11), which preferentially bind CC CKs. **See also**: Malaria

Chemokine Families

As discussed earlier, the 40 or so human CKs identified so far have been classified into four separate families. Although the amino acid sequence identity within CK families can be as high as 70%, there can be as little as 20% homology in the sequence between CKs from different families. In this short review, we will consider each of the four CK families separately and finally we will also briefly discuss some aspects of the molecules named 'viral chemokines'.

CXC chemokines

Most CXC CKs are clustered on chromosome 4q12–13 and 4q21 (Huising *et al*., 2003).

On the basis of the identity of the three amino acids that precede the first C residue in the CXC motif, CXC CKs can be further subdivided into two groups: ELR and non-ELR. The ELR (glutamic acid-leucine-arginine) CXC human CKs include from CXCL1 to CXCL8 (except CXCL4), whereas human non-ELR CKs group include from CXCL9 to CXCL17 and CXCL4. Distinctive features of the ELR CKs are their ability to chemoattract and activate neutrophils expressing CXCR1 and CXCR2 receptors (Bizzarri *et al*., 2006). CXCL8 can bind with high affinity and activate both receptors, whereas the other ELR CKs can bind with high affinity and activate mainly the CXCR2 receptor. A number of studies have revealed that ELR CKs like CXCL8 are potent angiogenic factors, inducing both *in vitro* endothelial chemotaxis and *in vivo* corneal neovascularization (Strieter *et al*., 2005). In contrast, CKs that lack the ELR motif like CXCL4, CXCL9 and CXCL10, are potent angiostatic agents and inhibit tumour growth (Yang *et al*., 2009). A variety of experimental data from model systems support the idea that these CKs can overcome the angiogenic effects not only of the ELR CKs but also of the powerful angiogenic growth factors like fibroblast growth factor and vascular endothelial growth factor. **See also**: Neutrophils

CC chemokines

Most CC CKs are clustered on chromosome 17q11–21 and 9p13.

In contrast to CXC CKs, CC CKs do not act on neutrophils and mostly activate monocytes, lymphocytes, eosinophils and basophils. Consequently they appear to play a greater role in chronic inflammatory processes. *N*-terminal amino acids (like in CXC CKs) are the key region that defines the main activity of CC CKs: addition of one amino acid at the *N*-terminus of CCL5 or CCL2 has no effect on receptor binding, but reduces the potency at least two log orders (protein change from a potent agonist to a potent antagonist); similarly, cleavage of the *N*-terminal amino acid of CCL2 changes the target cell specificity of the protein from basophils to eosinophils and cleavage of CCL3 or CCL4 produce high active forms. These data are interesting given that immune cells express aminopeptidases on their cell surface (especially CD26) that are involved in trimming CKs, modulating their interactions to CKRs (Mortier *et al*., 2008).

Next to chemotaxis, CC CKs show other interesting functions. Some examples are:

CCL3 has been reported to be a mediator of haematopoietic cell proliferation in synergy with other growth factors, including granulocyte–macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) (Cook, 1996). **See also**: Haematopoietic Growth Factors

A variety of tumour cells have been reported to express CKs, particularly CCL2 proteins. In fact CCL2 was first identified from a human tumour cell line. Since CCL2 proteins can stimulate the production of lytic proteins such as gelatinase and urokinase-type plasminogen activator by macrophages, it will aid in the localized digestion of extracellular matrix components to provide a route for the transmigration of tumour cells from tissues across the endothelial cell wall and into the circulation (metastasis). Since tumour cells can bind to endothelial cells, it is possible that CKs could play a role in this process because of their effects on adhesion proteins.

CX_3C chemokines

Only one member of this family, CX_3CL1 (also called fractalkine or neurotactin), has so far been identified. This CK, which binds with high affinity to CX_3CR1, is unusual because, besides the long spacing of its first two Cs, it is attached to an extended mucin-like stalk that can exist either in a membrane-anchored or a soluble 95-kDa-glycoprotein form. This arrangement of the CK on its own stalk on the cell surface could allow the direct presentation of the molecule to passing immune cells, avoiding the need for presentation on GAGs. Several studies have demonstrated that this CK plays an important role in inflammation in the central nervous system (Milligan *et al*., 2008). **See also**: Multiple Sclerosis

C chemokines

XCL1 (also called lymphotactin) and XCL2 (called SCM-1β) are the two members of the C class of CKs, because they possess only two of the prototypical four Cs present in other CKs. Both genes localize into chromosome 1 and they are specific chemoattractants for lymphocytes. XCL1 message appears to be restricted to activated CD8+ thymocytes, CD8+ peripheral blood T cells, CD4+ T cells and human natural killer (NK) cells (Stievano *et al*., 2004). These features clearly distinguish C CKs from all other CKs. **See also**: CD Antigens

Viral chemokines

Several virus [human herpesviruses (Kaposi sarcoma-associated herpesvirus, HHV-8) and pox viruses (*Molluscum contagiosum virus*, MCV) have been shown to encode CK-like proteins (Boomker *et al*., 2005).

In HHV-8 two viral proteins with homology to CCL3–CCL4 (MIP proteins), called vMIP-I and vMIP-II, are produced. Both expressed proteins are angiogenic, showing a pathogenic role in Kaposi sarcoma. In addition, vMIP-II has unique biological activities in that it blocks infection by several different HIV-1 strains. This occurs because vMIP-II binds to a wide range of CKRs, some of which are used by HIV to gain cell entry (Mori *et al*., 2005). The HHV-8 virus thus appears to have 'hijacked' a human MIP-like CK, modifying it so that it can bind to more than one CKR and thereby increasing the pathogenicity of the virus, helping it to spread and proliferate (Benelli *et al*., 2000).

The poxvirus MCV CK proteins also closely resemble CCL3 and appear to share the inhibitory effect that this CK has on human haematopoietic progenitor cells. These proteins are potent antagonists and can inhibit the chemotactic response to the human CK (Krathwohl *et al*., 1997). It is likely that their major function in the virus is to aid it in immune evasion during infection. **See also**: Herpesviruses (Human); Poxviruses

High Variability in the Chemokine Network

In evolution, diversification through the generation of multiple alleles is very common and the immune system contains several groups of genes with prominent allelic variation. The CK superfamily constitutes a very revealing case of how, through evolution, a complex network of genes has acquired a very diverse set of related functions (Colobran *et al*., 2007a). Most, if not all, CKs probably arose by gene duplication of a single ancestral gene and, consequently, many CKs (just as many CKRs) are clustered in defined chromosomal locations. Two main clusters have been recognized, both of them codifying the essential inflammatory CKs: the CXC cluster, located in chromosome 4q12–21 and the CC cluster, located in chromosome

17q11.2. Those CKs that map in the CXC and CC clusters seem to maintain some similar functions: CXC cluster CKs recruit mainly neutrophils, whereas CC cluster members typically attract mononuclear cells. An important characteristic of CK genes from the same cluster is that they code for many ligands that interact with a few receptors. Therefore, CK clusters are single entities based on their overall function. **See also**: Evolution of the Human Immune System

Another important way by which CK variation increased during CK evolution at the genomic level is through the generation of polymorphisms, especially single nucleotide polymorphisms (SNPs). Other types of polymorphisms such as deletion/insertion polymorphisms (DIPs), copy number polymorphisms (CNPs) or those due to repeated elements (as minisatellites and microsatellites) also contributed importantly to the CK genomic variation, but their distribution is more restricted. Additionally, beyond the contribution of polymorphisms to the overall variability in CK superfamily, some CK genes that are polymorphic have alleles that are found to be repeatedly associated with disease. From among the most relevant examples stand out the *CXCL8* alleles associated with asthma, the *CXCL12* alleles associated with HIV and cancer and the *CCL2* and *CCL5* alleles associated with a number of inflammatory conditions (Colobran *et al*., 2007b). CKRs have also a similar situation. Among the polymorphisms in CKRs, the CCR5 32-base pair deletion (CCR5Δ32), common in Caucasian populations but absent in Japanese and black populations from Western and Central Africa, is probably the most clearly related with disease: homozygosity of this CCR5 deletion provides resistance against HIV-1 acquisition (Samson *et al*., 1996). Additionally, the recent long-term control of HIV by CCR5 Δ32/Δ32 stem-cell transplantation demonstrates the critical role CCR5 plays in maintaining HIV-1 infection (Hütter *et al*., 2009). **See also**: Single Nucleotide Polymorphisms in Human Disease and Evolution: Phylogenies and Genealogies

In spite of its broad variability, the CK superfamily has achieved a high degree of robustness, mainly through the redundancy and binding promiscuity of their ligands and receptors. CKs are redundant in their effects on the target cells (CKs are not for one leucocyte population; usually a given leucocyte population has receptors for different CKs), and the interaction with their receptors also has considerable promiscuity (most known receptors interact with multiple ligands and most ligands interact with more than one receptor). Although redundancy among CKs is not universal, there is a considerable degree of functional overlapping among some of them (this also applies to CKRs). The CK–CKR system robustness makes it possible that when one given CK or CKR is defective, there is usually an alternative set of CKs or CKRs that can maintain the main biological functions. Therefore, to preserve the overall function, the CK network is relatively insensitive to alterations of their individual components. This principle has a striking exception: the CXCL12–CXCR4 pair. CXCL12- and CXCR4-knockout mice show embryonic lethality (Tachibana *et al*., 1998), providing a clear example of the wide range of biological effects of CKs, whose functions extend beyond simply attracting leucocytes, taking part in organ development, angiogenesis, angiostasis and immune regulation.

Role of Chemokines in Normal Immune System

Several CKs, the so-called homeostatic CKs, play important roles in development, homeostatic trafficking and homing of various lymphoid subsets rather than in inflammation. Regarding the main homeostatic roles of the CXC CKs, the already mentioned CXCL12 is a CK widely expressed with a broad range of actions because its receptor (CXCR4) is widely distributed: that is, on neutrophils, monocytes, T and B cells, CD34+ hematopoietic progenitor cells, bone marrow derived dendritic cells (DCs), megakariocytes, endothelial cells, neurons, astroglial cells, and so on. Concordantly, it exhibits very different functions ranging from immune cell chemotaxis to neural development. CXCL12 appears to be particularly important for the regulation of homeostatic traffic and distribution of cells in the different compartments and subcompartments of the immune system, for instance directing naïve T-cell traffic through lymph nodes (LNs). CXCL13 is constitutively expressed in lymphoid follicles. It is the unique ligand of CXCR5 and essentially contributes to B-cell homing and proper positioning of these cells within the microanatomic compartments of secondary lymphoid organs and specifically in defining the B- and T-cell areas in the lymphoid follicles. CXCL14 is a CK with unknown receptor selectivity. It is constitutively expressed in epithelial tissues and is selective for DC precursors, indicating a possible function in the maintenance of epithelial DCs. Recent data indicate that CXCL14 expression also inhibits tumour growth and has a potent and broad-spectrum antimicrobial activity (Maerki *et al*., 2009; Ozawa *et al*., 2006).

Focusing on the main homeostatic CC CKs, CCL17 and CCL22, it is to be noted that they are constitutively expressed in the thymus, acting through CCR4. In the thymus, CCR4 is expressed mainly on CD4+ thymocytes in the cortex. Thus, CCL17 and CCL22, which are expressed in the medullary dentritic cells (DCs) and epithelial cells respectively, are involved in guiding the migration of positively selected CD4+ thymocytes from cortex to medulla for negative selection. Although CCL17 and CCL22 are mainly considered homeostatic CKs, they also play important pathophysiological roles in T_H2-type immune responses (Imai *et al*., 1999). CCL19 and CCL21 are the only two ligands of CCR7, and they have a potent chemotactic activity for naïve T- and B cells. They clearly play a pivotal role in naïve lymphocyte homing and traffic within lymphoid tissues (Förster *et al*., 2008). CCL25 is the

only CK binding to CCR9. It is constitutively and selectively expressed at high levels in the thymus and small intestine. CCL25 has been reported to chemoattract DCs, thymocytes and activated macrophages playing a significant role in the recruitment of developing thymocytes to discrete compartments within the thymus and, in general, in T-lymphocyte development. Recently, it has been shown that CCL25 attracts a subset of plasmacytoid DCs expressing CCR9, and these cells constitute a physiologically important tolerogenic DC subset, well positioned in lymphoid tissues to participate in homeostatic immune regulation and able to suppress acute graft-versus-host disease (Hadeiba *et al*., 2008). CCL27 is a skin-associated homeostatic CK that is upregulated upon inflammation. CCL27 mediates the migration of lymphocytes into the skin through binding to the CCR10 and plays an important role in both skin homeostasis and the initiation of skin inflammation (Homey *et al*., 2002).

Role of Chemokines in Disease

CKs have been shown to participate and control the process of a number of acute and chronic inflammatory conditions by promoting the infiltration and activation of inflammatory cells into injured or infected tissues (Gerard and Rollins, 2001).

Infectious diseases

In recent years, a good number of CKs have been shown to exert direct antibacterial activity (Yang *et al*., 2003). The CXCR3 ligands CXCL9, CXCL10 and CXCL11 display antimicrobial properties, especially anti-*E. coli* and antilisterial activities. Therefore, these interferon γ (IFNγ) inducible CKs may directly inactivate microbes before attracting other host defence cells to the area of infection. CXCL14, abundantly expressed in normal human skin, is a highly active antimicrobial peptide against Gram-positive and Gram-negative bacteria and also *Candida albicans*. Constitutive as opposed to inflammation-dependent expression supports the view that CXCL14 fulfills a critical function in the maintenance of skin integrity by keeping potentially infectious microbes at bay. CXCL6 is expressed by epithelial cells on mucosal surfaces prone to infection and is a potent antibacterial CK with activity against several bacterial pathogens relevant in mucosal infections. Similarly CCL28, a mucosa-associated epithelial CK, is also a broad-spectrum antimicrobial protein with a relevant role in mucosal immunity. CCL20 is the only human CK that binds to CCR6 but, interestingly, two cationic antimicrobial peptides involved in mucosal innate immunity, human β-defensin (HBD)-1 and HBD-2, also bind the highly selective CCR6 receptor. Although they share little primary sequence homology, CCL20 and the β-defensins share a high degree of structural homology. CCL20 exhibits a specific spectrum of antimicrobial activity, especially against Gram-negative organisms and participates in pulmonary innate immunity. **See also**: Antimicrobial, Host Defence Peptides and Proteins

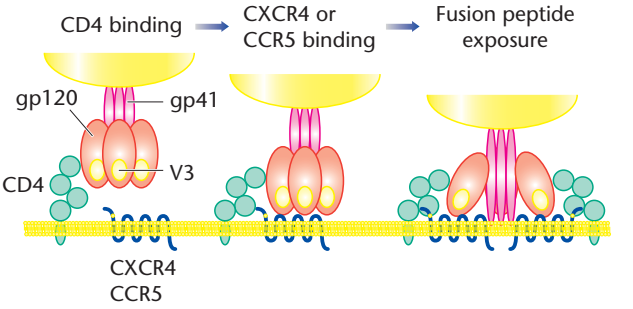

Figure 2 Proposed multistep mechanism of entry of HIV-1 by interaction with CD4 and chemokine receptors.

CKs have a special relevance in life cycle of several viruses, and specifically, in HIV infection. To initiate infection, the HIV-1 external envelope glycoprotein, gp120, sequentially interacts with two cellular receptors: CD4 and a CKR (or coreceptor) mainly CCR5 or CXCR4 (**Figure 2**). The differential use of CCR5 or CXCR4 defines three HIV-1 biological variants (R5, R5X4, X4), the prevalence of which varies along the course of the disease. The evolutionary choice of HIV-1 to exploit CKRs as cellular entry gateways has turned their CK ligands (CCL3, CCL3L, CCL4, CCL4L, CCL5 and CXCL12) into endogenous antiviral factors that variably modulate viral transmission, disease progression and vaccine responses (Lusso, 2006). The proof of principle for the critical role of CKRs in HIV pathogenesis lies in demonstrating that the majority of exposed, uninfected individuals are deficient in cell surface CCR5 expression owing to homozygous carriage of the Δ32 deletion. The importance of this finding reported more than 10 years ago emerges now that CCR5 has been validated as a promising target for HIV prevention strategies. In fact a CCR5 inhibitor (Maraviroc) has been recently approved in the United States as the first in a new class of anti-HIV therapeutic drugs (Kuhmann and Hartley, 2008). **See also**: HIV Life Cycle and Inherited Coreceptors; Human Immunodeficiency Viruses (HIV)

Cancer

In the last years, it has been demonstrated that tumour cells also constitutively express some CKs, which are inducible in normal tissues, as well as some functional CKRs. Compelling evidence has revealed the multifunctional role of the CK network in cancer, including acting as a growth or survival factor, regulating angiogenesis, determining metastatic spread and controlling leucocyte infiltration into tumours to hinder antitumor immune responses (Balkwill, 2004). The most important CK ligand–receptor interaction is the one of the CXCL12 ligand with its exclusive receptor CXCR4; this interaction has a pivotal role in the directional migration of cancer cells during the

metastatic process. CXCR4 is by far the most common CKR overexpressed in human cancer cells. In the preclinical setting, CXCR4 activation by CXCL12 induces migration or survival of brain, colorectal, prostate, renal and ovarian tumour cells, next to melanoma and neuroblastoma. Elevated CXCR4 expression in primitive tumours is associated with LN metastasis in breast, head and neck, colon and oesophageal carcinoma. CCR7 is also expressed by many cancers to mediate metastasis to the LNs. Breast cancer cells have shown chemotaxis and chemoinvasion toward CCL21 gradients, suggesting that CCR7–CCL21 interactions play a role in breast cancer metastasis to LNs (Müller *et al*., 2001). The skin is another frequent metastatic site for cancers, particularly in patients with breast carcinoma and melanoma, and CCR10–CCL27 may contribute to the skin infiltration of malignant cells. Conversely, metastases to the small intestine are rare and mostly occur in melanoma. Recent findings indicate that CCR9 is expressed on human melanoma cells and participates in the enhanced motility of melanoma cells to the small bowel, where CCL25 is constitutively expressed. Therefore, the CCR9–CCL25 axis may explain the high incidence of melanoma metastasis to this specific location. **See also**: Cancer

Asthma and allergy

Asthma is a complex immunological and inflammatory disease characterized by the presence of airway inflammation, airway wall remodelling and bronchial hyperresponsiveness. The inflammatory response characteristically comprises activated T_H2 lymphocytes, eosinophils and activated mast cells. CKs have diverse functions during asthmatic responses, which relate to recruitment, cellular activation/degranulation, differentiation, as well as directly altering the immune response. The identification of CKs in the airways of asthmatics after allergen provocation initially suggested that these molecules would have a significant role in the accumulation of leucocytes. Furthermore, the expression of distinct CK receptors on infiltrating cell populations, especially lymphocytes and eosinophils, provides an attractive opportunity to attenuate the influx of these cell populations.

The most recent findings show that STAT6-mediated CK production in the lung is required for T_H2 lymphocyte and eosinophil homing into the airways in allergic pulmonary inflammation and thus is a potential therapeutic target in asthma. STAT6 drives the production of CCL17, CCL22, CCL11 and CCL24, and these CKs play a crucial role for T_H2 lymphocyte and eosinophil recruitment into the allergic airway (Medoff *et al*., 2009). **See also**: Allergy; Asthma

Autoimmunity

Leucocyte recruitment, accumulation and activation constitute a unifying and enigmatic feature of a variety of autoimmune pathologies. These processes were not well known for decades, but recent scientific descriptions have underscored the importance of specific CKs in the evolution of autoimmunity (Kunkel and Godessart, 2002). **See also**: Autoimmune Disease

Although there are many other examples, rheumatoid arthritis (RA) and multiple sclerosis (MS) are two well-defined ones where the role of CKs in autoimmune diseases has been stated:

- RA is one of the most common human systemic autoimmune disease. This chronic and lifelong autoimmune disorder results in significant pain, disability and high mortality if untreated or inadequately treated; it is characterized by the presence of a mixed inflammatory cell infiltrate into synovium-lined joints. A critical role for TNF is indicated by the success of anti-TNFs and soluble receptor antagonists. TNF induces the expression of many CKs and targeting these downstream mediators of TNF activity is a rational therapeutic goal. Synovial fluid from actively involved joints contains a number of CKs, including CCL2, CCL3, CCL5, CXCL8 and CXCL10. Both synovial-lining cells and infiltrating leucocytes are the source of these CKs. CCR2, CCR5, CXCR2 and CXCR3 have been documented as appearing on infiltrating cells (Szekanecz *et al*., 2003). **See also**: Rheumatoid Arthritis
- MS is a chronic demyelinating disease of the human central nervous system of a still unknown aetiology. The autoimmune inflammatory process is believed to be essential for the development of the disease. Several different studies have shown that CKs and CKRs are involved in the pathogenesis of MS. CKs can mediate the trafficking of immune cells across the blood-brain barrier, and regulate their transfer to lesion sites. CKs were detected in actively demyelinating lesions and were found to be elevated in the cerebrospinal fluid of patients with MS during relapse. Different pairs of CKRs and their ligands seem to play a pathogenic role in MS (e.g. CXCR3 and CXCL9, CXCL10; CCR1 and CCL3, CCL4, CCL5; CCR2 and CCL2; CCR5 and CCL3, CCL4, CCL5). Interfering with the CK system may be an effective therapeutic approach in MS (Szczuciński and Losy, 2007). **See also**: Multiple Sclerosis

Transplantation

Because the CK system plays an essential role in host defence, it is not surprising that CKs and their receptors are involved in rejection of allogeneic transplants (Nelson and Krensky, 2001). CKs could influence at least three aspects of allograft biology. First, restoration of blood flow in the allograft could lead to ischemia-reperfusion injury in which CKs recruit leucocytes; second, host responses to infection during immune suppression involve CKs and third, the inflammatory components of acute and chronic rejection are likely to be controlled by CKs. **See also**: Graft

Rejection: Immunological Suppression; Graft Rejection: Mechanisms; Transplantation

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