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International Union of Pharmacology. XXX. Update on Chemokine Receptor Nomenclature

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***Abstract*——An update of the International Union of Pharmacology nomenclature for chemokines is outlined, defining one new receptor type, CXCR6, and disqualifying the putative receptor, CCR11.**

I. Introduction

In the year 2000, the International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (NC-IUPHAR[2]) approved a nomenclature system for chemokine receptors, the major seven transmembrane (7TM) receptors of the immune system, as recommended by the NC-IUPHAR Chemokine Receptor Subcommittee (Murphy et al., 2000). At that time, the chemokine receptor family consisted of 18 7TM proteins in humans, which were divided into four subfamilies based on chemokine subclass specificity. Two additional molecules, named Duffy and D6, which both have 7TM structure and bind chemokines but lack a known signaling function, were excluded from the nomenclature system, as were a group of functional 7TM chemokine receptors encoded by herpesviruses (Rosenkilde et al., 2001). The nomenclature system is logical, noncontroversial, and universally accepted and used (Table 1). Moreover, it has served as a template for the creation of a chemokine ligand nomenclature system (Zlotnik and Yoshie, 2000). Both systems have facilitated communication among immunologists and pharmacologists as these molecules have become important drug targets in immunologically mediated disease and HIV/acquired immunodeficiency syndrome. Since publication of the NC-IUPHAR document reporting the nomenclature system in the year 2000, one new receptor subtype, CXCR6, has been identified (Matloubian et al., 2000; Wilbanks et al., 2001), and one other subtype, CCR11, has been disqualified (Schweickart et al., 2000, 2001). Duffy and D6 remain as binding sites. The aim of the present article is to provide a brief update on these receptors.

A. CXCR6

CXCR6 was originally cloned as an orphan receptor in 1997 by three independent groups who assigned three different names to it: STRL33 (seven transmembrane receptor-like from clone 33), BONZO, and TYMSTR (T lymphocyte-expressed seven-transmembrane domain receptor) (Alkhatib et al., 1997; Deng et al., 1997; Liao et al., 1997; Loetscher et al., 1997). It was considered most likely to be a chemokine receptor because 1) the gene was located on human chromosome 3p21 within the major chemokine receptor cluster, 2) the sequence was most highly related to chemokine receptors, 3) the RNA was expressed in activated T lymphocytes, and 4) like many other chemokine receptors, it could function as a cell entry factor for HIV. A particularly interesting feature is its ability to support cell entry by simian immunodeficiency virus and both X4 and R5 strains of HIV.

Although many chemokine receptors have multiple shared ligands, CXCR6 binds a distinct ligand, designated CXCL16 (Matloubian et al., 2000; Wilbanks et al., 2001). CXCL16 has a unique hybrid structure, with features heretofore found separately in two other chemokine subclasses. In particular, it has the CXC motif,

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[2] Abbreviations: NC-IUPHAR, International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification; 7TM, seven transmembrane; HIV, human immunodeficiency virus.

TABLE 1
The chemokine receptor family

Name	Receptor Code	SWISSPROT	Main Agonists	Main Functions
CXC subgroup				
CXCR1	2.1:CHK:1:CXC1:	P25024	CXCL8	Neutrophil migration; innate immunity; acute inflammation
CXCR2	2.1:CHK:2:CXC2:	P25025	CXCL1–3; CXCL5–8	Neutrophil migration; innate immunity; acute inflammation; angiogenesis
CXCR3	2.1:CHK:3:CXC3:	P49682	CXCL9–11	T cell migration; adaptive immunity; Th1 inflammation
CXCR4	2.1:CHK:4:CXC4:	P30991	CXCL12	B cell lymphopoiesis; bone marrow myelopoiesis; central nervous system and vascular development; HIV infection
CXCR5	2.1:CHK:5:CXC5:	P32302	CXCL13	B cell trafficking; lymphoid development
CXCR6	2.1:CHK:19:CXC6:	O00574	CXCL16	T cell migration
CC subgroup				
CCR1	2.1:CHK:6:CC1:	P32246	CCL3, CCL5, CCL7, CCL8, CCL13–16, CCL23	T cell and monocyte migration; innate and adaptive immunity; inflammation
CCR2	2.1:CHK:7:CC2:	P41597	CCL2, CCL7, CCL8, CCL13	T cell and monocyte migration; innate and adaptive immunity; Th1 inflammation
CCR3	2.1:CHK:8:CC3:	P51677	CCL5, CCL7; CCL8; CCL11, CCL13; CCL15; CCL24; CCL26	Eosinophil, basophil, and T cell migration; allergic inflammation
CCR4	2.1:CHK:9:CC4:	P51679	CCL17, CCL22	T cell and monocyte migration; allergic inflammation
CCR5	2.1:CHK:10:CC5:	P51681	CCL3; CCL4; CCL5; CCL8, CCL14	T cell and monocyte migration; innate and adaptive immunity; HIV infection
CCR6	2.1:CHK:11:CC6:	P51684	CCL20	Dendritic cell migration
CCR7	2.1:CHK:12:CC7:	P32248	CCL19, CCL21	T cell and dendritic cell migration; lymphoid development; primary immune response
CCR8	2.1:CHK:13:CC8:	P51685	CCL1, CCL4; CCL17	T cell trafficking
CCR9	2.1:CHK:14:CC9:	P51686	CCL25	T cell homing to gut
CCR10	2.1:CHK:15:CC10:	P46092	CCL26–28	T cell homing to skin
CX_3C and C subgroups				
CX_3CR1	2.1:CHK:17:CX3C1	P49238	CX3CL1	T cell and NK cell trafficking and adhesion; innate and adaptive immunity; Th1 inflammation
XCR1	2.1:CHK:18:XC1:	P46094	XCL1–2	T cell trafficking

which defines members of the CXC subclass of chemokines, and a multimodular structure consisting of a transmembrane region and a chemokine domain suspended by a mucin-like stalk previously found only for the CX3C chemokine CX3CL1. The CXCL16 chemokine domain also has characteristics of the CC chemokine subclass. CXCL16 is expressed on the surface of antigen-presenting cells (B cells, macrophages, dendritic cells in lymphoid organ T cell zones) and by cells in the splenic red pulp (Matloubian et al., 2000). Functional CXCL16 is also shed from macrophages (Wilbanks et al., 2001). CXCR6 is expressed preferentially on memory T cells and on activated Th1 and Tc1 effector T cell subsets (Unutmaz et al., 2000; Kim et al., 2001). The exact biological role of CXCL16/CXCR6 is unknown, but reasonable hypotheses for this role include attraction of activated T lymphocyte subsets during inflammation, facilitation of immune responses via cell-cell contact, and guidance of T cell trafficking in the splenic red pulp. CXCL16 is also expressed in the thymic medulla and in some nonlymphoid tissues, suggesting roles in thymocyte development.

B. CCR11

The human homolog of the bovine orphan gustatory receptor PPR1 was originally designated CCR11 based on a report by Schweickart et al. (2000) indicating that, when expressed in a transformed mouse B cell line, it functioned as a chemotactic receptor for the monocyte chemoattractant protein family of chemokines (CCL2, CCL8 and CCL13). However, an independent report, published in the same month, found that this same molecule (which was designated by a different name, CCR10) did not bind these chemokines, but instead bound CCL19, CCL21 and CCL25 with high affinity (Gosling et al., 2000). Nevertheless, no signaling function could be identified. On review, the first group confirmed that CCR11 bound CCL19, CCL21 and CCL25 in two independent cell lines and found that the original transfected cell line used in their study expressed RNA for endogenous mouse CCR2, a known receptor for CCL2, CCL8, and CCL13, but lacked detectable RNA for exogenous CCR11 (Schweickart et al., 2001). They concluded that the original data were not due to CCR11 but

instead may be attributable to up-regulation of endogenous murine CCR2 gene. Since there is now no signaling response ascribed to the receptor, this molecule does not qualify for a CCR# designation and the terms CCR10 or CCR11 should no longer be used to describe it. Moreover, at approximately the same time in 2000, two groups independently identified the receptor for CCL27, which they named CCR10 (Homey et al., 2000; Jarmin et al., 2000). Since this molecule mediates chemotactic signaling, it is a bona fide chemokine receptor and qualifies for this designation.

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