FAST MOVING FRONTS - 2009

September 2009

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Françoise Bachelerie talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Front in the field of Biology & Biochemistry.

Article: The chemokine SDF-1/CXCL12 binds to and signals through the orphan receptor RDC1 in T lymphocytes
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Journal: J BIOL CHEM, 280 (42): 35760-35766 OCT 21 2005
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SW: Why do you think your paper is highly cited?

Chemokines are cytokines that display chemotactic functions and coordinate the homeostatic circulation of leukocytes by binding to G protein-coupled receptors (GPCRs). Dysfunction of the 50 chemokines and 20 receptors identified so far is also implicated in the pathogenesis of many diseases and these proteins consequently constitute very attractive targets for pharmaceutical intervention.

Whereas in many cases, chemokines and their receptors exhibit promiscuous binding properties, the CXC chemokine stromal cell-derived factor 1 (SDF-1/CXCL12) was long thought to exclusively bind to and signal through the CXC chemokine receptor 4 (CXCR4).

This article defines the orphan receptor RDC1 that was originally cloned from a dog cDNA library (Receptor Dog cDNA)—Libert, F *et al.*, "Complete nucleotide sequence of a putative G protein coupled receptor: RDC1" (*Nucleic Acids Res.* 18[7]: 1917, 1990) as CXCR7, a second receptor for CXCL12.

Thereafter, others identified that CXCR7 also bind to the CXC chemokine ITAC—Burns, JM *et al.*, "A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development," (*JEM* 23[9]: 2201-13, 2006). Owning to the pleiotropic activities of CXCL12, this discovery is of marked interest to investigators in many different research areas such as developmental biology, immunology, virology, and cancer.

SW: Would you summarize the significance of your paper in layman's terms?

The orphan receptor RDC1 was primarily believed to act as a receptor for vasointestinal peptide, a possibility later dismissed. On the bases of sequence similarity, chromosomal location, and phylogenetic studies, RDC1 was connected to the CXC chemokine receptors 1, 2, and 4, pointing to CXC chemokines as potential

ligands.

Supporting this hypothesis, RDC1 can serve in experimental systems as co-receptor for certain genetically divergent human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) strains, in particular for the HIV-2 ROD, an X4-tropic viral isolate.

In our paper, we provide evidence that RDC1 also shares with CXCR4 the chemokine CXCL12 as a natural ligand. The interaction of CXCL12 with CXCR7/RDC1 promotes internalization of the receptor and chemotactic signals of CXCR4-negative cells expressing CXCR7. This binding is specific, saturable, and with nanomolar affinity.

Because CXCR7/RDC1 displays a wide expression pattern in mammalian tissues and is also expressed in some tumor cells, primary tumors, and tumor-associated endothelial cells, these data support the view that engagement of CXCL12 to CXCR7 might contribute to physiological but also pathological functions of the chemokine.

"Future research will help define the molecular mechanisms underlying CXCR7 biological activities and particularly the signaling pathways set in motion downstream of the receptor and how they are spatially and temporarily regulated."

SW: How did you become involved in this research and were any particular problems encountered along the way? Where do you see your research leading in the future?

Recent studies indicated that, similarly to the CXCL12 or CXCR4 knockout mice, CXCR7-deficient animals died perinataly and pointed to a dedicated physiological role for CXCR7 in fetal endothelial biology, cardiac development, and B-cell localization.

We and others provide evidence that CXCR7 and CXCR4 can differentially contribute to CXCL12-mediated responses and that CXCR7 also displays the propensity to modulate CXCR4 functions notably by means of CXCL12 scavenging or formation of CXCR7/CXCR4 heterodimers. However, at a mechanistic level, it is not well understood how this GPCR functions.

Future research will help define the molecular mechanisms underlying CXCR7 biological activities and particularly the signaling pathways set in motion downstream of the receptor and how they are spatially and temporarily regulated.

CXCL12 dysfunctions are involved in pathological processes which include the profusion of papillomavirus-induced warts associated with the rare immunodeficiency syndrome myelokathexis (WHIM), and the development of primary epithelial tumors, where the chemokine regulates proliferation and survival of tumor cells, tumor angiogenesis, and metastasis. We anticipate that a more detailed comprehension of the contribution of CXCR7 and CXCR4 in these processes will facilitate their therapeutic manipulation.

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KEYWORDS: PROTEIN-COUPLED RECEPTOR; IMMUNODEFICIENCY-VIRUS CORECEPTOR; VIP RECEPTOR; BONE-MARROW; FACTOR-I; CXCR4; EXPRESSION; CLONING; HIV-1; SDF-1.

PDF

back to top

2009 : September 2009 - Fast Moving Fronts : Françoise Bachelerie

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