Gene name: CX3CR1 **Previous HGNC Symbols for CX3CR1 Gene:** GPR13, CMKBRL1
External Ids for CX3CR1 Gene: HGNC: 2558 NCBI Gene: 1524 Ensembl: ENSG00000168329
OMIM®: 601470 UniProtKB/Swiss-Prot: P49238

NCBI Gene Summary: Fractalkine is a transmembrane protein and chemokine **involved in the adhesion and migration of leukocytes**. The protein encoded by this gene is a receptor for fractalkine. The encoded protein also is a coreceptor for HIV-1, and some variations in this gene lead to increased susceptibility to HIV-1 infection and rapid progression to AIDS. Four transcript variants encoding two different isoforms have been found for this gene.
GeneCards Summary: CX3CR1 (C-X3-C Motif Chemokine Receptor 1) is a Protein Coding gene. Diseases associated with CX3CR1 include Macular Degeneration, Age-Related, 12 and Human Immunodeficiency Virus Type 1. Among its related pathways are Class A/1 (Rhodopsin-like receptors) and GPCR downstream signalling. Gene Ontology (GO) annotations related to this gene include *G protein-coupled receptor activity* and *chemokine receptor activity*. An important paralog of this gene is CCR2.
UniProtKB/Swiss-Prot Summary: Receptor for the C-X3-C chemokine fractalkine (CX3CL1) present on many early leukocyte cells; CX3CR1-CX3CL1 signaling exerts distinct functions in different tissue compartments, such as immune response, inflammation, cell adhesion and chemotaxis (PubMed:12055230, 23125415, 9390561, 9782118). CX3CR1-CX3CL1 signaling mediates cell migratory functions (By similarity). Responsible for the recruitment of natural killer (NK) cells to inflamed tissues (By similarity). Acts as a regulator of inflammation process leading to atherogenesis by mediating macrophage and monocyte recruitment to inflamed atherosclerotic plaques, promoting cell survival (By similarity). Involved in airway inflammation by promoting interleukin 2-producing T helper (Th2) cell survival in inflamed lung (By similarity). Involved in the migration of circulating monocytes to non-inflamed tissues, where they differentiate into macrophages and dendritic cells (By similarity). Acts as a negative regulator of angiogenesis, probably by promoting macrophage chemotaxis (PubMed:14581400, 18971423). Plays a key role in brain microglia by regulating inflammatory response in the central nervous system (CNS) and regulating synapse maturation (By similarity). Required to restrain the microglial inflammatory response in the CNS and the resulting parenchymal damage in response to pathological stimuli (By similarity). Involved in brain development by participating in synaptic pruning, a natural process during which brain microglia eliminates extra synapses during postnatal development (By similarity). Synaptic pruning by microglia is required to promote the maturation of circuit connectivity during brain development (By similarity). Acts as an important regulator of the gut microbiota by controlling immunity to intestinal bacteria and fungi (By similarity). Expressed in lamina propria dendritic cells in the small intestine, which form transepithelial dendrites capable of taking up bacteria in order to provide defense against pathogenic bacteria (By similarity). Required to initiate innate and adaptive immune responses against dissemination of commensal fungi (mycobiota) component of the gut: expressed in mononuclear phagocytes (MNPs) and acts by promoting induction of antifungal IgG antibodies response to confer protection against disseminated C.albicans or C.auris infection (PubMed:29326275). Also acts as a receptor for C-C motif chemokine CCL26, inducing cell chemotaxis (PubMed:20974991). (CX3C1_HUMAN,P49238)
Cellular localization: mainly in plasma membrane.

Full Name: *C-X3-C Motif Chemokine Receptor 1*
Protein Type: G protein-coupled receptor (GPCR)

🔬 Biological Function of CX3CR1

- CX3CR1 encodes a receptor for the chemokine fractalkine (CX3CL1).
- Expression:

    1. Monocytes (especially non-classical/inflammatory monocytes)
    2. Natural Killer (NK) cells
    3. CD8+ T cells
    4. Microglia in the brain
    5. Some subsets of dendritic cells

- Key biological actions:
    1. Cell adhesion:
        - Unlike most chemokine-receptor interactions, fractalkine/CX3CL1 is membrane-bound, allowing firm adhesion of CX3CR1-expressing cells to the endothelium.
    2. Chemotaxis (directed cell migration):
        - Soluble CX3CL1 (after cleavage from membrane) acts as a chemoattractant for CX3CR1+ immune cells.
    3. Immune surveillance and inflammation:
        - Guides monocytes and cytotoxic lymphocytes to sites of infection, tissue damage, or inflammation.

🛠️ How CX3CR1 Works:

- Binds fractalkine (CX3CL1), the only known ligand.
- Activates G protein signaling cascades:
    - Induces chemotaxis, survival signals, and cytokine production.
- Can promote firm arrest on endothelium under shear flow (important for vascular immune surveillance).

🦠 Role of CX3CR1 in Sepsis

In sepsis, CX3CR1 plays dynamic and complex roles depending on disease phase:
Early Sepsis:

- CX3CR1+ monocytes are recruited to sites of infection.
- Help in:
    - Pathogen clearance
    - Debris removal
    - Tissue repair
- CX3CR1 expression on immune cells supports protective inflammation and early host defense.

Severe/Prolonged Sepsis:

- Dysregulation of CX3CR1 signaling may contribute to:
    - Persistent inflammation
    - Endothelial damage (due to excessive monocyte and cytotoxic T cell recruitment)
    - Microvascular injury and organ dysfunction
- Alternatively, loss of CX3CR1+ monocytes can lead to immunosuppression, reducing the ability to clear infections later.

📈 Clinical Relevance of CX3CR1 in Sepsis

Diagnostic Role:

- Changes in CX3CR1 expression on blood monocytes and NK cells are being studied as biomarkers of immune activation or exhaustion in sepsis.

Prognostic Role:

- Reduced CX3CR1 expression on monocytes correlates with:
    - Greater immune dysfunction
    - Higher risk of secondary infections
    - Worse overall outcomes
- High expression on some immune subsets may be protective in early sepsis but harmful if persistent.

Therapeutic Interest:

- Modulating the CX3CR1-CX3CL1 axis could potentially:
    - Enhance immune response when needed.
    - Prevent excessive tissue injury caused by over-infiltration.

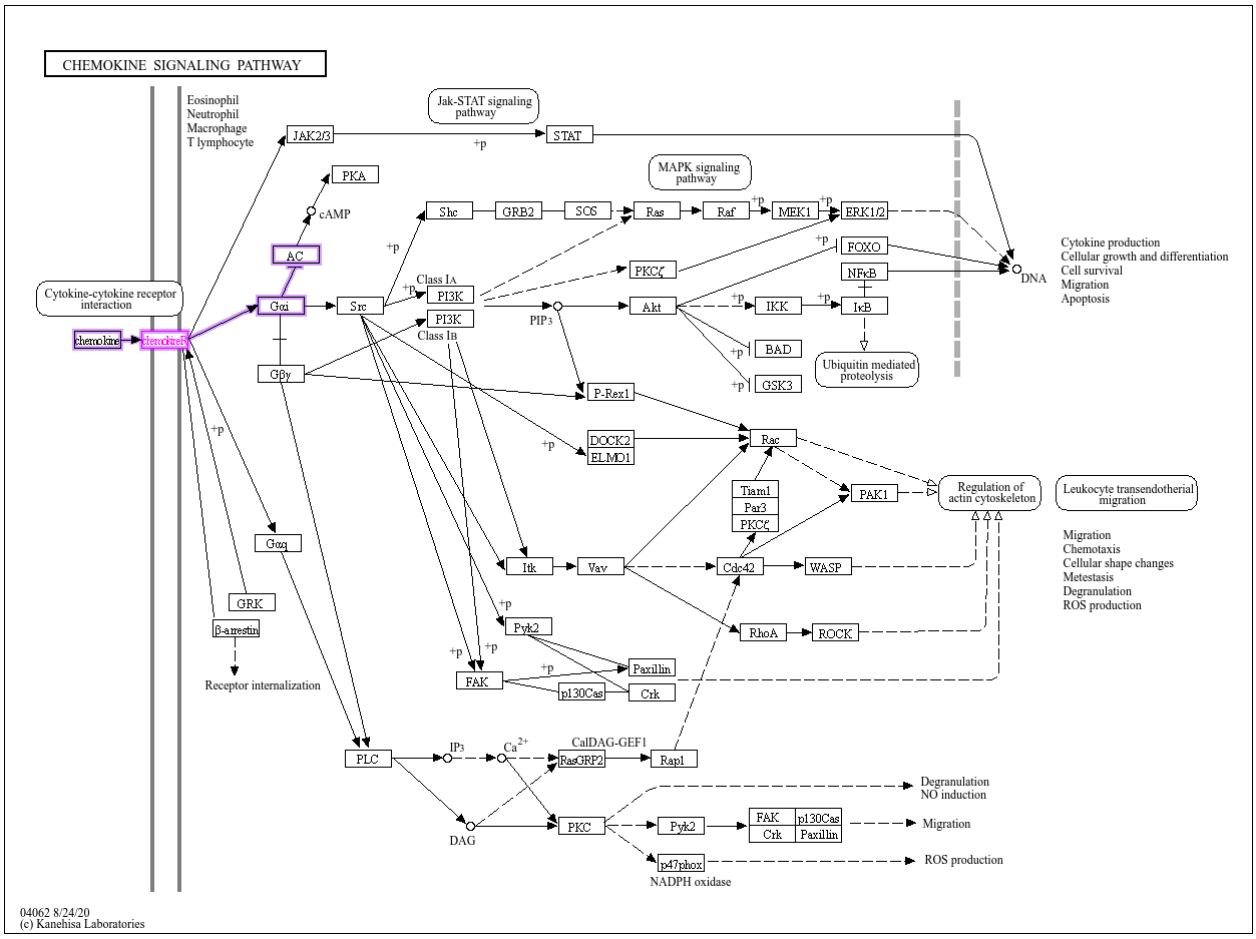
🔬 Pathways Involving CX3CR1

- **Chemokine signaling pathway (KEGG hsa04062)** → regulates migration and adhesion.
- **Cytokine-cytokine receptor interaction (KEGG hsa04060)** → interaction with CX3CL1.

🧪 Supporting Literature

Doi: 10.4049/jimmunol.180.9.6421
Doi: 10.4049/jimmunol.181.6.4208
Doi: 10.1016/j.cyto.2012.08.034

KEGG:



Enrichr-KG: