Protein focus
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Chemokine receptor type 4 (CXCR4): diseases, drugs and druggable target molecules

Related links

InterPro website: CXCR4 family (IPR001277)

PSI nature: CXCR4, featured molecule January 2011

Modern day science attempts to conquer diseases by looking for small druggable target molecules whose interactions are implicated in disease states in the body. Through the years, drug discovery has evolved from a “magic bullet” concept (where a compound is used to target a particular biomolecule) to a search for molecules whose behaviour can be modified to achieve a desired biochemical effect and phenotypic outcome. Obviously, the more disease states a protein is involved in, the more potentially useful it is as a druggable target molecule.

One example of such a molecule is Chemokine Receptor type 4 (CXCR4) which is of increasing interest as a drug target[1]. This molecule is thought to be involved in many disease states including more than 23 types of cancer[2] and several immunodeficiency disorders. The major diseases CXCR4 is involved in are outlined below; with so many links to disease, it is easy to see why CXCR4 has great potential in drug therapy development.

CXCR4 in disease states

CXCR4 and developmental defects

In the normal state, CXCR4 is expressed by cells of the central nervous and immune systems where in the extra-cellular matrix it binds its ligand, stromal development factor 1 (SDF1), also known as CXCL12. This particular interaction is vital in early embryonic development as it is required for the correct formation of vascular, nervous, hematopoietic and cardiac systems[3]. Faults in the CXCR4/CXCL12 interaction during the embryonic stage can lead to several defects including cardiac dysfunction and bone marrow defects. The interaction is equally

important during adult life, where it is vital for the direction of hematopoietic precursor cells in the bone marrow[4].

CXCR4 and cancer

When cancer cells express CXCR4, the receptor is still able to interact with CXCL12 (as in normal cells); this leads to cancerous cell retention in tissues that are rich in CXCL12 and facilitates the growth and spread of tumours. Recent studies have suggested that malignant cells use chemokine receptor/ligand interactions to home in on common metastatic sites like bone marrow and the lungs. In some cancers, over-expression of CXCR4 has been observed to lead to metastasis[5] Several independent studies have shown that cancer cells have higher levels of CXCR4 expression compared to normal cells[6,7]. In breast and lung cancer in particular, over-expression of CXCR4 in patients led to a worse prognosis compared to those who did not over-express the molecule. CXCR4 is the predominant chemokine receptor in ovarian cancer and has also been implicated in many other cancers including prostate, colon, ovary and bladder.

CXCR4 and HIV

The human immunodeficiency virus is a lentivirus whose invasion of human cells can lead to a compromised host immune system known as Acquired Immune Deficiency Syndrome (AIDS). In this condition, a compromised immune system leaves the host vulnerable to opportunistic viral and bacterial infections. CXCR4 and another receptor, CCR5, are used as co-receptors by the HIV virus to facilitate its entry into host T cells. CXCR4 is thought to be the main receptor facilitating viral entry for the HIV strain HIV-2[8].

CXCR4 and WHIM syndrome

WHIM Syndrome is a group of immunodeficiency diseases including warts, Hypogammaglobulinemia, Infections and Myelokathexis syndrome. This syndrome is caused by CXCR4 mutations[9] where the carboxy-terminus is truncated between the 10th and 19th residues, causing the receptor to remain in a permanently activated state. Patients with this rare disorder show increased susceptibility to bacterial and viral infections. Infection by the Human papilloma virus leads to development of warts, while in hypogammaglobulinemia, a reduction in gammaglobulins leads to reduced immunity. In myelokathexis, neutrophils are retained in the bone marrow and, in addition to this, lymphocytes and antibody levels (gammaglobulins) are often deficient. All these states contribute to a compromised immune system.

Structure of human CXCR4

To date, the structure of Human CXCR4 has been solved bound to various ligands. The figure below shows CXCR4 bound to a cyclic peptide binding CVX15

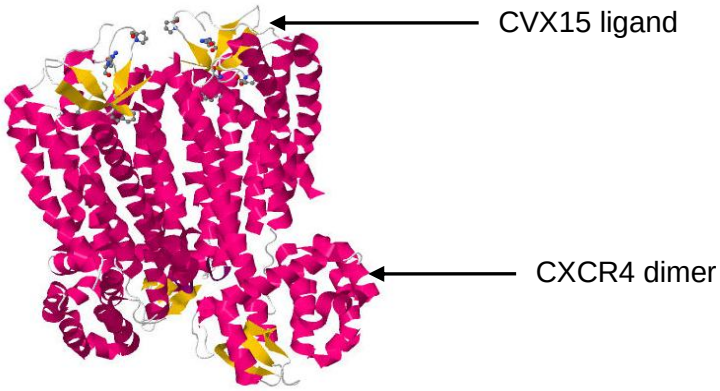


Fig 1. The crystal structure of the CXCR4 chemokine receptor in complex with a cyclic peptide antagonist CVX15. (PDB entry 3Oe0)

The molecule is described as resembling a wine glass wedged in the cell membrane with the ligand binding site as the glass opening[10]. Figure 1 shows two molecules of CXCR4 contributing to the formation of a ligand binding site which is fully occupied by the CVX15 peptide. CXCR4 molecules self-associate and this oligomerisation behaviour is thought to play a role in the regulation of its signalling function[11] Preventing the dimerisation of CXCR4 may therefore provide a means of inhibiting its activity within cells, which could be of great importance in drug development.

What InterPro tells us

In InterPro, information on the CXCR4 family is found in entry IPR001277. Using an example protein Human CXCR4 we can obtain further information about CXCR4.

Family membership

7TM GPCR, rhodopsin-like
- Chemokine receptor
  - CXC chemokine receptor, type 4

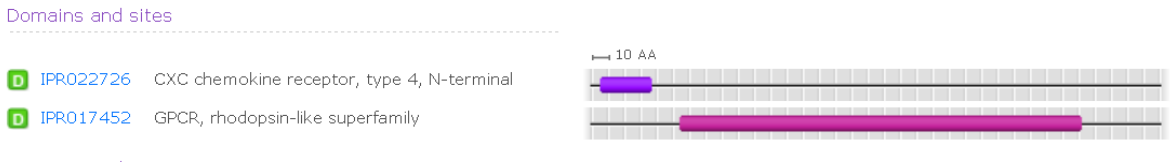
From the protein page in InterPro we can obtain detailed information about the type of family CXCR4 belongs to. CXCR4 is a rhodopsin-like GPCR, which is to date one of the most investigated families in drug development. This could in part be due to the structure, location and function of GPCRs in almost every organ system. A large variety of ligands bind to GPCRs; they have important roles in signaling and the family is characterized by the presence of a 7TM (7-transmembrane) helical domain. Further information on this interesting family can be found in InterPro entry IPR000276.

The chemokines are a subfamily of GPCRs that are primarily involved in facilitating the migration of immune cells. In general, chemokine receptor/ligand pairs direct the migration of leukocytes that express a subset of receptors to areas of tissue damage or inflammation.

The four subclasses of chemokine receptors are: CC, CXC, CX3C and C (XCL1 and XCL2), which are classified based on the spacing of the first two cysteine residues in the protein sequence (where X represents any amino acid)[12].

Domains and sites

In this section, we can discover which domains are found in the protein. InterPro describes the organization of human CXCR4 as consisting of an N-terminal extra-cellular chemokine domain (IPR022726) and an adjacent characteristic set of 7-transmembrane helices (IPR017452).



Mousing over the coloured domain bar gives us further information of the domain position along the protein length: the chemokine receptor type 4 domain lies between residues 6 and 37 at the N-terminus of the human CXCR4 protein. This extracellular domain is responsible for specific chemokine receptor binding and is currently described by a single PFAM signature (PF12109).Upon ligand binding, intracellular signal transduction pathways are activated within the cell via the receptor's intracellular loops and C-terminal tail which extend into the cytosol. From the entry page describing the N-terminal domain in more detail, you can view other proteins from UniProt which are predicted to also contain this domain.

Unintegrated signatures

The unintegrated signatures section shows contributing signatures from member databases that may provide further information on the CXCR4 protein, but have not yet been manually curated.

By clicking on the member database signature, you will be directed to additional information as provided by the individual member database.

Structural features

Transmembrane proteins are very difficult to crystallize and it is only recently that the crystal structure of the full CXCR4 human protein in complex with a ligand has been solved[14]. This complex is also described in full in the Structural Biology Knowledgebase Featured Molecule for January 2011. Prior to this breakthrough, only the N terminal domain of human CXCR4 had been characterized[15]. There is a link to the PDB entry from the structural features section in InterPro.

Structural predictions

When a solved structure does not exist in the PDB for a protein, it can be useful to look at structural predictions instead. For this protein, both SWISS-Model and Modbase have predicted a structure for human CXCR4. The prediction can be viewed by clicking on the identifiers which will take you to the appropriate pages in SWISS-Model and Modbase.

GO term prediction

The Gene Ontology terms provided by InterPro for this protein tell us that it is involved in the G protein coupled receptor pathway and is integral to the membrane. The specific molecular function of CXC chemokine receptor activity is consistent with the structural domains described for the protein, as described above.

Summary

For effective and safe drug development, it is vital to understand the structure and interactions that CXCR4 is involved in, as modifications of the molecule in one area can have a knock on effect on other pathways and interactions. InterPro provides detailed information on the structure and function of this important protein, thereby helping to build our understanding of its pivotal role in biology and medicine.

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