The Concise Guide to Pharmacology 2017/18: Overview

Abstract

The Concise Guide to Pharmacology 2017/18 is the third in this series of biennial publications. This version provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates.

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Searchable database: http://www.guidetopharmacology.org/index.jsp

Introduction


S.P.H. Alexander
Adiponectin receptors

Overview: Adiponectin receptors

Adiponectin (ADIPOQ, Q15848) is a 30kD complement-related protein hormone which is predominantly expressed in adipose tissue. Adiponectin receptors have been categorized into two major types: adiponectin receptors (Adipo1 and Adipo2) and other protein targets.

Adiponectin receptors

- Nomenclature:
  - Adipo1 receptor: ADIPOR1, Q96A54
  - Adipo2 receptor: ADIPOR2, Q86V24

- Rank order of potency: Globular adiponectin (ADIPOQ, Q15848) > adiponectin (ADIPOQ, Q15848) = globular adiponectin (ADIPOQ, Q15848)

- Comments:
  - Cadherin (CDH13, P55290) has also been suggested to be a receptor for adiponectin.

Other protein targets

Family structure

- Adiponectin receptors
  - Other protein targets
    - Family structure
      - Other pattern recognition receptors
        - Notch receptors
          - Pentaxins
            - Serum pentaxins
        - Regulators of G protein Signaling (RGS) proteins
          - R4 family
            - Repulsive guidance molecules
              - Reticulons and associated proteins
                - Ribosomal factors
                  - Sigma receptors
                    - Tubulins
                      - Tumour-associated proteins
                        - WD repeat-containing proteins

- Searchable database:
  - http://www.guidetopharmacology.org
Blood coagulation components

Further reading on Blood coagulation components

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Non-enzymatic BRD containing proteins

Overview: Bromodomain-containing proteins interact with acetylated lysine residues, such as histones, to regulate gene transcription. Loss of function in these enzymes causes cancer cell proliferation and tumor growth.

Other protein targets

Overview: Transferrin (TRF) is a hormone-receptor protein.

Carrier proteins

Other protein targets → Carrier proteins

Overview: Transferrin (TRF) is a hormone-receptor protein.

Further reading on Non-enzymatic BRD containing proteins


Further reading on Carrier proteins


CD molecules

Overview: Cluster of differentiation refers to a group of over 300 cell-surface proteins associated with immunophenotyping. Many members of the group have identified functions as enzymes (e.g., CD73 ecto-5'-nucleotidase) or receptors (e.g., CD41 integrin, alpha 2b subunit). Many CDs are targeted for therapeutic gain using antibodies for the treatment of proliferative disorders. A full listing of all Cluster of Differentiation is not possible in the Guide to PHARMACOLOGY; listed here are selected members of the family targeted for therapeutic gain.

Nomenclature

CD2 CD3e CD20 (membrane-spanning 4-domains, subfamily A, member 1)

HGNC, UniProt

CD2, P06729

CD3E, P07766

MS4A1, P11836

CD33, P20138

CD52, P31358

Common abbreviations

SIGLEC-3

Selective inhibitors

alefacept (Inhibition) [17, 53]

Antibodies

catumaxomab (Binding) [43], muromonab-CD3 (Binding) [25], otezolizumab (pKd 9.9) [47], rituximab (Binding) (pKd 8.5) [75], ibritumomab tiuxetan (Binding), obinutuzumab (Binding) [3, 66], tositumomab (Binding)

lintuzumab (Binding) (pKd ∼10) [10], gemtuzumab ozogamicin (Binding) [7], alemtuzumab (Binding) [24, 79]

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CD80, CD86, cytotoxic T-lymphocyte-associated protein 4 (CD152), programmed cell death 1 (CD279), CD300a

HGNC, UniProt

CD80, P33681
CD86, P42081
CTLA4, P16410
PDCD1, Q15116
CD300A, Q9UGN4

Common abbreviation: C T L A - 4 P D - 1 –

Antibodies: ipilimumab (pKd > 9), [28], tremelimumab (pKd 8.9), [30], pembrolizumab (pKd ∼ 10), [11], nivolumab (pKd 9.1), [28, 38, 40]

Comment: The endogenous ligand for human PD-1 are programmed death ligand 1 (PD-L1 aka CD274, Q9NZQ7) and programmed death ligand 2 (PD-L2; PDCD1LG2). These ligands are cell surface peptides, normally involved in immune system regulation. Expression of PD-1 by cancer cells induces immune tolerance and evasion of immune system attack. Anti-PD-1 monoclonal antibodies are used to induce immune checkpoint blockade as a therapeutic intervention in cancer. Effective anti-PD-1 monoclonal antibodies provide a survival advantage to PD-L1-positive melanoma cancer cells by reducing the expression of PD-L1, which inhibits the function of immune cells that destroy cancer cells. Pembrolizumab was the first anti-PD-1 antibody to be approved by the US FDA.

Further reading on CD molecules

Methyllysine reader proteins

Other protein targets → Chromatin-interacting transcriptional repressors → Methyllysine reader proteins

Overview: Methyllysine reader proteins bind to methylated proteins, such as histones, allowing regulation of gene expression.

Further reading on Methyllysine reader proteins

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Fatty acid-binding proteins

Other protein targets

Overview: Fatty acid-binding proteins are low molecular weight proteins, which are involved in the transport and metabolism of fatty acids and related molecules. They are typically found in plasma, where they bind to fatty acids and transport them to other tissues. These proteins also play a role in regulating the activity of nuclear receptors and metabolic enzymes.

Nomenclature

- Fatty acid binding protein 1 (FABP1)
- Fatty acid binding protein 2 (FABP2)
- Fatty acid binding protein 3 (FABP3)
- Fatty acid binding protein 4 (FABP4)
- Fatty acid binding protein 5 (FABP5)
- Fatty acid binding protein 6 (FABP6)
- Fatty acid binding protein 7 (FABP7)
- Fatty acid binding protein 9 (FABP9)
- Fatty acid binding protein 12 (FABP12)

Inhibitors

- Fenofibrate (pK_i 7.6)
- Fenofibric acid (pK_i 6.5)
- HTS01037 (pK_i 5.1)

Comments

- A broader substrate specificity than other FABPs, binding two fatty acids per protein.
- Crystal structure of the rat FABP2.
- Crystal structure of the human FABP3.
- Able to transport bile acids.
- Crystal structure of the human FABP5.
- In silico modelling suggests that PMP2/FABP8 can bind both fatty acids and cholesterol.

Searchable database: 
http://www.guidetopharmacology.org/index.jsp?reportId=4610822

Full contents of ConciseGuide: 
Nomenclature
retinol binding protein 1
RBP1, P09455
retinol binding protein 2
RBP2, P50120
retinol binding protein 3
RBP3, P10745
retinol binding protein 4
RBP4, P02753
retinol binding protein 5
RBP5, P82980
retinol binding protein 7
RBP7, Q96R05

Rank order of potency – stearic acid > palmitic acid, oleic acid, linoleic acid, α-linolenic acid, arachidonic acid

Inhibitors – A1120 (pIC_{50} 7.8) [86] – –

Nomenclature
retinaldehyde binding protein 1
RLBP1, P12271

CRABP1, P29762

CRABP2, P29373

Rank order of potency
11-cis-retinal, 11-cis-retinol > 9-cis-retinal, 13-cis-retinal, 13-cis-retinol, all-trans-retinal, retinol

Comments:
Although not tested at all FABPs, BMS309403 exhibits high affinity for FABP4 (pIC_{50} 8.8) compared to FABP3 or FABP5 (pIC_{50} < 6.6) [21,81]. HTS01037 is reported to interfere with FABP4 action [30]. Ibuprofen displays some selectivity for FABP4 (pIC_{50} 5.5) relative to FABP3 (pIC_{50} 3.5) and FABP5 (pIC_{50} 3.8) [48]. Fenofibric acid displays some selectivity for FABP5 (pIC_{50} 5.5) relative to FABP3 (pIC_{50} 4.5) and FABP4 (pIC_{50} 4.6) [48]. Multiple pseudogenes for the FABPs have been identified in the human genome.

Further reading on Fatty acid-binding proteins:


Searchable database: http://www.guidetopharmacology.org/index.jsp
Notch receptors

Overview

The canonical Notch signaling pathway has four type I transmembrane Notch receptors (Notch1-4) and five ligands (DLL1, 2 and 3, and Jagged 1-2). Each member of this highly conserved receptor family plays a unique role in cell-fate determination during embryogenesis, differentiation, tissue patterning, proliferation and cell death [2]. As the Notch ligands are also membrane bound, cells have to be in close proximity for receptor-ligand interactions to occur. Cleavage of the intracellular domain (ICD) of activated Notch receptors by \(\gamma\)-secretase is required for downstream signalling and Notch-induced transcriptional modulation [18, 57, 71, 89]. This is why \(\gamma\)-secretase inhibitors can be used to downregulate Notch signalling and explains their anti-cancer action. One such small molecule is RO4929097 [47], although development of this compound has been terminated following an unsuccessful Phase II single agent clinical trial in metastatic colorectal cancer [78].

Aberrant Notch signalling is implicated in a number of human cancers [41, 59, 74, 85]. Pharmaceutical inhibitors of Notch signalling such as demcizumab and tarextumab are being actively investigated as novel anti-cancer agents [64].

Regulators of G protein Signaling (RGS) proteins

Overview

Regulators of G protein signalling (RGS) proteins increase the deactivation rate of G protein signalling pathways through enhancing the GTPase activity of the G protein alpha subunit. Interactions through protein:protein interactions of many RGS proteins have been identified for targets other than heteromeric G proteins. The 20 RGS proteins are commonly divided into our families (R4, R7, R12 and RZ) based on sequence and domain homology. Described here is RGS4 for which a number of pharmacological inhibitors have been described.

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Sigma receptors

**Overview:**

Although termed 'receptors', the evidence for coupling through conventional signalling pathways is lacking. Initially described as a subtype of opioid receptors, there is only a modest pharmacological overlap and no structural convergence with the G protein-coupled receptors; the crystal structure of the sigma1 receptor suggests a trimeric structure forming a single short transmembrane domain traversing the endoplasmic reticulum membrane, with the bulk of the protein facing the cytosol. A wide range of compounds, ranging from psychoactive agents to antihistamines, have been observed to bind to these sites.

**Nomenclature:**

- **Sigma non-opioid intracellular receptor 1**
  - **σ**
  - **HGNC, UniProt**
  - **SIGMAR1**
  - **Q99720**

**Selective agonists**

- **PRE-084**
  - **(+)-SKF 10.047**

**Selective antagonists**

- **NE-100**
  - **BD-1047**
    - **(pIC**<sub>50</sub>**7.4)**

**Labelled ligands**

- **[3H]pentazocine**
  - **[3H]-di-o-tolylguanidine**

**Comments:**

(-)-pentazocine also shows activity at opioid receptors. The sigma2 receptor has recently been reported to be TMEM97 Q5BJF2, a partner of NPC1, the Niemann-Pick C1 protein, a 13TM cholesterol-binding protein.

**Further reading on Sigma receptors**

- **Chu UB et al.** (2016) *Biochemical Pharmacology of the Sigma-1 Receptor.*
  - **Mol Pharmacol**
  - **89**:142-53
  - **[PMID:26560551]**

- **Gris G et al.** (2015) *Sigma-1 receptor and inflammatory pain.*
  - **Inflamm Res**
  - **64**:377-81
  - **[PMID:25902777]**

  - **J Recept Signal Transduct Res**
  - **1-62**
  - **[PMID:26056947]**

- **Su TP et al.** (2016) *The Sigma-1 Receptor as a Pluripotent Modifier in Living Systems.*
  - **Trends Pharmacol Sci**
  - **37**:262-78
  - **[PMID:26869505]**

  - **Biochim Biophys Acta**
  - **1848**:2703-14
  - **[PMID:25173780]**

**Searchable database:**

[http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)
Tubulins

Overview: Tubulins are a family of integral plasma membrane proteins that are commonly associated with microtubules, part of the cytoskeleton. They are exploited for their potential in cancer chemotherapy.

**Nomenclature**

- **Tubulin alpha 1a**
- **Tubulin alpha 4a**
- **Tubulin beta class I**
- **Tubulin beta 3 class III**
- **Tubulin beta 4B class IVb**
- **Tubulin beta 8 class VIII**

**HGNC, UniProt**

- **TUBA1A**
- **Q71U36**
- **TUBA4A**
- **P68366**
- **TUBB**
- **P07437**
- **TUBB3**
- **Q13509**
- **TUBB4B**
- **P68371**
- **TUBB8**
- **Q3ZCM7**

**Inhibitors**

- **vinblastine** (pIC$_{50}$ 9)
- **vincristine**
- **eribulin** (pIC$_{50}$ 8.2)
- **paclitaxel** (pEC$_{50}$ 8.1)
- **colchicine** (pIC$_{50}$ 8)
- **cabazitaxel**, **docetaxel**, **ixabepilone**
- **combretastatin A4** (pIC$_{50}$ 8.2)

**Further reading on Tubulins**

- Gadadhar S et al. (2017) The tubulin code a 8 France: J Cell Sci 130:1347-1353

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

References