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






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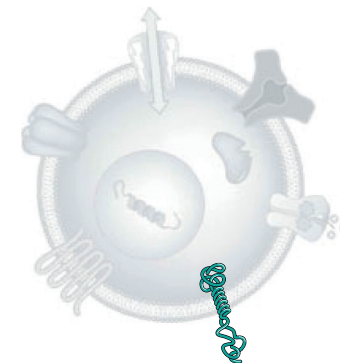
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The Concise Guide to PHARMACOLOGY 2023/24: Catalytic receptors

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Abstract

The Concise Guide to PHARMACOLOGY 2023/24 is the sixth in this series of biennial publications. The Concise Guide provides concise overviews, mostly in tabular format, of the key properties of approximately 1800 drug targets, and nearly 6000 interactions with about 3900 ligands. There is an emphasis on selective pharmacology (where available), plus links to the open access knowledgebase source of drug targets and their ligands (<https://www.guidetopharmacology.org/>), which provides more detailed views of target and ligand properties. Although the Concise Guide constitutes almost 500 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. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.16180>. Catalytic receptors are one of the six major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ion channels, nuclear hormone receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2023, and supersedes data presented in the 2021/22, 2019/20, 2017/18, 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

The authors state that there are no conflicts of interest to disclose.

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Overview: Catalytic receptors are cell-surface proteins, usually dimeric in nature, which encompass ligand binding and functional domains in one polypeptide chain. The ligand binding domain is placed on the extracellular surface of the plasma membrane and separated from the functional domain by a single transmembrane-spanning domain of 20-25 hydrophobic amino acids. The functional domain on the intracellular face of the plasma membrane has catalytic activity, or interacts with particular enzymes, giving the superfamily of receptors its name. Endogenous agonists of the catalytic receptor superfamily are peptides or proteins, the binding of which may induce dimerization of the receptor, which is the functional version of the receptor.

Amongst the catalytic receptors, particular subfamilies may be readily identified dependent on the function of the enzymatic portion of the receptor. The smallest group is the particulate guanylyl cyclases of the natriuretic peptide receptor family. The most widely recognized group is probably the receptor tyrosine kinase (RTK) family, epitomized by the neurotrophin receptor family, where a crucial initial step is the activation of a signalling cascade by autophosphorylation of the receptor on intracellular tyrosine residue(s) catalyzed by enzyme activity intrinsic to the receptor. A third group is the extrinsic protein tyrosine kinase receptors, where the catalytic activity resides in a separate protein from the binding site. Examples of this group include the GDNF and ErbB receptor families, where one, catalytically silent,

member of the heterodimer is activated upon binding the ligand, causing the second member of the heterodimer, lacking ligand binding capacity, to initiate signaling through tyrosine phosphorylation. A fourth group, the receptor threonine/serine kinase (RTSK) family, exemplified by TGF- β and BMP receptors, has intrinsic serine/threonine protein kinase activity in the heterodimeric functional unit. A fifth group is the receptor tyrosine phosphatases (RTP), which appear to lack cognate ligands, but may be triggered by events such as cell:cell contact and have identified roles in the skeletal, hematopoietic and immune systems. A further group of catalytic receptors for the Guide is the integrins, which have roles in cell:cell communication, often associated with signaling in the blood.

Family structure

| | | | | | |
|------|--|------|---|------|--|
| S243 | Cytokine receptor family | S264 | Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase | S273 | Type XII RTKs: TIE family of angiopoietin receptors |
| S243 | IL-2 receptor family | – | Receptor kinases | S273 | Type XIII RTKs: Ephrin receptor family |
| S245 | IL-3 receptor family | – | TK: Tyrosine kinase | S274 | Type XIV RTKs: RET |
| S245 | IL-6 receptor family | S265 | Receptor tyrosine kinases (RTKs) | S274 | Type XV RTKs: RYK |
| S247 | IL-12 receptor family | S265 | Type I RTKs: ErbB (epidermal growth factor) receptor family | S275 | Type XVI RTKs: DDR (collagen receptor) family |
| S248 | Prolactin receptor family | S266 | Type II RTKs: Insulin receptor family | S275 | Type XVII RTKs: ROS receptors |
| S248 | Interferon receptor family | S267 | Type III RTKs: PDGFR, CSFR, Kit, FLT3 receptor family | S276 | Type XVIII RTKs: LMR family |
| S249 | IL-10 receptor family | S268 | Type IV RTKs: VEGF (vascular endothelial growth factor) receptor family | S276 | Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family |
| S250 | Immunoglobulin-like family of IL-1 receptors | S269 | Type V RTKs: FGF (fibroblast growth factor) receptor family | S277 | Type XX RTKs: STYK1 |
| S251 | IL-17 receptor family | S270 | Type VI RTKs: PTK7/CCK4 | – | TKL: Tyrosine kinase-like |
| – | Fc epsilon receptors | S270 | Type VII RTKs: Neurotrophin receptor/Trk family | S278 | Receptor serine/threonine kinase (RSTK) family |
| S252 | GDNF receptor family | S270 | Type VIII RTKs: ROR family | S278 | Type I receptor serine/threonine kinases |
| – | Immune checkpoint catalytic receptors | S271 | Type IX RTKs: MuSK | S279 | Type II receptor serine/threonine kinases |
| S253 | Integrins | S271 | Type X RTKs: HGF (hepatocyte growth factor) receptor family | S280 | Type III receptor serine/threonine kinases |
| S258 | Pattern recognition receptors | S272 | Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family | S280 | RSTK functional heteromers |
| S258 | Toll-like receptor family | | | S282 | Receptor tyrosine phosphatase (RTP) family |
| S259 | NOD-like receptor family | | | S283 | Tumour necrosis factor (TNF) receptor family |
| S261 | RIG-I-like receptor family | | | | |
| S262 | Receptor guanylyl cyclase (RGC) family | | | | |
| S262 | Transmembrane guanylyl cyclases | | | | |

Cytokine receptor family

Catalytic receptors → Cytokine receptor family

Overview: Cytokines are not a clearly defined group of agents, other than having an impact on immune signalling pathways, although many cytokines have effects on other systems, such as in development. A feature of some cytokines, which allows them to be distinguished from hormones, is that they may be produced by “non-secretory” cells, for example, endothelial cells. Within the cytokine receptor family, some subfamilies may be identified, which are described elsewhere in the Guide to PHARMACOLOGY, receptors for the **TNF family**, the **TGF- β family** and the **chemokines**. Within this group of records are described Type I cytokine receptors, typified by interleukin receptors, and Type II cytokine receptors, exemplified by interferon receptors. These receptors possess a conserved extracellular region, known as the cytokine receptor homology domain (CHD), along with a range of other structural modules, including extracellular immunoglobulin (Ig)-like and fibronectin type III (FNIII)-like domains, a transmem-

brane domain, and intracellular homology domains. An unusual feature of this group of agents is the existence of soluble and decoy receptors. These bind cytokines without allowing signalling to occur. A further attribute is the production of endogenous antagonist molecules, which bind to the receptors selectively and prevent signalling. A commonality of these families of receptors is the ligand-induced homo- or hetero-oligomerisation, which results in the recruitment of intracellular protein partners to evoke cellular responses, particularly in inflammatory or haematopoietic signalling. Although not an exclusive signalling pathway, a common feature of the majority of cytokine receptors is activation of the JAK/STAT pathway. This cascade is based around the protein tyrosine kinase activity of the Janus kinases (JAK), which phosphorylate the receptor and thereby facilitate the recruitment of signal transducers and activators of transcription (STATs). The

activated homo- or heterodimeric STATs function principally as transcription factors in the nucleus.

Type I cytokine receptors are characterized by two pairs of conserved cysteines linked via disulfide bonds and a C-terminal WSXWS motif within their CHD. Type I receptors are commonly classified into five groups, based on sequence and structural homology of the receptor and its cytokine ligand, which is potentially more reflective of evolutionary relationships than an earlier scheme based on the use of common signal transducing chains within a receptor complex.

Type II cytokine receptors also have two pairs of conserved cysteines but with a different arrangement to Type I and also lack the WSXWS motif.

IL-2 receptor family

Catalytic receptors → Cytokine receptor family → IL-2 receptor family

Overview: The IL-2 receptor family consists of one or more ligand-selective subunits, and a common γ chain (γ c): *IL2RG*, **P31785**), though IL-4 and IL-7 receptors can form complexes with other receptor chains. Receptors of this family associate with Jak1 and Jak3, primarily activating Stat5, although certain family members can also activate Stat1, Stat3, or Stat6. Ro264550 has been described as a selective IL-2 receptor antagonist, which binds to IL-2 **[231]**.

Complexes

| Nomenclature | Interleukin-2 receptor | Interleukin-4 receptor type I | Interleukin-4 receptor type II | Interleukin-7 receptor |
|------------------------|---|---|---|---|
| Subunits | Interleukin-2 receptor subunit α (Ligand-binding subunit), Interleukin-2 receptor subunit β (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit) | Interleukin-4 receptor subunit α (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit) | Interleukin-4 receptor subunit α (Ligand-binding subunit), Interleukin-13 receptor subunit α1 (Other subunit) | Interleukin-7 receptor subunit α (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit) |
| Endogenous agonists | IL-2 (<i>IL2</i> , P60568) | IL-4 (<i>IL4</i> , P05112) | IL-13 (<i>IL13</i> , P35225), IL-4 (<i>IL4</i> , P05112) | IL-7 (<i>IL7</i> , P13232) |
| Endogenous antagonists | IL-1 receptor antagonist (<i>IL1RN</i> , P18510) | – | – | – |
| Selective antagonists | AF12198 [1] | – | – | – |

| | | | | |
|---------------------|---|--|--|--|
| Nomenclature | Interleukin-9 receptor | Interleukin-15 receptor | Interleukin-21 receptor | Thymic stromal lymphopoietin receptor |
| Subunits | Interleukin 9 receptor (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit) | Interleukin-2 receptor subunit β (Ligand-binding subunit), Interleukin-15 receptor subunit α (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit) | Interleukin 21 receptor (Ligand-binding subunit), Interleukin-2 receptor subunit γ (Other subunit) | Interleukin-7 receptor subunit α (Ligand-binding subunit), Cytokine receptor-like factor 2 (Other subunit) |
| Endogenous agonists | IL-9 (IL9 , P15248) | IL-15 (IL15 , P40933) [274] | IL-21 (IL21 , Q9HBE4) | thymic stromal lymphopoietin (TSLP , Q969D9) |

Subunits

| | | | | | |
|---------------|---|--|---|--|--|
| Nomenclature | Interleukin 13 receptor, $\alpha 2$ | Interleukin-2 receptor subunit α | Interleukin-2 receptor subunit β | Interleukin-2 receptor subunit γ | Interleukin-4 receptor subunit α |
| HGNC, UniProt | IL13RA2 , Q14627 | IL2RA , P01589 | IL2RB , P14784 | IL2RG , P31785 | IL4R , P24394 |
| Antibodies | – | daclizumab (Binding) ($pK_d > 8$) [197], basiliximab (Binding) | – | – | dupilumab (Binding) (pIC_{50} 11.1) [158] |
| Comments | Decoy receptor that binds IL-13 (IL13 , P35225) as a monomer. | – | – | – | – |

| | | | | | | |
|---------------|--|---|---|---|--|---|
| Nomenclature | Interleukin-7 receptor subunit α | Interleukin 9 receptor | Interleukin-13 receptor subunit $\alpha 1$ | Interleukin-15 receptor subunit α | Interleukin 21 receptor | Cytokine receptor-like factor 2 |
| HGNC, UniProt | IL7R , P16871 | IL9R , Q01113 | IL13RA1 , P78552 | IL15RA , Q13261 | IL21R , Q9HBE5 | CRLF2 , Q9HC73 |

Further reading on IL-2 receptor family

- Cagdas D *et al.* (2021) Genomic Spectrum and Phenotypic Heterogeneity of Human IL-21 Receptor Deficiency. *J Clin Immunol* **41**: 1272-90 [[PMID:33929673](#)]
- Leonard WJ *et al.* (2019) The γ_c Family of Cytokines: Basic Biology to Therapeutic Ramifications. *Immunity* **50**: 832-850 [[PMID:30995502](#)]

IL-3 receptor family

Catalytic receptors → Cytokine receptor family → IL-3 receptor family

Overview: The IL-3 receptor family signal through a receptor complex comprising of a ligand-specific α subunit and a common β chain (*CSF2RB*, [P32927](#)), which is associated with Jak2 and signals primarily through Stat5.

Complexes

| | | | |
|-----------------------|---|---|--|
| Nomenclature | Interleukin-3 receptor | Interleukin-5 receptor | Granulocyte macrophage colony-stimulating factor receptor |
| Subunits | Interleukin 3 receptor, α subunit (Ligand-binding subunit), Cytokine receptor common β subunit (Other subunit) | Interleukin 5 receptor, α subunit (Ligand-binding subunit), Cytokine receptor common β subunit (Other subunit) | GM-CSF receptor, α subunit (Ligand-binding subunit), Cytokine receptor common β subunit (Other subunit) |
| Endogenous agonists | IL-3 (<i>IL3</i> , P08700) | IL-5 (<i>IL5</i> , P05113) | G-CSF (<i>CSF3</i> , P09919), GM-CSF (<i>CSF2</i> , P04141) |
| Selective antagonists | – | YM90709 [171] | – |

Subunits

| | | | | |
|---------------------|---|--|--|---|
| Nomenclature | Interleukin 3 receptor, α subunit | Interleukin 5 receptor, α subunit | GM-CSF receptor, α subunit | Cytokine receptor common β subunit |
| HGNC, UniProt | IL3RA , P26951 | IL5RA , Q01344 | CSF2RA , P15509 | CSF2RB , P32927 |
| Endogenous agonists | IL-3 (<i>IL3</i> , P08700) | IL-5 (<i>IL5</i> , P05113) | GM-CSF (<i>CSF2</i> , P04141) | – |
| Antibodies | – | benralizumab (Binding) (pK_d 8.7) [126] | mavrilimumab (Binding) ($pI_{C_{50}}$ 9.9) [35] | – |

IL-6 receptor family

Catalytic receptors → Cytokine receptor family → IL-6 receptor family

Overview: The IL-6 receptor family signal through a ternary receptor complex consisting of the cognate receptor and either the IL-6 signal transducer gp130 (*IL6ST*, [P40189](#)) or the oncostatin M-specific receptor, β subunit (*OSMR*, [Q99650](#)), which then activates the JAK/STAT, Ras/Raf/MAPK and PI 3-kinase/PKB signalling modules. Unusually amongst the cytokine receptors, the CNTF receptor is a glycerophosphatidylinositol-linked protein.

Complexes

| | | | | | | | |
|---------------------|---|---|---|---|--|--|---|
| Nomenclature | Interleukin-6 receptor | Interleukin-11 receptor | Interleukin-27 receptor | Interleukin-31 receptor | Ciliary neurotrophic factor receptor | Leukemia inhibitory factor receptor | Oncostatin-M receptor |
| Subunits | Interleukin-6 receptor, α subunit (Ligand-binding subunit), Interleukin-6 receptor, β subunit (Other subunit) | Interleukin-11 receptor, α subunit (Ligand-binding subunit), Interleukin-6 receptor, β subunit (Other subunit) | Interleukin-6 receptor, β subunit (Other subunit), Interleukin 27 receptor, alpha (Ligand-binding subunit) | Interleukin-31 receptor, α subunit (Ligand-binding subunit), Oncostatin M-specific receptor, β subunit (Other subunit) | Ciliary neurotrophic factor receptor α subunit (Ligand-binding subunit), Leukemia inhibitory factor receptor (Other subunit), Interleukin-6 receptor, β subunit | Leukemia inhibitory factor receptor (Ligand-binding subunit), Interleukin-6 receptor, β subunit (Other subunit) | Oncostatin M-specific receptor, β subunit (Ligand-binding subunit), Interleukin-6 receptor, β subunit (Other subunit) |
| Endogenous agonists | IL-6 (IL6 , P05231) (Murine NIH/3T3 fibroblasts with human IL6R exhibited a single class of binding sites for 125I-labeled recombinant human interleukin-6 (125I-rhIL-6) (Kd = 440 pM, 20,000 receptors per cell).) [200] | IL-11 (IL11 , P20809) | IL-27 (EBI3 IL27 , Q14213 Q8NEV9) | IL-31 (IL31 , Q6EBC2) | CRCF1/CLCF1 heterodimer (CLCF1 CRLF1 , O75462 Q9UBD9), ciliary neurotrophic factor (CNTF , P26441) | LIF (LIF , P15018), cardiotrophin-1 (CTF1 , Q16619), oncostatin M (OSM , P13725) | oncostatin M (OSM , P13725) |
| Agonists | – | oprelvekin [13 , 252] | – | – | – | – | – |
| Antibodies | vobarilizumab (Binding) (pK _d 12.7) [241], satralizumab (Binding) (pK _d 8.9) [107], tocilizumab (Binding) (pK _d 8.6) | – | – | – | – | – | – |

Subunits

| | | |
|-------------------------|--|--|
| Nomenclature | Interleukin-6 receptor, α subunit | Interleukin-6 receptor, β subunit |
| Systematic nomenclature | interleukin 6 receptor | interleukin 6 signal transducer |
| Common abbreviation | IL6R | IL6ST |
| HGNC, UniProt | IL6R , P08887 | IL6ST , P40189 |
| Endogenous agonists | IL-6 (IL6 , P05231) (IL6R) expressed stably in murine NIH/3T3 fibroblasts. exhibited a single class of binding sites for 125I-labeled recombinant human interleukin-6 (125I-rhIL-6) (Kd = 440 pM, 20,000 receptors per cell).) [200] | – |
| Antibodies | sarilumab (Binding) (pK _d 10.6–11.1) [225] | – |

| | | | | | | | |
|---------------------|---|---|---|---|---|---|---|
| Nomenclature | Interleukin-11 receptor, α subunit | Interleukin 27 receptor, alpha | Interleukin-31 receptor, α subunit | Ciliary neurotrophic factor receptor α subunit | Leptin receptor | Leukemia inhibitory factor receptor | Oncostatin M-specific receptor, β subunit |
| HGNC, UniProt | IL11RA , Q14626 | IL27RA , Q6UWB1 | IL31RA , Q8NI17 | CNTFR , P26992 | LEPR , P48357 | LIFR , P42702 | OSMR , Q99650 |
| Endogenous agonists | – | – | – | – | leptin (LEP , P41159) [242] – Mouse | – | – |

Further reading on IL-6 receptor family

- Ho LJ *et al.* (2015) Biological effects of interleukin-6: Clinical applications in autoimmune diseases and cancers. *Biochem Pharmacol* **97**: 16-26 [PMID:26080005]
- Kang S *et al.* (2019) Targeting Interleukin-6 Signaling in Clinic. *Immunity* **50**: 1007-1023 [PMID:30995492]
- Murakami M *et al.* (2019) Pleiotropy and Specificity: Insights from the Interleukin 6 Family of Cytokines. *Immunity* **50**: 812-831 [PMID:30995501]
- Rothaug M *et al.* (2016) The role of interleukin-6 signaling in nervous tissue. *Biochim Biophys Acta* **1863**: 1218-27 [PMID:27016501]

IL-12 receptor family

Catalytic receptors → Cytokine receptor family → IL-12 receptor family

Overview: IL-12 receptors are a subfamily of the IL-6 receptor family. IL12RB1 is shared between receptors for IL-12 and IL-23; the functional agonist at IL-12 receptors is a heterodimer of IL-12A/IL-12B, while that for IL-23 receptors is a heterodimer of IL-12B/IL-23A.

Complexes

| | | |
|---------------------|---|---|
| Nomenclature | Interleukin-12 receptor | Interleukin-23 receptor |
| Subunits | Interleukin-12 receptor, β 1 subunit (Ligand-binding subunit), Interleukin-12 receptor, β 2 subunit (Other subunit) | Interleukin-12 receptor, β 1 subunit (Ligand-binding subunit), Interleukin 23 receptor (Ligand-binding subunit) |
| Endogenous agonists | IL-12 (IL12A IL12B , P29459 P29460) | IL-23 (IL12B IL23A , P29460) |

Subunits

| | | | |
|---------------|--|--|--|
| Nomenclature | Interleukin-12 receptor, β 1 subunit | Interleukin-12 receptor, β 2 subunit | Interleukin 23 receptor |
| HGNC, UniProt | IL12RB1 , P42701 | IL12RB2 , Q99665 | IL23R , Q5VWKS |

Further reading on IL-12 receptor family

Tait Wojno ED *et al.* (2019) The Immunobiology of the Interleukin-12 Family: Room for Discovery. *Immunity* **50**: 851-870 [PMID:30995503]

Prolactin receptor family

Catalytic receptors → Cytokine receptor family → Prolactin receptor family

Overview: Prolactin family receptors form homodimers in the presence of their respective ligands, associate exclusively with Jak2 and signal via Stat5.

| | | | | | |
|---------------------|--|--|---|---|--|
| Nomenclature | Erythropoietin receptor | Granulocyte colony-stimulating factor receptor | Growth hormone receptor | Prolactin receptor | Thrombopoietin receptor |
| HGNC, UniProt | <i>EPOR</i> , P19235 | <i>CSF3R</i> , Q99062 | <i>GHR</i> , P10912 | <i>PRLR</i> , P16471 | <i>MPL</i> , P40238 |
| Endogenous agonists | erythropoietin (<i>EPO</i> , P01588) [57] | G-CSF (<i>CSF3</i> , P09919) | growth hormone 1 (<i>GH1</i> , P01241) [98], growth hormone 2 (<i>GH2</i> , P01242) | prolactin (<i>PRL</i> , P01236) [62] – Mouse, choriomammotropin (<i>CSH1</i> , <i>CSH2</i> , <i>PODML2</i> , <i>PODML3</i>), chorionic somatomammotropin hormone-like 1 (<i>CSHL1</i> , Q14406) | thrombopoietin (<i>THPO</i> , P40225) |
| Agonists | peginesatide [57] | pegfilgrastim | – | – | hetrombopag, romiplostim |
| Selective agonists | – | – | – | – | eltrombopag [155] |
| Antagonists | – | – | pegvisomant [235] | – | – |

Further reading on Prolactin receptor family

Cabrera-Reyes EA *et al.* (2017) Prolactin function and putative expression in the brain. *Endocrine* **57**: 199-213 [PMID:28634745]

Goffin V. (2017) Prolactin receptor targeting in breast and prostate cancers: New insights into an old challenge. *Pharmacol Ther* **179**: 111-126 [PMID:28549597]

Interferon receptor family

Catalytic receptors → Cytokine receptor family → Interferon receptor family

Overview: The interferon receptor family includes receptors for type I (α , β , κ and ω) and type II (γ) interferons. There are at least 13 different genes encoding IFN- α subunits in a cluster on human chromosome 9p22: $\alpha 1$ (*IFNA1*, P01562), $\alpha 2$ (*IFNA2*, P01563), $\alpha 4$ (*IFNA4*, P05014), $\alpha 5$ (*IFNA5*, P01569), $\alpha 6$ (*IFNA6*, P05013), $\alpha 7$ (*IFNA7*, P01567), $\alpha 8$ (*IFNA8*, P32881), $\alpha 10$ (*IFNA10*, P01566), $\alpha 13$ (*IFNA13*, P01562), $\alpha 14$ (*IFNA14*, P01570), $\alpha 16$ (*IFNA16*, P05015), $\alpha 17$ (*IFNA17*, P01571) and $\alpha 21$ (*IFNA21*, P01568).

Complexes

| | | |
|---------------------|---|--|
| Nomenclature | Interferon-α/β receptor | Interferon-γ receptor |
| Subunits | Interferon α/β receptor 2 (Other subunit), interferon α/β receptor 1 (Ligand-binding subunit) | Interferon γ receptor 1 (Ligand-binding subunit), Interferon γ receptor 2 (Other subunit) |
| Endogenous agonists | IFN-α1/13 (IFNA1 IFNA13 , P01562), IFN-α10 (IFNA10 , P01566), IFN-α14 (IFNA14 , P01570), IFN-α16 (IFNA16 , P05015), IFN-α17 (IFNA17 , P01571), IFN-α2 (IFNA2 , P01563), IFN-α21 (IFNA21 , P01568), IFN-α4 (IFNA4 , P05014), IFN-α5 (IFNA5 , P01569), IFN-α6 (IFNA6 , P05013), IFN-α7 (IFNA7 , P01567), IFN-α8 (IFNA8 , P32881), IFN-β (IFNB1 , P01574), IFN-κ (IFNK , Q9POWO), IFN-ω (IFNW1 , P05000) | IFN-γ (IFNG , P01579) |
| Selective agonists | peginterferon alfa-2b [247] | – |

Subunits

| | | | | |
|---------------------|--|---|---|---|
| Nomenclature | interferon α/β receptor 1 | Interferon α/β receptor 2 | Interferon γ receptor 1 | Interferon γ receptor 2 |
| HGNC, UniProt | IFNAR1 , P17181 | IFNAR2 , P48551 | IFNGR1 , P15260 | IFNGR2 , P38484 |
| Endogenous agonists | IFN-β (IFNB1 , P01574) [268] | – | – | – |
| Selective agonists | peginterferon alfa-2b [247] | – | – | – |
| Antibodies | anifrolumab (Binding) (pK _d >10) [28] | – | – | – |

Further reading on Interferon receptor family

Kotenko SV *et al.* (2017) Contribution of type III interferons to antiviral immunity: location, location, location. *J Biol Chem* **292**: 7295-7303 [PMID:28289095]
 Lazear HM *et al.* (2019) Shared and Distinct Functions of Type I and Type III Interferons. *Immunity* **50**: 907-923 [PMID:30995506]

Ng CT *et al.* (2016) Alpha and Beta Type 1 Interferon Signaling: Passage for Diverse Biologic Outcomes. *Cell* **164**: 349-52 [PMID:26824652]
 Schreiber G. (2017) The molecular basis for differential type I interferon signaling. *J Biol Chem* **292**: 7285-7294 [PMID:28289098]

IL-10 receptor family

Catalytic receptors → Cytokine receptor family → IL-10 receptor family

Overview: The IL-10 family of receptors are heterodimeric combinations of family members: IL10RA/IL10RB responds to IL-10; IL20RA/IL20RB responds to IL-19, IL-20 and IL-24; IL22RA1/IL20RB responds to IL-20 and IL-24; IL22RA1/IL10RB responds to IL-22; IFNLR1 (previously known as IL28RA)/IL10RB responds to IFN- λ 1, - λ 2 and - λ 3 (previously known as IL-29, IL-28A and IL-28B respectively).

Complexes

| | | | | | |
|---------------------|--|---|--|--|--|
| Nomenclature | Interleukin-10 receptor | Interleukin-20 receptor | Interleukin-22α1/20β heteromer | Interleukin-22α1/10β heteromer | Interferon-λ receptor 1 |
| Subunits | Interleukin 10 receptor, α subunit (Ligand-binding subunit), Interleukin 10 receptor, β subunit (Other subunit) | Interleukin 20 receptor, α subunit (Ligand-binding subunit), Interleukin 20 receptor, β subunit (Other subunit) | Interleukin 20 receptor, β subunit (Ligand-binding subunit), Interleukin 22 receptor, α1 subunit (Ligand-binding subunit) | Interleukin 10 receptor, β subunit (Ligand-binding subunit), Interleukin 22 receptor, α1 subunit (Ligand-binding subunit) | Interleukin 10 receptor, β subunit (Other subunit), Interferon-λ receptor subunit 1 (Ligand-binding subunit) |
| Endogenous agonists | IL-10 (IL10 , P22301) | IL-19 (IL19 , Q9UHD0), IL-20 (IL20 , Q9NYY1), IL-24 (IL24 , Q13007) | IL-20 (IL20 , Q9NYY1), IL-24 (IL24 , Q13007) | IL-22 (IL22 , Q9GZX6) [224] | IFN-λ1 (IFNL1 , Q8IU54), IFN-λ2 (IFNL2 , Q8IZJ0), IFN-λ3 (IFNL3 , Q8IZI9) |

Subunits

| | | | | | | | |
|---------------|---|--|---|--|---|---|--|
| Nomenclature | Interleukin-22 receptor α2 | Interleukin 10 receptor, α subunit | Interleukin 10 receptor, β subunit | Interleukin 20 receptor, α subunit | Interleukin 20 receptor, β subunit | Interleukin 22 receptor, α1 subunit | Interferon-λ receptor subunit 1 |
| HGNC, UniProt | IL22RA2 , Q969J5 | IL10RA , Q13651 | IL10RB , Q08334 | IL20RA , Q9UHF4 | IL20RB , Q6UXL0 | IL22RA1 , Q8N6P7 | IFNLR1 , Q8IU57 |
| Comments | Soluble decoy receptor that binds IL-22 (IL22 , Q9GZX6) as a monomer. | – | – | – | – | – | – |

Further reading on IL-10 receptor family

Felix J *et al.* (2017) Mechanisms of immunomodulation by mammalian and viral decoy receptors: insights from structures. *Nat Rev Immunol* **17**: 112-129 [[PMID:28028310](#)]

Ouyang W *et al.* (2019) IL-10 Family Cytokines IL-10 and IL-22: from Basic Science to Clinical Translation. *Immunity* **50**: 871-891 [[PMID:30995504](#)]

Immunoglobulin-like family of IL-1 receptors

[Catalytic receptors](#) → [Cytokine receptor family](#) → [Immunoglobulin-like family of IL-1 receptors](#)

Overview: The immunoglobulin-like family of IL-1 receptors are heterodimeric receptors made up of a cognate receptor subunit and an IL-1 receptor accessory protein, [IL1RAP](#) ([Q9NPH3](#)), also known as C3orf13, IL-1RAcP, IL1R3). They are characterised by extracellular immunoglobulin-like domains and an intracellular Toll/Interleukin-1R (TIR) domain.

Complexes

| | | | | | |
|------------------------|--|---|---|--|--|
| Nomenclature | Interleukin-1 receptor, type I | Interleukin-33 receptor | Interleukin-36 receptor | Interleukin-1 receptor, type II | Interleukin-18 receptor |
| Subunits | Interleukin 1 receptor, type I (Ligand-binding subunit), IL-1 receptor accessory protein (Other subunit) | Interleukin-1 receptor-like 1 (Ligand-binding subunit), IL-1 receptor accessory protein (Other subunit) | Interleukin-1 receptor-like 2 (Ligand-binding subunit), IL-1 receptor accessory protein (Other subunit) | IL-1 receptor accessory protein (Other subunit), Interleukin 1 receptor, type II (Ligand-binding subunit) | Interleukin-18 receptor 1 (Ligand-binding subunit), IL-18 receptor accessory protein (Other subunit) |
| Inhibitors | anakinra (pK _d 7.8) [51] | – | – | – | – |
| Endogenous agonists | IL-1 α (<i>IL1A</i> , P01583), IL-1 β (<i>IL1B</i> , P01584) | IL-33 (<i>IL33</i> , O95760) | IL-36 α (<i>IL36A</i> , Q9UHA7), IL-36 β (<i>IL36B</i> , Q9NZH7), IL-36 γ (<i>IL36G</i> , Q9NZH8) | – | IL-18 (<i>IL18</i> , Q14116), IL-37 (<i>IL37</i> , Q9NZH6) |
| Endogenous antagonists | IL-1 receptor antagonist (<i>IL1RN</i> , P18510) | – | IL-36 receptor antagonist (<i>IL36RN</i> , Q9UBH0) | – | – |
| Selective antagonists | AF12198 [1] | – | – | – | – |
| Comments | – | – | IL-36 receptor antagonist (<i>IL36RN</i> , Q9UBH0) is a highly specific antagonist of the response to IL-36 γ (<i>IL36G</i> , Q9NZH8). | Decoy receptor that binds IL-1 α (<i>IL1A</i> , P01583), IL-1 β (<i>IL1B</i> , P01584) and IL-1 receptor antagonist (<i>IL1RN</i> , P18510). | – |

Subunits

| | | | | | |
|---------------|--------------------------------|---------------------------------|-------------------------------|-------------------------------|---------------------------|
| Nomenclature | Interleukin 1 receptor, type I | Interleukin 1 receptor, type II | Interleukin-1 receptor-like 1 | Interleukin-1 receptor-like 2 | Interleukin-18 receptor 1 |
| HGNC, UniProt | <i>IL1R1</i> , P14778 | <i>IL1R2</i> , P27930 | <i>IL1RL1</i> , Q01638 | <i>IL1RL2</i> , Q9HB29 | <i>IL18R1</i> , Q13478 |

Further reading on Immunoglobulin-like family of IL-1 receptors

Afonina IS *et al.* (2015) Proteolytic Processing of Interleukin-1 Family Cytokines: Variations on a Common Theme. *Immunity* **42**: 991-1004 [PMID:26084020]

Mantovani A *et al.* (2019) Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity. *Immunity* **50**: 778-795 [PMID:30995499]

IL-17 receptor family

Catalytic receptors → Cytokine receptor family → IL-17 receptor family

Overview: The IL17 cytokine family consists of six ligands (IL-17A-F), which signal through five receptors (IL-17RA-E).

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16180/full>

IL-17 receptor family S251

Complexes

| | | | |
|---------------------|---|--|---|
| Nomenclature | Interleukin-17 receptor | Interleukin-25 receptor | Interleukin-17C receptor |
| Subunits | Interleukin 17 receptor A (Ligand-binding subunit), interleukin 17 receptor C (Other subunit) | Interleukin 17 receptor A (Other subunit), Interleukin 17 receptor B (Ligand-binding subunit) | Interleukin 17 receptor A (Other subunit), Interleukin 17 receptor E (Ligand-binding subunit) |
| Endogenous agonists | IL-17A (IL17A , Q16552), IL-17A/IL-17F (IL17A IL17F , Q16552 Q96PD4), IL-17F (IL17F , Q96PD4) | IL-17B (IL17B , Q9UHF5), IL-25 (IL25 , Q9H293) | IL-17C (IL17C , Q9P0M4) |

Subunits

| | | | | | |
|---------------|--|---|---|--|---|
| Nomenclature | Interleukin 17 receptor A | Interleukin 17 receptor B | interleukin 17 receptor C | Interleukin-17 receptor D | Interleukin 17 receptor E |
| HGNC, UniProt | IL17RA , Q96F46 | IL17RB , Q9NRM6 | IL17RC , Q8NAC3 | IL17RD , Q8NFM7 | IL17RE , Q8NFR9 |
| Antibodies | brodalumab (Binding) (pK _d 9.2) [234] | – | – | – | – |
| Comments | – | – | – | The endogenous agonist for this receptor is unknown. | – |

Further reading on IL-17 receptor family

- Beringer A *et al.* (2016) IL-17 in Chronic Inflammation: From Discovery to Targeting. *Trends Mol Med* **22**: 230-241 [[PMID:26837266](#)]
- Lubberts E. (2015) The IL-23-IL-17 axis in inflammatory arthritis. *Nat Rev Rheumatol* **11**: 415-29 [[PMID:25907700](#)]
- McGeachy MJ *et al.* (2019) The IL-17 Family of Cytokines in Health and Disease. *Immunity* **50**: 892-906 [[PMID:30995505](#)]

GDNF receptor family

[Catalytic receptors](#) → [GDNF receptor family](#)

Overview: GDNF family receptors (provisional nomenclature) are extrinsic tyrosine kinase receptors. Ligand binding to the extracellular domain of the glycosylphosphatidylinositol-linked cell-surface receptors (tabulated below) activates a transmembrane tyrosine kinase enzyme, [RET](#) (see [Receptor Tyrosine Kinases](#)). The endogenous ligands are typically dimeric, linked through disulphide bridges: glial cell-derived neurotrophic factor [GDNF](#) ([GDNF](#), [P39905](#)) (211 aa); [neurturin](#) ([NRTN](#), [Q99748](#)) (197 aa); [artemin](#) ([ARTN](#), [Q5T4W7](#)) (237 aa) and [persephin](#) ([PSPN](#), [O60542](#)) (PSPN, 156 aa).

| Nomenclature | GDNF family receptor $\alpha 1$ | GDNF family receptor $\alpha 2$ | GDNF family receptor $\alpha 3$ | GDNF family receptor $\alpha 4$ |
|---------------------|--|--|---|---|
| Common abbreviation | GFR $\alpha 1$ | GFR $\alpha 2$ | GFR $\alpha 3$ | GFR $\alpha 4$ |
| HGNC, UniProt | GFRA1 , P56159 | GFRA2 , O00451 | GFRA3 , O60609 | GFRA4 , Q9GZZ7 |
| Potency order | GDNF (GDNF , P39905) > neurturin (NRTN , Q99748) > artemin (ARTN , Q5T4W7) | neurturin (NRTN , Q99748) > GDNF (GDNF , P39905) | artemin (ARTN , Q5T4W7) | persephin (PSPN , O60542) |
| Labelled ligands | [¹²⁵ I]GDNF (rat) (pK _d 10.2–11.5) [124 , 236] | – | – | – |

Comments: Inhibitors of other receptor tyrosine kinases, such as [semaxanib](#), which inhibits VEGF receptor function, may also inhibit Ret function [[169](#)]. Mutations of RET and GDNF genes may be involved in Hirschsprung's disease, which is characterized by the absence of intramural ganglion cells in the hindgut, often resulting in intestinal obstruction.

Further reading on GDNF receptor family

Allen SJ *et al.* (2013) GDNF, NGF and BDNF as therapeutic options for neurodegeneration. *Pharmacol Ther* **138**: 155-75 [[PMID:23348013](#)]

Ibáñez CF *et al.* (2017) Biology of GDNF and its receptors - Relevance for disorders of the central nervous system. *Neurobiol Dis* **97**: 80-89 [[PMID:26829643](#)]

Merighi A. (2016) Targeting the glial-derived neurotrophic factor and related molecules for controlling normal and pathologic pain. *Expert Opin Ther Targets* **20**: 193-208 [[PMID:26863504](#)]

Integrins

Catalytic receptors → Integrins

Overview: Integrins are unusual signalling proteins that function to signal both from the extracellular environment into the cell, but also from the cytoplasm to the external of the cell. The intracellular signalling cascades associated with integrin activation focus on protein kinase activities, such as focal adhesion kinase and Src. Based on this association between extracellular signals and intracellular protein kinase activity, we have chosen to include integrins in the 'Catalytic receptors' section of the database until more stringent criteria from NC-IUPHAR allows precise definition of their classification.

Integrins are heterodimeric entities, composed of α and β subunits, each ITM proteins, which bind components of the extracellular matrix or counter-receptors expressed on other cells. One class of integrin contains an inserted domain (I) in its α subunit, and if present (in $\alpha 1$, $\alpha 2$, $\alpha 10$, $\alpha 11$, αD , αE , αL , αM and αX), this I domain contains the ligand binding site. All β subunits possess a similar I-like domain, which has the capacity to bind ligand, often recognising the RGD motif. The presence of an α subunit I domain precludes ligand binding through the β subunit. Integrins provide a link between ligand and the actin cytoskeleton (through typically short intracellular domains). Integrins bind several divalent cations, including a Mg²⁺ ion in the I or I-like domain that is essential for ligand binding. Other cation binding

sites may regulate integrin activity or stabilise the 3D structure. Integrins regulate the activity of particular protein kinases, including focal adhesion kinase and integrin-linked kinase. Cellular activation regulates integrin ligand affinity *via* inside-out signalling and ligand binding to integrins can regulate cellular activity *via* outside-in signalling.

Several drugs that target integrins are in clinical use including: (1) [abciximab](#) ($\alpha IIb\beta 3$) for short term prevention of coronary thrombosis, (2) [vedolizumab](#) ($\alpha 4\beta 7$) to reduce gastrointestinal inflammation, and (3) [natalizumab](#) ($\alpha 4\beta 1$) in some cases of severe multiple sclerosis.

Complexes

| | | | | |
|--------------|---|--|---|--|
| Nomenclature | integrin $\alpha 1\beta 1$ | integrin $\alpha 2\beta 1$ | integrin $\alpha 11\beta 3$ | integrin $\alpha 4\beta 1$ |
| Subunits | integrin, alpha 1 subunit, integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) | integrin, alpha 2 subunit (CD49B, alpha 2 subunit of VLA-2 receptor), integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) | integrin, alpha 11b subunit (platelet glycoprotein 11b of 11b/IIIa complex, antigen CD41), integrin, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61) | integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor), integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) |
| Ligands | collagen, laminin | collagen, laminin, thrombospondin | fibronogen (<i>FGA FGB FGG</i> , P02671 P02675 P02679), fibronectin (<i>FN1</i> , P02751), von Willebrand factor (<i>VWF</i> , P04275), vitronectin (<i>VTN</i> , P04004), thrombospondin | fibronectin (<i>FN1</i> , P02751), vascular cell adhesion protein 1 (<i>VCAM1</i> , P19320), osteopontin (<i>SPP1</i> , P10451), thrombospondin |
| Inhibitors | obtustatin (pIC ₅₀ 9.1) [154] | TC115 (pIC ₅₀ 7.9) [166], BTT-3033 [178] | tirofiban (pIC ₅₀ 9.4) [237], G4120 (pK _i 8.4) [161, 263], GR 144053 (pIC ₅₀ 7.4) [53], eptifibatide (pIC ₅₀ 6.2–6.8) [206] | BIO1211 (pIC ₅₀ 8.3–9) [141], carotegrast (pIC ₅₀ 7.2) [151], TCS2314, firategrast [81], valategrast [99], zaurategrast [256] |
| Antibodies | – | – | abciximab (Binding) [37] | natalizumab (Inhibition) [179] |
| Comments | – | – | – | LDV-FITC is used as a probe at this receptor. |

| | | | | |
|--------------|--|---|---|--|
| Nomenclature | integrin $\alpha 4\beta 7$ | integrin $\alpha 5\beta 1$ | integrin $\alpha 6\beta 1$ | integrin $\alpha 10\beta 1$ |
| Subunits | integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor), integrin, beta 7 subunit | integrin, alpha 5 subunit (fibronectin receptor, alpha polypeptide), integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) | integrin, alpha 6 subunit, integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) | integrin, alpha 10 subunit, integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) |
| Ligands | – | fibronectin (<i>FN1</i> , P02751) | laminin | collagen |
| Inhibitors | firategrast [81], valategrast [99], zaurategrast [256] | – | – | – |
| Antibodies | vedolizumab (Antagonist) (pIC ₅₀ 8.3) [195] | volociximab (Binding) (pK _d 9.5) [14, 15] | – | – |

| | | | | |
|--------------|--|--|---|--|
| Nomenclature | integrin $\alpha 11\beta 1$ | integrin $\alpha E\beta 7$ | integrin $\alpha L\beta 2$ | integrin $\alpha V\beta 3$ |
| Subunits | integrin, alpha 11 subunit, integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) | integrin, alpha E subunit (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide), integrin, beta 7 subunit | integrin, alpha L subunit (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide), integrin, beta 2 subunit (complement component 3 receptor 3 and 4 subunit) | integrin, alpha V subunit, integrin, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61) |
| Ligands | collagen | E-cadherin | ICAM-1 (<i>ICAM1</i> , P05362), ICAM-2 (<i>ICAM2</i> , P13598) | vitronectin (<i>VTN</i> , P04004), fibronectin (<i>FN1</i> , P02751), fibrinogen (<i>FGA FGB FGG</i> , P02671 P02675 P02679), osteopontin (<i>SPP1</i> , P10451), von Willebrand factor (<i>VWF</i> , P04275), thrombospondin, tenascin |
| Activators | – | – | – | TP508 (pK _d 7.9) [48] |
| Inhibitors | – | – | A286982 (pIC ₅₀ 7.4–7.5) [144] | – |
| Antagonists | – | – | – | echistatin (pIC ₅₀ 11.7) [135], P11 (pIC ₅₀ 11.6) [135], CWHM12 (pIC ₅₀ 9.1) [97], cilengitide (pIC ₅₀ 8.5) [78], GSK2603566A (pIC ₅₀ 8.4) [4] |
| Antibodies | – | etrolizumab (Inhibition) [223] | – | etaracizumab (Binding) (pK _d 6.3) [258] |

Subunits

| | | | | | | |
|---------------|----------------------------------|---|--|---|--|--|
| Nomenclature | integrin, alpha 1 subunit | integrin, alpha 2 subunit (CD49B, alpha 2 subunit of VLA-2 receptor) | integrin, alpha IIb subunit (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41) | integrin, alpha 3 subunit (antigen CD49C, alpha 3 subunit of VLA-3 receptor) | integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor) | integrin, alpha 5 subunit (fibronectin receptor, alpha polypeptide) |
| HGNC, UniProt | <i>ITGA1</i> , P56199 | <i>ITGA2</i> , P17301 | <i>ITGA2B</i> , P08514 | <i>ITGA3</i> , P26006 | <i>ITGA4</i> , P13612 | <i>ITGA5</i> , P08648 |
| Ligands | – | – | – | peptide ligand 2 (Binding) (pIC ₅₀ 7.2) [262] | – | – |
| Inhibitors | – | – | – | – | carotegrast, carotegrast methyl [65], fimategrast [81], valategrast [99], zaurategrast [256] | – |
| Antibodies | – | – | – | – | abrilumab (Inhibition) (pK _d 11.1) [188], natalizumab (Inhibition) [179] | volociximab (Binding) (pK _d 9.5) [14, 15] |

| | | | | | | | |
|--------------------|--------------------------------|---|--------------------------------|---|---------------------------------|---------------------------------|--------------------------------|
| Nomenclature | integrin, alpha 6 subunit | integrin, alpha 7 subunit | integrin, alpha 8 subunit | integrin, alpha 9 subunit | integrin, alpha 10 subunit | integrin, alpha 11 subunit | integrin, alpha D subunit |
| HGNC, UniProt | ITGA6 , P23229 | ITGA7 , Q13683 | ITGA8 , P53708 | ITGA9 , Q13797 | ITGA10 , O75578 | ITGA11 , Q9UKX5 | ITGAD , Q13349 |
| Endogenous ligands | – | – | – | SVEP1 (SVEP1 , Q4LDES) (Binding) [204] | – | – | – |
| Antagonists | – | – | – | BOP (pK _d 11.5) [192] | – | – | – |
| Antibodies | – | etrolizumab (Binding) [223] | – | – | – | – | – |

| | | | | | | |
|---------------|--|---|---|---|---|--|
| Nomenclature | integrin, alpha E subunit (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide) | integrin, alpha L subunit (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide) | integrin, alpha M subunit (complement component 3 receptor 3 subunit) | integrin, alpha V subunit | integrin, alpha X subunit (complement component 3 receptor 4 subunit) | integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) |
| HGNC, UniProt | ITGAE , P38570 | ITGAL , P20701 | ITGAM , P11215 | ITGAV , P06756 | ITGAX , P20702 | ITGB1 , P05556 |
| Antagonists | – | lifitegrast (Inhibition) [20, 270] | – | MK-0429 (pIC ₅₀ 7.1) [105] | – | – |
| Antibodies | – | efalizumab (Binding) (pK _d 11.4) [111] | – | – | – | – |

| | | | | | | | |
|----------------------|--|---|--------------------------------|---|--|--------------------------------|---|
| Nomenclature | integrin, beta 2 subunit (complement component 3 receptor 3 and 4 subunit) | integrin, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61) | integrin, beta 4 subunit | integrin, beta 5 subunit | integrin, beta 6 subunit | integrin, beta 7 subunit | integrin, beta 8 subunit |
| HGNC, UniProt | ITGB2 , P05107 | ITGB3 , P05106 | ITGB4 , P16144 | ITGB5 , P18084 | ITGB6 , P18564 | ITGB7 , P26010 | ITGB8 , P26012 |
| Inhibitors | – | compound 7 (pK _i 6.8) [10] | – | compound 7 (pK _i 7.3) [10] | – | – | compound 7 (pK _i 7.6) [10] |
| Selective inhibitors | – | – | – | – | compound 7 (pK _i 10) [10] | – | – |

Comments: Integrin ligands

Collagen is the most abundant protein in metazoa, rich in glycine and proline residues, made up of cross-linked triple helical structures, generated primarily by fibroblasts. Extensive post-translational processing is conducted by prolyl and lysyl hydroxylases, as well as transglutaminases. Over 40 genes for collagen- α subunits have been identified in the human genome. The collagen-binding integrins $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$ and $\alpha 11\beta 1$ recognise a range of triple-helical peptide motifs including GFOGER (O = hydroxyproline), a synthetic peptide derived from the primary sequence of collagen I (**COL1A1** (*COL1A1*, **P02452**)) and collagen II (**COL2A1** (*COL2A1*, **P02458**)).

Laminin is an extracellular glycoprotein composed of α , β and γ chains, for which five, four and three genes, respectively, are identified in the human genome. It binds to $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 7\beta 1$ and $\alpha 6\beta 4$ integrins¹⁰.

Further reading on Integrins

- Clemetson KJ. (2017) The origins of major platelet receptor nomenclature. *Platelets* **28**: 40-42 [PMID:27715379]
- Emsley J *et al.* (2000) Structural basis of collagen recognition by integrin $\alpha 2\beta 1$. *Cell* **101**: 47-56 [PMID:10778855]
- Hamidi H *et al.* (2016) The complexity of integrins in cancer and new scopes for therapeutic targeting. *Br J Cancer* **115**: 1017-1023 [PMID:27685444]
- Horton ER *et al.* (2016) The integrin adhesome network at a glance. *J Cell Sci* **129**: 4159-4163 [PMID:27799358]

fibrinogen (**FGA** **FGB** **FGG**, **P02671** **P02675** **P02679**) is a glycosylated hexamer composed of two α (**FGA**, **P02671**), two β (**FGB**, **P02675**) and two γ (**FGG**, **P02679**) subunits, linked by disulphide bridges. It is found in plasma and alpha granules of platelets. It forms cross-links between activated platelets mediating aggregation by binding $\alpha \text{IIb}\beta 3$; proteolysis by thrombin cleaves short peptides termed fibrinopeptides to generate fibrin, which polymerises as part of the blood coagulation cascade.

fibronectin (**FNI**, **P02751**) is a disulphide-linked homodimer found as two major forms; a soluble dimeric form found in the plasma and a tissue version that is polymeric, which is secreted into the extracellular matrix by fibroblasts. Splice variation of the gene product (**FNI**, **P02751**) generates multiple isoforms.

vitronectin (**VTN**, **P04004**) is a serum glycoprotein and extracellular matrix protein which is found either as a monomer or, following proteolysis, a disulphide-linked dimer.

osteopontin (**SPPI**, **P10451**) forms an integral part of the mineralized matrix in bone, where it undergoes extensive post-translational processing, including proteolysis and phosphorylation.

von Willebrand factor (**VWF**, **P04275**) is a glycoprotein synthesised in vascular endothelial cells as a disulphide-linked homodimer, but multimerises further in plasma and is deposited on vessel wall collagen as a high molecular weight multimer. It is responsible for capturing platelets under arterial shear flow (*via* GPIb) and in thrombus propagation (*via* integrin $\alpha \text{IIb}\beta$)

- Ley K *et al.* (2016) Integrin-based therapeutics: biological basis, clinical use and new drugs. *Nat Rev Drug Discov* **15**: 173-83 [PMID:26822833]
- Manninen A *et al.* (2017) A proteomics view on integrin-mediated adhesions. *Proteomics* **17**: [PMID:27723259]
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Pattern recognition receptors

Catalytic receptors → Pattern recognition receptors

Overview: Pattern Recognition Receptors (PRRs, [228]) (nomenclature as agreed by **NC-IUPHAR sub-committee on Pattern Recognition Receptors**, [24]) participate in the innate immune response to microbial agents, the stimulation of which leads to activation of intracellular enzymes and regulation of gene transcription. PRRs express multiple leucine-rich regions to bind a range of microbially-derived ligands, termed PAMPs or pathogen-associated molecular patterns or endogenous ligands, termed DAMPS or damage-associated molecular patterns. These include peptides, carbohydrates, peptidoglycans, lipoproteins, lipopolysaccharides, and nucleic acids. PRRs include both cell-surface and intracellular proteins. PRRs may be divided into signalling-associated members, identified here, and endocytic members, the function of which appears to be to recognise

particular microbial motifs for subsequent cell attachment, internalisation and destruction. Some are involved in inflammasome formation, and modulation of IL-1 β cleavage and secretion, and others in the initiation of the type I interferon response.

PRRs included in the Guide To PHARMACOLOGY are:

Catalytic PRRs (see links below this overview)

Toll-like receptors (TLRs)

Nucleotide-binding oligomerization domain, leucine-rich repeat containing receptors (NLRs, also known as NOD (Nucleotide oligomerisation domain)-like receptors)

RIG-I-like receptors (RLRs)

Caspase 4 and caspase 5

Non-catalytic PRRs

Absent in melanoma (AIM)-like receptors (ALRs)

C-type lectin-like receptors (CLRs)

Other pattern recognition receptors

Advanced glycosylation end-product specific receptor (RAGE)

Toll-like receptor family

Catalytic receptors → Pattern recognition receptors → Toll-like receptor family

Overview: Members of the toll-like family of receptors (nomenclature recommended by the NC-IUPHAR subcommittee on pattern recognition receptors, [24]) share significant homology with the interleukin-1 receptor family and appear to require dimerization either as homo- or heterodimers for functional

activity. Heterodimerization appears to influence the potency of ligand binding substantially (*e.g.* TLR1/2 and TLR2/6, [229, 230]). TLR1, TLR2, TLR4, TLR5, TLR6 and TLR11 are cell-surface proteins, while other members are associated with intracellular organelles, signalling through the MyD88-dependent pathways

(with the exception of TLR3). As well as responding to exogenous infectious agents [59], it has been suggested that selected members of the family may be activated by endogenous ligands, such as *hsp60* (*HSPD1*, *P10809*) [180].

| | | | | | |
|-----------------------|---|--|---|--|---|
| Nomenclature | TLR1 | TLR2 | TLR3 | TLR4 | TLR5 |
| HGNC, UniProt | TLR1 , Q15399 | TLR2 , O60603 | TLR3 , O15455 | TLR4 , O00206 | TLR5 , O60602 |
| Agonists | – | compound 13 [106], peptidoglycan [210, 265] | poly(I:C) [3] | LPS [194], paclitaxel [118] – Mouse | flagellin [91] |
| Selective antagonists | – | – | – | resatorvid [108] | – |
| Comments | Functions as a heterodimer with TLR2 in detection of triacylated lipoproteins. Activated by the synthetic analogue Pam3CSK4 . | Functions as a heterodimer with either TLR1 or TLR6 in the detection of triacylated and diacylated lipopeptides respectively. TLR1/2 and 2/6 heterodimers can be activated by the synthetic lipopeptides Pam3CSK4 and Pam2CSK4 respectively. There is some debate in the field as to whether or not peptidoglycan is a direct agonist of TLR2, or whether the early studies reporting this contained contaminating lipoproteins. | Involved in endosomal detection of dsRNA; pro-inflammatory. | Eritoran (E5564) is a lipid A analogue, which has been described as a TLR4 antagonist [110]. TLR4 signals in conjunction with the co-factor MD-2 (LY96). | Involved in the detection of bacterial flagellin; pro-inflammatory. |

| Nomenclature | TLR6 | TLR7 | TLR8 | TLR9 | TLR10 | TLR11 |
|---------------|---|---|---|--|--|----------------|
| HGNC, UniProt | TLR6 , Q9Y2C9 | TLR7 , Q9NYK1 | TLR8 , Q9NR97 | TLR9 , Q9NR96 | TLR10 , Q9BXR5 | – |
| Agonists | – | resiquimod [95, 115, 132], imiquimod [132], loxoribine [93] | resiquimod [95, 115, 132] | – | – | – |
| Antagonists | – | hydroxychloroquine (pIC ₅₀ 5.6) [131] | – | hydroxychloroquine (pIC ₅₀ 7.1) [131] | – | – |
| Comments | Functions as a heterodimer with TLR2. Involved in the pro-inflammatory response to diacylated bacterial lipopeptides. | Activated by imidazoquinoline derivatives and RNA oligoribonucleotides. Involved in endosomal detection of ssRNA; pro-inflammatory. | Activated by imidazoquinoline derivatives and RNA oligoribonucleotides. Endosomal detection of ssRNA; pro-inflammatory. | Toll-like receptor 9 interacts with unmethylated CpG dinucleotides from bacterial DNA [96]. Activated by CpG rich DNA sequences; pro-inflammatory. | TLR10 is the only pattern-recognition receptor without known ligand specificity and biological function. Evidence suggests it plays a modulatory role with predominantly inhibitory (anti-inflammatory) actions [186]. Murine TLR10 has a retroviral insertion that makes it non-functional. | Found in mouse |

Further reading on Toll-like receptor family

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NOD-like receptor family

Catalytic receptors → Pattern recognition receptors → NOD-like receptor family

Overview: The nucleotide-binding oligomerization domain, leucine-rich repeat (NLR) family of receptors (nomenclature recommended by the NC-IUPHAR subcommittee on pattern recognition receptors [24]) share a common domain organisation. This consists of an N-terminal effector domain, a central nucleotide-binding and oligomerization domain (NOD; also referred to as a NACHT domain), and C-terminal leucine-rich repeats (LRR) which have regulatory and ligand recognition functions. The type of effector domain has resulted in the division of NLR family members into two major sub-families, NLRC and NLRP,

along with three smaller sub-families NLRA, NLRB and NLRX [232]. NLRC members express an N-terminal caspase recruitment domain (CARD) and NLRP members an N-terminal Pyrin domain (PYD).

Upon activation the NLRC family members NOD1 (NLRC1) and NOD2 (NLRC2) recruit a serine/threonine kinase [RIPK2](#) (receptor interacting serine/threonine kinase 2, [O43353](#), also known as CARD3, CARDIAK, RICK, RIP2) leading to signalling through

NFκB and MAP kinase. Activation of NLRC4 (previously known as IPAF) and members of the NLRP3 family, including NLRP1 and NLRP3, leads to formation of a large multiprotein complex known as the inflammasome. In addition to NLR proteins other key members of the inflammasome include the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD, also known as *PYCARD*, *CARD5*, *TMS1*, [Q9ULZ3](#)) and inflammatory caspases. The inflammasome activates the pro-inflammatory cytokines *IL-1β* ([IL1B](#), [P01584](#)) and *IL-18* ([IL18](#), [Q14116](#)) [24, 43].

| | | | | | | | |
|---------------------|--|--|-------------------------------|--|-------------------------------|-------------------------------|-------------------------------|
| Nomenclature | nucleotide binding oligomerization domain containing 1 | nucleotide binding oligomerization domain containing 2 | NLRC3 | NLRC4 | NLRC5 | NLRX1 | CIITA |
| Common abbreviation | NOD1 | NOD2 | – | – | – | – | – |
| HGNC, UniProt | NOD1, Q9Y239 | NOD2, Q9HC29 | NLRC3, Q7RTR2 | NLRC4, Q9NPP4 | NLRC5, Q86W13 | NLRX1, Q86UT6 | CIITA, P33076 |
| Agonists | meso-DAP | muramyl dipeptide | – | – | – | – | – |
| Comments | – | NOD2 has also been reported to be activated by ssRNA [202] although this has not been widely reproduced. | – | NLRC4 forms an inflammasome with the NAIP proteins following recognition of bacterial flagellin and type III secretion system rod proteins by the NAIPs. | – | – | – |

| | | | | | | | |
|---------------|---|--|--|---|-------------------------------|-------------------------------|---|
| Nomenclature | NLRP1 | NLRP2 | NLRP3 | NLRP4 | NLRP5 | NLRP6 | NLRP7 |
| HGNC, UniProt | NLRP1, Q9C000 | NLRP2, Q9NX02 | NLRP3, Q96P20 | NLRP4, Q96MN2 | NLRP5, P59047 | NLRP6, P59044 | NLRP7, Q8WX94 |
| Inhibitors | – | – | MCC950 (pIC ₅₀ >8) [36] | – | – | – | – |
| Agonists | muramyl dipeptide | – | – | – | – | – | – |
| Comments | NLRP1 has 3 murine orthologues which lack the N-terminal Pyrin domain. Murine NLRP1b (ENSMUSG0000070390) is the best characterised, responding to Anthrax Lethal Toxin. | Along with NLRP7, NLRP2 is the product of a primate-specific gene duplication. | NLRP3 has been shown to be activated following disruption of cellular haemostasis by a wide-variety of exogenous and endogenous molecules. The identity of the precise agonist that interacts with NLRP3 remains enigmatic. Efflux of potassium ions appears to be a common event for NLRP3 activating molecules. In addition to MCC950 [36] other small molecules including CY-09 [113], β -hydroxybutyrate [266], and various boron containing compounds [9] modulate NLRP3. | Expanded in the mouse resulting in 7 orthologues. | – | – | Absent in mouse. Along with NLRP2 the product of a primate-specific gene duplication. |

| | | | | | | | |
|---------------|-------------------------------|---|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Nomenclature | NLRP8 | NLRP9 | NLRP10 | NLRP11 | NLRP12 | NLRP13 | NLRP14 |
| HGNC, UniProt | NLRP8, Q86W28 | NLRP9, Q7RTR0 | NLRP10, Q86W26 | NLRP11, P59045 | NLRP12, P59046 | NLRP13, Q86W25 | NLRP14, Q86W24 |
| Comments | Absent in mouse | This receptor has three murine orthologues. | NLRP10 lacks the LRR region. | Absent in mouse | – | Absent in mouse | – |

Comments: NLRP3 has also been reported to respond to host-derived products, known as danger-associated molecular patterns, or DAMPs, including [uric acid](#) [159], [ATP](#), [L-glucose](#), [hyaluronan](#) and [amyloid \$\beta\$](#) (*APP*, [P05067](#)) [208].

Loss-of-function mutations of NLRP3 are associated with cold autoinflammatory and Muckle-Wells syndromes.

This family also includes [NLR family, apoptosis inhibitory protein \(NAIP, Q13075\)](#) which can be found in the 'Inhibitors of apoptosis (IAP) protein family' in the [Other protein targets](#) section of the Guide.

Further reading on NOD-like receptor family

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RIG-I-like receptor family

Catalytic receptors → Pattern recognition receptors → RIG-I-like receptor family

Overview: There are three human RIG-I-like receptors (RLRs) which are cytoplasmic pattern recognition receptors (PRRs) of the innate immune system. They detect non-self cytosolic double-stranded RNA species and and 5'-triphosphate single-stranded RNA from various sources and are essential for inducing production of type I interferons, such as IFN β , type III interferons, and other anti-pathogenic effectors [23, 24]. They function as RNA helicases (EC 3.6.4.13) using the energy from ATP hydrolysis to unwind RNA.

| | | | |
|---------------------|---|--|---|
| Nomenclature | DExD/H-box helicase 58 | interferon induced with helicase C domain 1 | DExH-box helicase 58 |
| Common abbreviation | RIG-1 | MDA5 | LGP2 |
| HGNC, UniProt | RIG1, O95786 | IFIH1, Q9BYX4 | DHX58, Q96C10 |
| EC number | 3.6.4.13 RNA helicase: uses the energy from ATP hydrolysis to unwind RNA: ATP + H(2)O \rightleftharpoons ADP + phosphate | 3.6.4.13 RNA helicase; uses the energy from ATP to unwind RNA: ATP + H(2)O \rightleftharpoons ADP + phosphate | 3.6.4.13 RNA helicase: uses the energy from ATP hydrolysis to unwind RNA: ATP + H(2)O \rightleftharpoons ADP + phosphate |

Further reading on RIG-I-like receptor family

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Ma Z *et al.* (2018) Innate Sensing of DNA Virus Genomes. *Annu Rev Virol* **5**: 341-362 [[PMID:30265633](#)]
 Yong HY *et al.* (2018) RIG-I-Like Receptors as Novel Targets for Pan-Antivirals and Vaccine Adjuvants Against Emerging and Re-Emerging Viral Infections. *Front Immunol* **9**: 1379 [[PMID:29973930](#)]

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- Unterholzner L. (2013) The interferon response to intracellular DNA: why so many receptors? *Immunobiology* **218**: 1312-21 [PMID:23962476]
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Receptor guanylyl cyclase (RGC) family

Catalytic receptors → Receptor guanylyl cyclase (RGC) family

Overview: The mammalian genome encodes seven guanylyl cyclases, GC-A to GC-G, that are homodimeric transmembrane receptors activated by a diverse range of endogenous ligands. These enzymes convert **guanosine-5'-triphosphate** to the intracellular second messenger cyclic guanosine-3',5'-monophosphate (**cyclic GMP**). GC-A, GC-B and GC-C are expressed predominantly in the cardiovascular system, skeletal system and intestinal epithelium, respectively. GC-D and GC-G are found in the olfactory neuroepithelium and Grueneberg ganglion of rodents, respectively. GC-E and GC-F are expressed in retinal photoreceptors.

Transmembrane guanylyl cyclases

Catalytic receptors → Receptor guanylyl cyclase (RGC) family → Transmembrane guanylyl cyclases

Overview: Transmembrane guanylyl cyclases are homodimeric receptors activated by a diverse range of endogenous ligands. GC-A, GC-B and GC-C are expressed predominantly in the cardiovascular system, skeletal system and intestinal epithelium, respectively. GC-D and GC-G are found in the olfactory

neuroepithelium and Grueneberg ganglion of rodents, respectively. GC-E and GC-F are expressed in retinal photoreceptors. Family members have conserved ligand-binding, catalytic (guanylyl cyclase) and regulatory domains with the exception of NPR-C which has an extracellular binding domain homologous

to that of other NPRs, but with a truncated intracellular domain which appears to couple, *via* the $G_{i/o}$ family of G proteins, to activation of phospholipase C, inwardly-rectifying potassium channels and inhibition of adenylyl cyclase activity [173].

| | | | | |
|------------------------|--|---|---|---|
| Nomenclature | Guanylyl cyclase-A | Guanylyl cyclase-B | Guanylyl cyclase-C | natriuretic peptide receptor 3 |
| Common abbreviation | GC-A | GC-B | GC-C | NPR-C |
| HGNC, UniProt | <i>NPR1</i> , P16066 | <i>NPR2</i> , P20594 | <i>GUCY2C</i> , P25092 | <i>NPR3</i> , P17342 |
| Potency order | atrial natriuretic peptide (<i>NPPA</i> , P01160) ≥ brain natriuretic peptide (<i>NPPB</i> , P16860) >> C-type natriuretic peptide (<i>NPPC</i> , P23582) [227] | C-type natriuretic peptide (<i>NPPC</i> , P23582) >> atrial natriuretic peptide (<i>NPPA</i> , P01160) >> brain natriuretic peptide (<i>NPPB</i> , P16860) [227] | uroguanylin (<i>GUCA2B</i> , Q16661) > guanylin (<i>GUCA2A</i> , Q02747) | atrial natriuretic peptide (<i>NPPA</i> , P01160) > C-type natriuretic peptide (<i>NPPC</i> , P23582) ≥ brain natriuretic peptide (<i>NPPB</i> , P16860) [227] |
| Endogenous agonists | atrial natriuretic peptide (<i>NPPA</i> , P01160) (Binding) [185], brain natriuretic peptide (<i>NPPB</i> , P16860) (Binding) [185], mutant ANP [162] | C-type natriuretic peptide (<i>NPPC</i> , P23582) (Binding) [227] | guanylin (<i>GUCA2A</i> , Q02747) (Binding), uroguanylin (<i>GUCA2B</i> , Q16661) (Binding) | – |
| Agonists | – | – | dolcanatide [213] | – |
| Selective agonists | <i>Dendroaspis</i> natriuretic peptide [217], PL-3994 [52], cenderitide [157], sANP [185] | cenderitide [157], vosoritide [147] | linaclotide [26, 89], <i>E. coli</i> heat-stable enterotoxin (ST _a) [26], plecanatide [212] | cANF ⁴⁻²³ [149] |
| Endogenous antagonists | – | – | – | osteocrin (<i>OSTN</i> , P61366) [167] |
| Selective antagonists | A-71915 (pK _i 9.2–9.5) [47], [Asu7,23']β-ANP-(7-28) (pK _i 7.5) [116], HS-142-1 [170], anantin [249, 259] | peptide P19 (pK _d 7.8) [49], HS-142-1 [170], [Ser ¹¹](N-CNP,C-ANP)pBNP ²⁻¹⁵ [49], compound C10 [8] | – | M372049 [101] |
| Labelled ligands | [¹²⁵ I]ANP (human) (Agonist) | [¹²⁵ I]CNP (human) | [¹²⁵ I]St _a (Agonist) [87] | [¹²⁵ I]ANP (human) |

| | | | | |
|-----------------------|----------------------|--------------------------|--------------------------|----------------------|
| Nomenclature | Guanylyl cyclase-D | Guanylyl cyclase-E | Guanylyl cyclase-F | Guanylyl cyclase-G |
| Common abbreviation | GC-D | GC-E | GC-F | GC-G |
| HGNC, UniProt | – | <i>GUCY2D</i> , Q02846 | <i>GUCY2F</i> , P51841 | <i>GUCY2GP</i> , – |
| Localisation | – | Retinal photoreceptors | Retinal photoreceptors | Grüneberg ganglion |
| Principal function(s) | – | Vision/phototransduction | Vision/phototransduction | Thermosensation |
| Endogenous ligands | – | – | – | Cold |
| Comments | Pseudogene in humans | – | – | Pseudogene in humans |

Comments: GC-D and GC-G have been reported to be activated intracellularly by guanylyl cyclase-activating protein 1 (*GUCA1A*, P43080) and guanylyl cyclase-activating protein 2 (*GUCA1B*, Q9UMX6). GC-D and GC-G may be activated by atmospheric levels of CO₂ through the formation of intracellular bicarbonate ions [31, 102]. GC-G may be activated at cooler temperatures (20–25°C) through apparent stabilisation of the dimer [30].

Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

Catalytic receptors → Receptor guanylyl cyclase (RGC) family → Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase

Overview: Nitric oxide (NO)-sensitive (soluble) guanylyl cyclase (GTP diphosphate-lyase (cyclising)), E.C. 4.6.1.2, is a heterodimer comprising a β_1 subunit and one of two alpha subunits (α_1 , α_2) giving rise to two functionally indistinguishable isoforms, GC-1 ($\alpha_1\beta_1$) and GC-2 ($\alpha_2\beta_1$) [201, 267]. A haem group is associated with the β subunit and is the target for the endogenous ligand NO, and, potentially, carbon monoxide [64].

Complexes

| | | |
|----------------------|--|---|
| Nomenclature | Guanylyl cyclase, $\alpha_1\beta_1$ | Guanylyl cyclase, $\alpha_2\beta_1$ |
| Common abbreviation | GC-1 | GC-2 |
| Subunits | Guanylyl cyclase α_1 subunit, Guanylyl cyclase β_1 subunit | Guanylyl cyclase α_2 subunit, Guanylyl cyclase β_1 subunit |
| EC number | 4.6.1.2 | 4.6.1.2 |
| Endogenous ligands | NO | NO |
| Selective activators | praliciguat (pEC ₅₀ 6.6) [233], YC-1 [64, 125, 201], ataciguat [207], cinaciguat [apo-GC-1] [222], olinciguat [27], riociguat [220, 221], runcaciguat [86], vericiguat [60] | YC-1 [125, 201], cinaciguat [apo-GC-2] [222], olinciguat [27], riociguat [220, 221] |
| Selective inhibitors | NS 2028 (pIC ₅₀ 8.1) [183] – Bovine, ODQ (pIC ₅₀ 7.5) [70] | ODQ |

Subunits

| | | | | |
|---------------|-------------------------------------|-------------------------------------|------------------------------------|------------------------------------|
| Nomenclature | Guanylyl cyclase α_1 subunit | Guanylyl cyclase α_2 subunit | Guanylyl cyclase β_1 subunit | Guanylyl cyclase β_2 subunit |
| HGNC, UniProt | <i>GUCY1A1</i> , Q02108 | <i>GUCY1A2</i> , P33402 | <i>GUCY1B1</i> , Q02153 | <i>GUCY1B2</i> , O75343 |

Comments: ODQ also shows activity at other haem-containing proteins [58], while YC-1 may also inhibit cGMP-hydrolysing phosphodiesterases [63, 67].

Further reading on Receptor guanylyl cyclase (RGC) family

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Receptor tyrosine kinases (RTKs)

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs)

Overview: Receptor tyrosine kinases (RTKs), a family of cell-surface receptors, which transduce signals to polypeptide and protein hormones, cytokines and growth factors are key regulators of critical cellular processes, such as proliferation and differentiation, cell survival and metabolism, cell migration and cell cycle control [16, 79, 240]. In the human genome, 58 RTKs have been identified, which fall into 20 families [136].

All RTKs display an extracellular ligand binding domain, a single transmembrane helix, a cytoplasmic region containing the protein tyrosine kinase activity (occasionally split into two domains

by an insertion, termed the kinase insertion), with juxta-membrane and C-terminal regulatory regions. Agonist binding to the extracellular domain evokes dimerization, and sometimes oligomerization, of RTKs (a small subset of RTKs forms multimers even in the absence of activating ligand). This leads to autophosphorylation in the tyrosine kinase domain in a trans orientation, serving as a site of assembly of protein complexes and stimulation of multiple signal transduction pathways, including phospholipase C- γ , mitogen-activated protein kinases and phosphatidylinositol 3-kinase [240].

RTKs are of widespread interest not only through physiological functions, but also as drug targets in many types of cancer and other disease states. Many diseases result from genetic changes or abnormalities that either alter the activity, abundance, cellular distribution and/or regulation of RTKs. Therefore, drugs that modify the dysregulated functions of these RTKs have been developed which fall into two categories. One group is often described as 'biologicals', which block the activation of RTKs directly or by chelating the cognate ligands, while the second are small molecules designed to inhibit the tyrosine kinase activity directly.

Type I RTKs: ErbB (epidermal growth factor) receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type I RTKs: ErbB (epidermal growth factor) receptor family

Overview: ErbB family receptors are Class I receptor tyrosine kinases [79]. ERBB2 (also known as HER-2 or NEU) appears to act as an essential partner for the other members of the family without itself being activated by a cognate ligand [80]. Ligands

of the ErbB family of receptors are peptides, many of which are generated by proteolytic cleavage of cell-surface proteins. HER/ErbB is the viral counterpart to the receptor tyrosine kinase EGFR. All family members heterodimerize with each other to

activate downstream signalling pathways and are aberrantly expressed in many cancers, particularly forms of breast cancer and lung cancer. Mutations in the EGFR are responsible for acquired resistance to tyrosine kinase inhibitor chemotherapeutics.

| | | | | |
|---------------------|--|--|--|---|
| Nomenclature | epidermal growth factor receptor | erb-b2 receptor tyrosine kinase 2 | erb-b2 receptor tyrosine kinase 3 | erb-b2 receptor tyrosine kinase 4 |
| Common abbreviation | EGFR | HER2 | HER3 | HER4 |
| HGNC, UniProt | EGFR , P00533 | ERBB2 , P04626 | ERBB3 , P21860 | ERBB4 , Q15303 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | EGF (EGF , P01133) (Binding), HB-EGF (HBEGF , Q99075) (Binding), TGFα (TGFA , P01135) (Binding), amphiregulin (AREG , P15514) (Binding), beta-cellullin (BTC , P35070) (Binding), epigen (EPGN , Q6UW88) (Binding), epiregulin (EREG , O14944) (Binding) | – | neuregulin-1 (NRG1 , Q02297), neuregulin-2 (NRG2 , O14511) | HB-EGF (HBEGF , Q99075), betacellullin (BTC , P35070), epiregulin (EREG , O14944), neuregulin-1 (NRG1 , Q02297), neuregulin-2 (NRG2 , O14511), neuregulin-3 (NRG3 , P56975), neuregulin-4 (NRG4 , Q8WWG1) |
| Inhibitors | afatinib (pK _d 9.6) [44], tesevatinib (pIC ₅₀ 9.5) [72], afatinib (pIC ₅₀ 8–9.3) [39, 137] | poziotinib (pIC ₅₀ 8.3) [176], CP-724714 (pIC ₅₀ 7.9) [83], tesevatinib (pIC ₅₀ 7.8) [72], BMS-690514 (pIC ₅₀ 7.7) [153] | – | poziotinib (pIC ₅₀ 7.6) [176] |
| Antibodies | necitumumab (Binding) (pK _d 9.5) [145], cetuximab (Binding) (pK _d 9.4) [75] | pertuzumab (Inhibition) (pIC ₅₀ >8) [117], trastuzumab (Inhibition) | – | – |

Comments: [¹²⁵I]EGF (human) has been used to label the ErbB1 EGF receptor. The extracellular domain of ErbB2 can be targeted by the antibodies [trastuzumab](#) and [pertuzumab](#) to inhibit ErbB family action. The intracellular ATP-binding site of the tyrosine kinase domain can be inhibited by [GW583340](#) (7.9–8.0, [71]), [gefitinib](#), [erlotinib](#) and tyrphostins [AG879](#) and [AG1478](#).

Further reading on Type I RTKs: ErbB (epidermal growth factor) receptor family

Kobayashi Y *et al.* (2016) Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. *Cancer Sci* **107**: 1179-86 [PMID:27323238]

Type II RTKs: Insulin receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type II RTKs: Insulin receptor family

Overview: The circulating peptide hormones [insulin](#) ([INS](#), [P01308](#)) and the related insulin-like growth factors (IGF) activate Class II receptor tyrosine kinases [79], to evoke cellular responses, mediated through multiple intracellular adaptor proteins. Exceptionally amongst the catalytic receptors, the functional receptor in the insulin receptor family is derived from a single gene product, cleaved post-translationally into two peptides, which then cross-link via disulphide bridges to form a heterotetramer. Intriguingly, the endogenous peptide ligands are formed in

a parallel fashion with post-translational processing producing a heterodimer linked by disulphide bridges. Signalling through the receptors is mediated through a rapid autophosphorylation event at intracellular tyrosine residues, followed by recruitment of multiple adaptor proteins, notably [IRS1](#) ([P35568](#)), [IRS2](#) ([Q9Y4H2](#)), [SHC1](#) ([P29353](#)), [GRB2](#) ([P62993](#)) and [SOS1](#) ([Q07889](#)).

Serum levels of free IGFs are kept low by the action of IGF binding proteins (IGFBP1-5, [P08833](#), [P18065](#), [P17936](#), [P22692](#), [P24593](#)), which sequester the IGFs; overexpression of IGFBPs may induce apoptosis, while IGFBP levels are also altered in some cancers.

| | | | |
|----------------------|--|---|---|
| Nomenclature | Insulin receptor | Insulin-like growth factor I receptor | Insulin receptor-related receptor |
| Common abbreviation | InsR | IGF1R | IRR |
| HGNC, UniProt | INSR, P06213 | IGF1R, P08069 | INSRR, P14616 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Inhibitors | – | BMS-754807 (pIC ₅₀ 8.7) [255], GSK-1838705A (pIC ₅₀ 8.7) [203], GSK-1838705A (pK _d 8.1) [44], PQ401 (pIC ₅₀ >6) [66], AG 1024 (pIC ₅₀ 4.7) [189] | – |
| Selective inhibitors | – | NVP-AEW541 (pIC ₅₀ 9.4) [69] | – |
| Endogenous agonists | insulin (INS , P01308) | insulin-like growth factor 1 (IGF1 , P05019), insulin-like growth factor 2 (IGF2 , P01344) | – |

Comments: There is evidence for low potency binding and activation of insulin receptors by IGF1. IGF2 also binds and activates the cation-independent mannose 6-phosphate receptor (also known as the insulin-like growth factor 2 receptor; [IGF2R](#);

[P11717](#)), which lacks classical signalling capacity and appears to subserve a trafficking role [150]. INSR, which has a much more discrete localization, being predominant in the kidney [128], currently lacks a cognate ligand or evidence for functional impact.

Antibodies targeting IGF1, IGF2 and the extracellular portion of the IGF1 receptor are in clinical trials.

[PQ401](#) inhibits the insulin-like growth factor receptor [5], while [BMS-536924](#) inhibits both the insulin receptor and the insulin-like growth factor receptor [254].

Type III RTKs: PDGFR, CSFR, Kit, FLT3 receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type III RTKs: PDGFR, CSFR, Kit, FLT3 receptor family

Overview: Type III RTKs include PDGFR, CSF-1R (Ems), Kit and FLT3, which function as homo- or heterodimers. Endogenous ligands of PDGF receptors are homo- or heterodimeric: PDGFA, PDGFB, VEGFE and [PDGFD](#) ([PDGFD](#), [Q9GZP0](#)) combine as homo- or heterodimers to activate homo- or heterodimeric PDGF receptors. SCF is a dimeric ligand for KIT. Ligands for CSF1R are either monomeric or dimeric glycoproteins, while the endogenous agonist for FLT3 is a homodimer.

| | | | |
|----------------------|---|---|---|
| Nomenclature | platelet derived growth factor receptor alpha | platelet derived growth factor receptor beta | KIT proto-oncogene, receptor tyrosine kinase |
| Common abbreviation | PDGFR α | PDGFR β | Kit |
| HGNC, UniProt | PDGFRA, P16234 | PDGFRB, P09619 | KIT, P10721 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | PDGF | PDGF | – |
| Inhibitors | PP121 (pIC ₅₀ 8.7) [5], crenolanib (pK _d 8.7) [94], ENMD-2076 (pIC ₅₀ 7.2) [193] | crenolanib (pK _d 8.5) [94], SU-14813 (pIC ₅₀ 8.4) [190], famitinib (pIC ₅₀ 8.4) [32], sunitinib (pIC ₅₀ 8.2) [123], sunitinib (pK _i 8.1) [164] | sunitinib (pK _d 9.4) [44], famitinib (pIC ₅₀ 8.7) [32], masitinib (pK _d 8.1) [44], SU-14813 (pIC ₅₀ 7.8) [190], AKN-028 (pIC ₅₀ 7.5) [55], sorafenib (pIC ₅₀ 7.2) [253] |
| Selective inhibitors | CP-673451 (pIC ₅₀ 8) [199] | CP-673451 (pIC ₅₀ 9) [199] | – |
| Endogenous agonists | – | – | stem cell factor (KITLG , P21583) [238] |

| | | |
|----------------------|---|--|
| Nomenclature | colony stimulating factor 1 receptor | fms related receptor tyrosine kinase 3 |
| Common abbreviation | CSFR | FLT3 |
| HGNC, UniProt | CSF1R , P07333 | FLT3 , P36888 |
| EC number | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | G-CSF (CSF3, P09919) , GM-CSF (CSF2, P04141) , M-CSF (CSF1, P09603) | Fms-related tyrosine kinase 3 ligand (FLT3LG, P49771) |
| Inhibitors | JNJ-28312141 (pIC ₅₀ 9.2) [152], Ki-20227 (pK _d 9.1) [44], Ki-20227 (pIC ₅₀ 8.7) [182], GW-2580 (pK _d 8.7) [44], JNJ-28312141 (pK _d 8.5) [44] | AC710 (pK _d 9.3) [143], linifanib (pK _d 9.2) [44], crenolanib (pK _d 9.1) [94], ENMD-2076 (pIC ₅₀ 8.5) [193], tandutinib (pK _d 8.5) [44], tandutinib (pIC ₅₀ 6.7) [119] |
| Selective inhibitors | GW-2580 (pIC ₅₀ 7.2) [38] | denfivontinib (pIC ₅₀ 9.4) [133] |
| Comments | Upregulation of CSF1R expression is associated with microglial activation and immune pathology in Alzheimer's disease (AD) [76, 77]. Pharmacological inhibition of CSF1R with GW-2580 reduces microglial proliferation and prevents disease progression in a mouse model of AD, but this does not correlate with amyloid- β plaque numbers [184]. | 5'-fluoroindirubinoxime has been described as a selective FLT3 inhibitor [33]. |

Comments: Various small molecular inhibitors of type III RTKs have been described, including [imatinib](#) and [nilotinib](#) (targetting PDGFR, KIT and CSF1R); [midostaurin](#) and [AC220 \(quizartinib; FLT3\)](#), as well as pan-type III RTK inhibitors such as [sunitinib](#) and [sorafenib](#) [191]; 5'-fluoroindirubinoxime has been described as a selective FLT3 inhibitor [2].

Type IV RTKs: VEGF (vascular endothelial growth factor) receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type IV RTKs: VEGF (vascular endothelial growth factor) receptor family

Overview: [VEGF receptors](#) are homo- and heterodimeric proteins, which are characterized by seven Ig-like loops in their extracellular domains and a split kinase domain in the cytoplasmic region. They are key regulators of angiogenesis and lymphangiogenesis; as such, they have been the focus of drug discovery for conditions such as metastatic cancer. Splice vari-

ants of VEGFR1 and VEGFR2 generate truncated proteins limited to the extracellular domains, capable of homodimerisation and binding VEGF ligands as a soluble, non-signalling entity. Ligands at VEGF receptors are typically homodimeric. [VEGFA \(VEGFA, P15692\)](#) is able to activate VEGFR1 homodimers, VEGFR1/2 heterodimers and VEGFR2/3 heterodimers. [VEGFB](#)

([VEGFB, P49765](#)) and [placental growth factor \(PGF, P49763\)](#) activate VEGFR1 homodimers, while [VEGFC \(VEGFC, P49767\)](#) and [VEGFD \(VEGFD, O43915\)](#) activate VEGFR2/3 heterodimers and VEGFR3 homodimers, and, following proteolysis, VEGFR2 homodimers.

| | | | |
|---------------------|---|---|---|
| Nomenclature | fms related receptor tyrosine kinase 1 | kinase insert domain receptor | fms related receptor tyrosine kinase 4 |
| Common abbreviation | VEGFR-1 | VEGFR-2 | VEGFR-3 |
| HGNC, UniProt | FLT1 , P17948 | KDR , P35968 | FLT4 , P35916 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | VEGFA (VEGFA, P15692) , VEGFB (VEGFB, P49765) | VEGFA (VEGFA, P15692) , VEGFC (VEGFC, P49767) , VEGFE (PDGFC, Q9NRA1) | VEGFC (VEGFC, P49767) , VEGFD (VEGFD, O43915) , VEGFE (PDGFC, Q9NRA1) |

| | | | |
|---------------------------------|---|---|---|
| Inhibitors | SU-14813 (pIC ₅₀ 8.7) [190], CEP-11981 (pIC ₅₀ 8.5) [104], semaxanib (pIC ₅₀ 8.1) [17] | cabozantinib (pIC ₅₀ 10.5) [260], axitinib (pIC ₅₀ 9.6) [134], foretinib (pIC ₅₀ 8.2–9.1) [174], cediranib (pK _d 9) [44], tesevatinib (pIC ₅₀ 8.8) [72], motesanib (pK _d 8.6) [44], famitinib (pIC ₅₀ 8.3) [32], axitinib (pK _d 8.2) [44] | tesevatinib (pIC ₅₀ 8.1) [72], sunitinib (pIC ₅₀ 8.1) [120], nintedanib (pIC ₅₀ 7.9) [100] |
| Sub/family-selective inhibitors | pazopanib (pIC ₅₀ 8) [90] | pazopanib (pK _d 7.8) [44], pazopanib (pIC ₅₀ 7.5) [90] | pazopanib (pIC ₅₀ 7.3) [90] |
| Antibodies | – | ramucirumab (Antagonist) (pIC ₅₀ 9) [148] | – |

Comments: The VEGFR, as well as VEGF ligands, have been targeted by antibodies and tyrosine kinase inhibitors. DMH4 [61], Ki8751 [127] and ZM323881, a novel inhibitor of vascular endothelial growth factor-receptor-2 tyrosine kinase activity [251] are described as VEGFR2-selective tyrosine kinase inhibitors. Bevacizumab is a monoclonal antibody directed against VEGF-A, used clinically for the treatment of certain metastatic cancers; an antibody fragment has been used for wet age-related macular degeneration.

Type V RTKs: FGF (fibroblast growth factor) receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type V RTKs: FGF (fibroblast growth factor) receptor family

Overview: Fibroblast growth factor (FGF) family receptors act as homo- and heterodimers, and are characterized by Ig-like loops in the extracellular domain, in which disulphide bridges may form across protein partners to allow the formation of covalent dimers which may be constitutively active. FGF recep-

tors have been implicated in achondroplasia, angiogenesis and numerous congenital disorders. At least 22 members of the FGF gene family have been identified in the human genome [11]. Within this group, subfamilies of FGF may be divided into canonical, intracellular and hormone-like FGFs. FGF1-FGF10 have

been identified to act through FGF receptors, while FGF11-14 appear to signal through intracellular targets. Other family members are less well characterized [250].

| Nomenclature | fibroblast growth factor receptor 1 | fibroblast growth factor receptor 2 | fibroblast growth factor receptor 3 | fibroblast growth factor receptor 4 |
|---------------------------------|--|--|--|--|
| Common abbreviation | FGFR1 | FGFR2 | FGFR3 | FGFR4 |
| HGNC, UniProt | <i>FGFR1</i> , P11362 | <i>FGFR2</i> , P21802 | <i>FGFR3</i> , P22607 | <i>FGFR4</i> , P22455 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | FGF-1 (<i>FGF1</i> , P05230), FGF-2 (<i>FGF2</i> , P09038), FGF-4 (<i>FGF4</i> , P08620) > FGF-5 (<i>FGF5</i> , P12034), FGF-6 (<i>FGF6</i> , P10767) [187] | FGF-1 (<i>FGF1</i> , P05230) > FGF-4 (<i>FGF4</i> , P08620), FGF-7 (<i>FGF7</i> , P21781), FGF-9 (<i>FGF9</i> , P31371) > FGF-2 (<i>FGF2</i> , P09038), FGF-6 (<i>FGF6</i> , P10767) [187] FGF-10 (<i>FGF10</i> , O15520) [264] | FGF-1 (<i>FGF1</i> , P05230), FGF-2 (<i>FGF2</i> , P09038), FGF-9 (<i>FGF9</i> , P31371) > FGF-4 (<i>FGF4</i> , P08620), FGF-8 (<i>FGF8</i> , P55075) [187] FGF-3 (<i>FGF3</i> , P11487) | FGF-1 (<i>FGF1</i> , P05230), FGF-2 (<i>FGF2</i> , P09038), FGF-4 (<i>FGF4</i> , P08620), FGF-9 (<i>FGF9</i> , P31371) > FGF-6 (<i>FGF6</i> , P10767), FGF-8 (<i>FGF8</i> , P55075): FGF-19 (<i>FGF19</i> , O95750) [187] |
| Sub/family-selective inhibitors | LY2874455 (pIC ₅₀ 8.6) [269] | LY2874455 (pIC ₅₀ 8.6) [269] | LY2874455 (pIC ₅₀ 8.2) [269] | LY2874455 (pIC ₅₀ 8.2) [269] |
| Selective inhibitors | – | – | – | BLU-9931 (Irreversible inhibition) (pIC ₅₀ 8.5) [85] |
| Agonists | – | palifermin | – | – |

Comments: Splice variation of the receptors can influence agonist responses. *FGFRL1* (Q8N441) is a truncated kinase-null analogue.

Various antibodies and tyrosine kinase inhibitors have been developed against FGF receptors [140, 273]. PD161570 is an FGFR tyrosine kinase inhibitor [11], while PD173074 has been described to inhibit FGFR1 and FGFR3 [218].

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16180/full>

Type V RTKs: FGF (fibroblast growth factor) receptor family S269

Type VI RTKs: PTK7/CCK4

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type VI RTKs: PTK7/CCK4

Overview: The PTK7 receptor is associated with polarization of epithelial cells and the development of neural structures. Sequence analysis suggests that the gene product is catalytically inactive as a protein kinase, although there is evidence for a role in Wnt signalling [196].

| | |
|---------------------|--------------------------------------|
| Nomenclature | protein tyrosine kinase 7 (inactive) |
| Common abbreviation | CCK4 |
| HGNC, UniProt | <i>PTK7</i> , Q13308 |
| EC number | 2.7.10.1 |

Comments: Thus far, no selective PTK7 inhibitors have been described.

Type VII RTKs: Neurotrophin receptor/Trk family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type VII RTKs: Neurotrophin receptor/Trk family

Overview: The neurotrophin receptor family of RTKs include trkA, trkB and trkC (tropomyosin-related kinase) receptors, which respond to NGF, BDNF and neurotrophin-3, respectively. They are associated primarily with proliferative and migration

effects in neural systems. Various isoforms of neurotrophin receptors exist, including truncated forms of trkB and trkC, which lack catalytic domains. p75 (TNFRSF16, also known as nerve growth factor receptor), which has homologies with tumour

necrosis factor receptors, lacks a tyrosine kinase domain, but can signal via ceramide release and nuclear factor κ B (NF- κ B) activation. Both trkA and trkB contain two leucine-rich regions and can exist in monomeric or dimeric forms.

| | | | |
|---------------------------------|--|---|--|
| Nomenclature | neurotrophic receptor tyrosine kinase 1 | neurotrophic receptor tyrosine kinase 2 | neurotrophic receptor tyrosine kinase 3 |
| Common abbreviation | trkA | trkB | trkC |
| HGNC, UniProt | <i>NTRK1</i> , P04629 | <i>NTRK2</i> , Q16620 | <i>NTRK3</i> , Q16288 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | NGF (<i>NGF</i> , P01138) > neurotrophin-3 (<i>NTF3</i> , P20783) | BDNF (<i>BDNF</i> , P23560), neurotrophin-4 (<i>NTF4</i> , P34130) > neurotrophin-3 (<i>NTF3</i> , P20783) | neurotrophin-3 (<i>NTF3</i> , P20783) |
| Inhibitors | selitrectinib (pIC ₅₀ >9.3) [177], compound 2c (pIC ₅₀ 8.9) [246], miliciclib (pIC ₅₀ 7.3) [19], ONO-7579 [109] | ONO-7579 [109] | ONO-7579 [109] |
| Sub/family-selective inhibitors | AZD1332 (pIC ₅₀ >8.3) [7], GNF-5837 (pIC ₅₀ 8) [2] | AZD1332 (pIC ₅₀ >8.3) [7], GNF-5837 (pIC ₅₀ 8.1) [2] | AZD1332 (pIC ₅₀ >8.3) [7], GNF-5837 (pIC ₅₀ 8.1) [2] |

Comments: [¹²⁵I]NGF (human) and [¹²⁵I]BDNF (human) have been used to label the trkA and trkB receptor, respectively. p75 influences the binding of NGF (NGF, P01138) and neurotrophin-3 (NTF3, P20783) to trkA. The ligand selectivity of p75 appears to be dependent on the cell type; for example, in sympathetic neu-

rones, it binds neurotrophin-3 (NTF3, P20783) with comparable affinity to trkC [46].

Small molecule agonists of trkB have been described, including LM22A4 [160], while ANA12 has been described as a non-com-

petitive antagonist of BDNF binding to trkB [29]. GNF5837 is a family-selective tyrosine kinase inhibitor [2], while the tyrosine kinase activity of the trkA receptor can be inhibited by GW441756 (pIC₅₀= 8.7, [257]) and tyrphostin AG879 [181].

Type VIII RTKs: ROR family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type VIII RTKs: ROR family

Overview: Members of the ROR family appear to be activated by ligands complexing with other cell-surface proteins. Thus, ROR1 and ROR2 appear to be activated by Wnt-5a (WNT5A, P41221) binding to a Frizzled receptor thereby forming a cell-surface multiprotein complex [82].

| | | |
|---------------------|---|---|
| Nomenclature | receptor tyrosine kinase like orphan receptor 1 | receptor tyrosine kinase like orphan receptor 2 |
| Common abbreviation | ROR1 | ROR2 |
| HGNC, UniProt | ROR1, Q01973 | ROR2, Q01974 |
| EC number | 2.7.10.1 | 2.7.10.1 |

Type IX RTKs: MuSK

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type IX RTKs: MuSK

Overview: The muscle-specific kinase MuSK is associated with the formation and organisation of the neuromuscular junction from the skeletal muscle side. Agrin (AGRN, O00468) forms a complex with low-density lipoprotein receptor-related protein 4 (LRP4, O75096) to activate MuSK [121].

| | |
|---------------------|--|
| Nomenclature | muscle associated receptor tyrosine kinase |
| Common abbreviation | MuSK |
| HGNC, UniProt | MUSK, O15146 |
| EC number | 2.7.10.1 |

Comments: Thus far, no selective MuSK inhibitors have been described.

Type X RTKs: HGF (hepatocyte growth factor) receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type X RTKs: HGF (hepatocyte growth factor) receptor family

Overview: HGF receptors regulate maturation of the liver in the embryo, as well as having roles in the adult, for example, in the innate immune system. HGF is synthesized as a single gene product, which is post-translationally processed to yield a heterodimer linked by a disulphide bridge. The maturation of HGF is enhanced by a serine protease, HGF activating complex, and inhibited by **HGF-inhibitor 1** (*SPINT1*, O43278), a serine protease inhibitor. MST1, the ligand of RON, is two disulphide-linked peptide chains generated by proteolysis of a single gene product.

| | | |
|----------------------|--|--|
| Nomenclature | MET proto-oncogene, receptor tyrosine kinase | macrophage stimulating 1 receptor |
| Common abbreviation | MET | Ron |
| HGNC, UniProt | <i>MET</i> , P08581 | <i>MST1R</i> , Q04912 |
| EC number | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | hepatocyte growth factor (<i>HGF</i> , P14210) | macrophage stimulating protein 1 (<i>MST1</i> , P09603) |
| Inhibitors | capmatinib (pIC ₅₀ 9.9) [146], SGX-523 (pK _d 9.7) [44], cabozantinib (pIC ₅₀ 8.9) [260] | BMS-777607 (pIC ₅₀ 8.7) [209] |
| Selective inhibitors | SGX-523 (pIC ₅₀ 8.4) [25] | – |

Comments: PF04217903 is a selective Met tyrosine kinase inhibitor [40]. SU11274 is an inhibitor of the HGF receptor [205], with the possibility of further targets [6].

Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type XI RTKs: TAM (TYRO3-, AXL- and MER-TK) receptor family

Overview: Members of this RTK family represented a novel structural motif, when sequenced. The ligands for this family, growth arrest specific protein 6 (*GAS6*, Q14393) and protein S (*PROS1*, P07225), are secreted plasma proteins which undergo vitamin K-dependent post-translational modifications generating carboxyglutamate-rich domains which are able to bind to negatively-charged surfaces of apoptotic cells.

| | | | |
|---------------------|--|--|--|
| Nomenclature | AXL receptor tyrosine kinase | TYRO3 protein tyrosine kinase | MER proto-oncogene, tyrosine kinase |
| Common abbreviation | Axl | Tyro3 | Mer |
| HGNC, UniProt | <i>AXL</i> , P30530 | <i>TYRO3</i> , Q06418 | <i>MERTK</i> , Q12866 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | growth arrest specific protein 6 (<i>GAS6</i> , Q14393) [175], protein S (<i>PROS1</i> , P07225) [226] | growth arrest specific protein 6 (<i>GAS6</i> , Q14393) [175], protein S (<i>PROS1</i> , P07225) [226] | growth arrest specific protein 6 (<i>GAS6</i> , Q14393) [175] |

Comments: AXL tyrosine kinase inhibitors have been described [168].

Searchable database: <https://www.guidetopharmacology.org/>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.16180/full>

Type X RTKs: HGF (hepatocyte growth factor) receptor family S272

Type XII RTKs: TIE family of angiopoietin receptors

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type XII RTKs: TIE family of angiopoietin receptors

Overview: The TIE family were initially associated with formation of blood vessels. Endogenous ligands are **angiopoietin-1** (*ANGPT1*, Q15389), **angiopoietin-2** (*ANGPT2*, O15123), and **angiopoietin-4** (*ANGPT4*, Q9Y264). **Angiopoietin-2** (*ANGPT2*, O15123) appears to act as an endogenous antagonist of angiopoietin-1 function.

| | | |
|---------------------|---|--|
| Nomenclature | tyrosine kinase with immunoglobulin like and EGF like domains 1 | TEK receptor tyrosine kinase |
| Common abbreviation | TIE1 | TIE2 |
| HGNC, UniProt | <i>TIE1</i> , P35590 | <i>TEK</i> , Q02763 |
| EC number | 2.7.10.1 | 2.7.10.1 |
| Endogenous ligands | – | angiopoietin-1 (<i>ANGPT1</i> , Q15389), angiopoietin-4 (<i>ANGPT4</i> , Q9Y264) |

Type XIII RTKs: Ephrin receptor family

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type XIII RTKs: Ephrin receptor family

Overview: Ephrin receptors are a family of 15 RTKs (the largest family of RTKs) with two identified subfamilies (EphA and EphB), which have a role in the regulation of neuronal development, cell migration, patterning and angiogenesis. Their ligands

are membrane-associated proteins, thought to be glycosylphosphatidylinositol-linked for EphA (**ephrin-A1** (*EFNA1*, P20827), **ephrin-A2** (*EFNA2*, O43921), **ephrin-A3** (*EFNA3*, P52797), **ephrin-A4** (*EFNA4*, P52798) and **ephrin-A5** (*EFNA5*, P52803)) and

1TM proteins for Ephrin B (**ENSM0025000002014: ephrin-B1** (*EFNB1*, P98172), **ephrin-B2** (*EFNB2*, P52799) and **ephrin-B3** (*EFNB3*, Q15768)), although the relationship between ligands and receptors has been incompletely defined.

| | | | | | | | |
|---------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Nomenclature | EPH receptor A1 | EPH receptor A2 | EPH receptor A3 | EPH receptor A4 | EPH receptor A5 | EPH receptor A6 | EPH receptor A7 |
| Common abbreviation | EphA1 | EphA2 | EphA3 | EphA4 | EphA5 | EphA6 | EphA7 |
| HGNC, UniProt | <i>EPHA1</i> , P21709 | <i>EPHA2</i> , P29317 | <i>EPHA3</i> , P29320 | <i>EPHA4</i> , P54764 | <i>EPHA5</i> , P54756 | <i>EPHA6</i> , Q9UF33 | <i>EPHA7</i> , Q15375 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |

| | | | | | | | |
|---------------------|--|---|---|--|--|--|--|
| Nomenclature | EPH receptor A8 | EPH receptor A10 | EPH receptor B1 | EPH receptor B2 | EPH receptor B3 | EPH receptor B4 | EPH receptor B6 |
| Common abbreviation | EphA8 | EphA10 | EphB1 | EphB2 | EphB3 | EphB4 | EphB6 |
| HGNC, UniProt | EPHA8 , P29322 | EPHA10 , Q5JZY3 | EPHB1 , P54762 | EPHB2 , P29323 | EPHB3 , P54753 | EPHB4 , P54760 | EPHB6 , O15197 |
| EC number | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 | 2.7.10.1 |
| Inhibitors | – | – | compound 66 (pIC ₅₀ 9) [130] | – | – | tesevatinib (pIC ₅₀ 8.9) [72] | – |

Type XIV RTKs: RET

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type XIV RTKs: RET

Overview: Ret proto-oncogene (Rearranged during transfection) is a transmembrane tyrosine kinase enzyme which is employed as a signalling partner for members of the [GDNF family receptors](#). Ligand-activated GFR appears to recruit Ret as a dimer, leading to activation of further intracellular signalling pathways. Ret appears to be involved in neural crest development, while mutations may be involved in multiple endocrine neoplasia, Hirschsprung's disease, and medullary thyroid carcinoma.

| | |
|---------------------|--|
| Nomenclature | ret proto-oncogene |
| Common abbreviation | Ret |
| HGNC, UniProt | RET , P07949 |
| EC number | 2.7.10.1 |
| Inhibitors | tamaninib (pIC ₅₀ 8.3) [34] |

Comments: A number of tyrosine kinase inhibitors targeting RET have been described [56].

Type XV RTKs: RYK

Catalytic receptors → Receptor kinases → TK: Tyrosine kinase → Receptor tyrosine kinases (RTKs) → Type XV RTKs: RYK

Overview: The 'related to tyrosine kinase receptor' (Ryk) is structurally atypical of the family of RTKs, particularly in the activation and ATP-binding domains. RYK has been suggested to lack kinase activity and appears to be involved, with FZD8, in the Wnt signalling system [196].

| | |
|---------------------|---|
| Nomenclature | receptor like tyrosine kinase |
| Common abbreviation | RYK |
| HGNC, UniProt | RYK, P34925 |
| EC number | 2.7.10.1 |

Comments: Thus far, no selective RYK inhibitors have been described.

Type XVI RTKs: DDR (collagen receptor) family

[Catalytic receptors](#) → [Receptor kinases](#) → TK: Tyrosine kinase → [Receptor tyrosine kinases \(RTKs\)](#) → [Type XVI RTKs: DDR \(collagen receptor\) family](#)

Overview: Discoidin domain receptors 1 and 2 (DDR1 and DDR2) are structurally-related membrane protein tyrosine kinases activated by collagen. Collagen is probably the most abundant protein in man, with at least 29 families of genes encoding proteins, which undergo splice variation and post-translational processing, and may exist in monomeric or polymeric forms, producing a triple-stranded, twine-like structure. In man, principal family members include [COL1A1 \(COL1A1, P02452\)](#), [COL2A1 \(COL2A1, P02458\)](#), [COL3A1 \(COL3A1, P02461\)](#) and [COL4A1 \(COL4A1, P02462\)](#).

| | | |
|---------------------|---|---|
| Nomenclature | discoidin domain receptor tyrosine kinase 1 | discoidin domain receptor tyrosine kinase 2 |
| Common abbreviation | DDR1 | DDR2 |
| HGNC, UniProt | DDR1, Q08345 | DDR2, Q16832 |
| EC number | 2.7.10.1 | 2.7.10.1 |

Comments: The tyrosine kinase inhibitors of DDR, [imatinib](#) and [nilotinib](#), were identified from proteomic analysis [45]. Other collagen receptors include glycoprotein VI ([Q9HCN6](#)), leukocyte-associated immunoglobulin-like receptor 1 ([Q6GTX8](#)), leukocyte-associated immunoglobulin-like receptor 2 ([Q6ISS4](#)) and osteoclast-associated immunoglobulin-like receptor ([Q8IYSS](#)).

Type XVII RTKs: ROS receptors

[Catalytic receptors](#) → [Receptor kinases](#) → TK: Tyrosine kinase → [Receptor tyrosine kinases \(RTKs\)](#) → [Type XVII RTKs: ROS receptors](#)

Overview: The *ROS1* gene encodes a receptor tyrosine kinase, whose endogenous substrate and normal physiological functions are not fully determined. Aberrant expression and mutated forms of ROS1 are drivers of malignant transformation in number of tumour types.

| | |
|---------------------|--|
| Nomenclature | c-ros oncogene 1, receptor tyrosine kinase |
| Common abbreviation | ROS |
| HGNC, UniProt | ROS1, P08922 |
| EC number | 2.7.10.1 |

Comments: [Crizotinib](#) is a tyrosine kinase inhibitor, anti-cancer drug targeting ALK and ROS1.

Type XVIII RTKs: LMR family

[Catalytic receptors](#) → [Receptor kinases](#) → [TK: Tyrosine kinase](#) → [Receptor tyrosine kinases \(RTKs\)](#) → [Type XVIII RTKs: LMR family](#)

Overview: The LMR kinases are unusual amongst the RTKs in possessing a short extracellular domain and extended intracellular domain (hence the 'Lemur' name reflecting the long tail). A precise function for these receptors has yet to be defined, although LMR1 was identified as a potential marker of apoptosis [68], giving rise to the name AATYK (Apoptosis-associated tyrosine kinase); while over-expression induces differentiation in neuroblastoma cells [198].

| | | | |
|---------------------|--|---|---|
| Nomenclature | apoptosis associated tyrosine kinase | lemur tyrosine kinase 2 | lemur tyrosine kinase 3 |
| Common abbreviation | Lmr1 | Lmr2 | Lmr3 |
| HGNC, UniProt | AATK, Q6ZMQ8 | LMTK2, Q8IWU2 | LMTK3, Q96Q04 |
| EC number | 2.7.11.1 | 2.7.11.1 | 2.7.11.1 |

Comments: As yet no selective inhibitors of the LMR family have been described.

Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family

[Catalytic receptors](#) → [Receptor kinases](#) → [TK: Tyrosine kinase](#) → [Receptor tyrosine kinases \(RTKs\)](#) → [Type XIX RTKs: Leukocyte tyrosine kinase \(LTK\) receptor family](#)

Overview: The LTK family appear to lack endogenous ligands. LTK is subject to tissue-specific splice variation, which appears to generate products in distinct subcellular locations. ALK fusions created by gene translocations and rearrangements are associated with many types of cancer, including large cell lymphomas, inflammatory myofibroblastic tumours and non-small cell lung cancer [156].

| | | |
|----------------------|--|--|
| Nomenclature | leukocyte receptor tyrosine kinase | ALK receptor tyrosine kinase |
| Common abbreviation | LTK | ALK |
| HGNC, UniProt | LTK, P29376 | ALK, Q9UM73 |
| EC number | 2.7.10.1 | 2.7.10.1 |
| Inhibitors | – | GSK-1838705A (pIC ₅₀ 9.3) [203], compound 8e (pIC ₅₀ 9.1) [103], crizotinib (pIC ₅₀ 9) [41], NVP-TAE684 (pK _d 9) [44], compound 25b (pIC ₅₀ 8.7) [74] |
| Selective inhibitors | – | ceritinib (pIC ₅₀ 9.7) [156] |
| Comments | – | Crizotinib appears to be a selective ALK inhibitor acting on the tyrosine kinase activity [73] |

Further reading on Type XIX RTKs: Leukocyte tyrosine kinase (LTK) receptor family

Orthofer M *et al.* (2020) Identification of ALK in Thinness *Cell* **181**: 1246-62 [PMID: 32442405]

Type XX RTKs: STYK1

[Catalytic receptors](#) → [Receptor kinases](#) → [TK: Tyrosine kinase](#) → [Receptor tyrosine kinases \(RTKs\)](#) → [Type XX RTKs: STYK1](#)

Overview: Similar to the LMR RTK family, STYK1 has a truncated extracellular domain, but also displays a relatively short intracellular tail beyond the split kinase domain. STYK1 (also known as [Novel Oncogene with Kinase-domain, NOK](#)) has been suggested to co-localize with activated EGF receptor [50].

| | |
|---------------------|--|
| Nomenclature | serine/threonine/tyrosine kinase 1 |
| Common abbreviation | STYK1 |
| HGNC, UniProt | STYK1, Q6J9G0 |
| EC number | 2.7.10.2 |

Comments: As yet, no selective inhibitors of STYK1 have been described.

Further reading on Receptor tyrosine kinases (RTKs)

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Receptor serine/threonine kinase (RSTK) family

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family

Overview: Receptor serine/threonine kinases (RSTK), EC 2.7.11.30, respond to particular cytokines, the transforming growth factor β (TGF β) and bone morphogenetic protein (BMP) families, and may be divided into two subfamilies on the basis of structural similarities. Agonist binding initiates formation of a cell-surface complex of type I and type II RSTK, possibly heterotetrameric, where both subunits express serine/threonine kinase activity. The type I receptor serine/threonine kinases are also known as activin receptors or activin receptor-like kinases, ALKs, for which a systematic nomenclature has been proposed (ALK1-7). The type II protein phosphorylates the kinase domain of the type I partner (sometimes referred to as the signal prop-

agating subunit), causing displacement of the protein partners, such as the FKBP12 FK506-binding protein *FKBP1A* (P62942) and allowing the binding and phosphorylation of particular members of the Smad family. These migrate to the nucleus and act as complexes to regulate gene transcription. Type III receptors, sometimes called co-receptors or accessory proteins, regulate the signalling of the receptor complex, in either enhancing (for example, presenting the ligand to the receptor) or inhibitory manners. TGF β family ligand signalling may be inhibited by endogenous proteins, such as *follistatin* (*FST*, P19883), which binds and neutralizes activins to prevent activation of the target receptors.

Endogenous agonists, approximately 30 in man, are often described as paracrine messengers acting close to the source of production. They are characterized by six conserved cysteine residues and are divided into two subfamilies on the basis of sequence comparison and signalling pathways activated, the TGF β /activin/nodal subfamily and the BMP/GDF (growth/differentiation factor)/MIS (Müllerian inhibiting substance) subfamily. Ligands active at RSTKs appear to be generated as large precursors which undergo complex maturation processes [139]. Some are known to form disulphide-linked homo- and/or heterodimeric complexes. Thus, inhibins are α subunits linked to a variety of β chains, while activins are combinations of β subunits.

Type I receptor serine/threonine kinases

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → Type I receptor serine/threonine kinases

Overview: The type I receptor serine/threonine kinases are also known as activin receptors or activin receptor-like kinases, ALKs, for which a systematic nomenclature has been proposed (ALK1-7).

| | | | | | | | |
|----------------------|--------------------------------|------------------------------------|---|---|---|---|--------------------------------|
| Nomenclature | activin A receptor type II | activin A receptor type I | bone morphogenetic protein receptor type IA | activin A receptor type 1B | transforming growth factor beta receptor 1 | bone morphogenetic protein receptor type IB | activin A receptor type 1C |
| Common abbreviation | ALK1 | ALK2 | BMPR1A | ALK4 | TGFBRI | BMPR1B | ALK7 |
| HGNC, UniProt | ACVRL1, P37023 | ACVR1, Q04771 | BMPR1A, P36894 | ACVR1B, P36896 | TGFBRI, P36897 | BMPR1B, O00238 | ACVR1C, Q8NER5 |
| EC number | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 |
| Inhibitors | – | ML347 (pIC ₅₀ 7.5) [54] | – | – | LY2109761 (pK _i 7.4) [163], compound 15b (pIC ₅₀ 7.1) [138] | – | – |
| Selective inhibitors | – | – | – | vactosertib (pIC ₅₀ 7.9) [114] | vactosertib (pIC ₅₀ 8) [114] | – | – |

Further reading on Type I receptor serine/threonine kinases

Battle E *et al.* (2019) Transforming Growth Factor- β Signaling in Immunity and Cancer. *Immunity* **50**: 924-940 [PMID:30995507]

Type II receptor serine/threonine kinases

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → Type II receptor serine/threonine kinases

Overview: The type II protein phosphorylates the kinase domain of the type I partner (sometimes referred to as the signal propagating subunit), causing displacement of the protein partners, such as the FKBP12 FK506-binding protein *FKBP1A* (P62942) and allowing the binding and phosphorylation of particular members of the Smad family.

| | | | | | |
|---------------------|--------------------------------|--|--|--|--|
| Nomenclature | activin A receptor type 2A | activin A receptor type 2B | anti-Mullerian hormone receptor type 2 | bone morphogenetic protein receptor type 2 | transforming growth factor beta receptor 2 |
| Common abbreviation | ActR2 | ActR2B | MISR2 | BMPR2 | TGFB2 |
| HGNC, UniProt | ACVR2A, P27037 | ACVR2B, Q13705 | AMHR2, Q16671 | BMPR2, Q13873 | TGFB2, P37173 |
| EC number | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 | 2.7.11.30 |
| Antibodies | – | bimagrumab (Binding) (pK _d 11.8) [12] | – | – | – |

Further reading on Type II receptor serine/threonine kinases

Battle E *et al.* (2019) Transforming Growth Factor- β Signaling in Immunity and Cancer. *Immunity* **50**: 924-940 [PMID:30995507]

Type III receptor serine/threonine kinases

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → Type III receptor serine/threonine kinases

Overview: Type III receptors, sometimes called co-receptors or accessory proteins, regulate (enhance or inhibit) the signalling of the RSTK complex.

| | |
|---------------------|--|
| Nomenclature | transforming growth factor beta receptor 3 |
| Common abbreviation | TGFBR3 |
| HGNC, UniProt | TGFB3 , Q03167 |

RSTK functional heteromers

Catalytic receptors → Receptor kinases → TKL: Tyrosine kinase-like → Receptor serine/threonine kinase (RSTK) family → RSTK functional heteromers

Overview: For the receptors listed on this page, the exact combination of subunits forming the functional heteromeric receptors is unknown.

| | | |
|---------------------|---|---|
| Nomenclature | Transforming growth factor β receptor | Bone morphogenetic protein receptors |
| Subunits | transforming growth factor beta receptor 1 (Type I), transforming growth factor beta receptor 2 (Type II), transforming growth factor beta receptor 3 (Type III) | bone morphogenetic protein receptor type IA (Type I), bone morphogenetic protein receptor type IB (Type I), activin A receptor type 1 (Type I), activin A receptor type IL (Type I), bone morphogenetic protein receptor type 2 (Type II), activin A receptor type 2A (Type II), activin A receptor type 2B (Type II) |
| Coupling | Smad2, Smad3 [172 , 216] | Smad1, Smad5, Smad8 [172 , 216] |
| Endogenous agonists | TGFβ1 (TGFB1 , P01137), TGFβ2 (TGFB2 , P61812), TGFβ3 (TGFB3 , P10600) | BMP-10 (BMP10 , O95393), BMP-2 (BMP2 , P12643), BMP-4 (BMP4 , P12644), BMP-5 (BMP5 , P22003), BMP-6 (BMP6 , P22004), BMP-7 (BMP7 , P18075), BMP-8A (BMP8A , Q7Z5Y6), BMP-8B (BMP8B , P34820), BMP-9 (GDF2 , Q9UK05) |

| | | | |
|---------------------|---|--|--|
| Nomenclature | Growth/differentiation factor receptors | Activin receptors | Anti-Müllerian hormone receptors |
| Subunits | bone morphogenetic protein receptor type IA (Type I), bone morphogenetic protein receptor type IB (Type I), activin A receptor type 1B (Type I), activin A receptor type 1C (Type I), transforming growth factor beta receptor 1 (Type I), bone morphogenetic protein receptor type 2 (Type II), activin A receptor type 2A (Type II), activin A receptor type 2B (Type II) | activin A receptor type 1B (Type I), activin A receptor type 1C (Type I), activin A receptor type 2A (Type II), activin A receptor type 2B (Type II) | bone morphogenetic protein receptor type IA (Type I), bone morphogenetic protein receptor type IB (Type I), activin A receptor type 1 (Type I), anti-Müllerian hormone receptor type 2 (Type II) |
| Coupling | Smad1, Smad5, Smad8 [172, 216] | Smad2, Smad3 [216] | Smad1, Smad5, Smad8 [172, 216] |
| Endogenous agonists | growth/differentiation factor-1 (<i>GDF1</i> , P27539), growth/differentiation factor-10 (<i>GDF10</i> , P55107), growth/differentiation factor-3 (<i>GDF3</i> , Q9NR23), growth/differentiation factor-7 (<i>GDF7</i> , Q7Z4P5), growth/differentiation factor-9 (<i>GDF9</i> , O60383) | activin A (<i>INHBA</i> , P08476), activin AB (<i>INHBA INHBB</i> , P08476 P09529), activin B (<i>INHBB</i> , P09529), inhibin A (<i>INHA INHBA</i> , P05111 P08476) | Müllerian inhibiting substance (<i>AMH</i> , P03971) |
| Comments | – | Activin receptors are heteromeric complexes comprising activin receptor type I and type II subunits. | – |

Further reading on RSTK functional heteromers

Battle E *et al.* (2019) Transforming Growth Factor- β Signaling in Immunity and Cancer. *Immunity* **50**: 924-940 [PMID:30995507]

Comments on Receptor serine/threonine kinase (RSTK) family: A number of endogenous inhibitory ligands have been identified for RSTKs, including BMP-3 (*BMP3*, P12645), inhibin α (*INHA*, P05111), inhibin β C (*INHBC*, P55103) and inhibin β E (*INHBE*, P58166).

An appraisal of small molecule inhibitors of TGF β and BMP signalling concluded that TGF β pathway inhibitors were more selective than BMP signalling inhibitors [243]. The authors confirmed the selectivity of TGF-beta RI inhibitor III to inhibit TGF β signalling through ALK4, ALK5, ALK7 [42]. Dorsomorphin inhibits BMP signalling through ALK2 and ALK3, it also inhibits AMP kinase [271].

Smads were identified as mammalian orthologues of Drosophila genes termed “mothers against decapentaplegic” and may be divided into Receptor-regulated Smads (R-Smads, including Smad1, Smad2, Smad3, Smad5 and Smad8), Co-mediated Smad (Co-Smad, Smad4) and Inhibitory Smads (I-Smad, Smad6 and Smad7). R-Smads form heteromeric complexes with Co-Smad. I-Smads compete for binding of R-Smad with both receptors and Co-Smad.

| Nomenclature | HGNC gene symbol | Uniprot ID | Other names |
|--------------|------------------|------------|-------------------------|
| Smad1 | <i>SMAD1</i> | Q15797 | JV4-1, MADH1, MADR1 |
| Smad2 | <i>SMAD2</i> | Q15796 | JV18-1, MADH2, MADR2 |
| Smad3 | <i>SMAD3</i> | P84022 | HsT17436, JV15-2, MADH3 |
| Smad4 | <i>SMAD4</i> | Q13485 | DPC4, MADH4 |
| Smad5 | <i>SMAD5</i> | Q99717 | Dwfc, JV5-1, MADH5 |
| Smad6 | <i>SMAD6</i> | O43541 | HsT17432, MADH6, MADH7 |
| Smad7 | <i>SMAD7</i> | O15105 | MADH7, MADH8 |
| Smad8 | <i>SMAD9</i> | O15198 | MADH6, MADH9 |

Further reading on Receptor serine/threonine kinase (RSTK) family

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Receptor tyrosine phosphatase (RTP) family

Catalytic receptors → Receptor tyrosine phosphatase (RTP) family

Overview: Receptor tyrosine phosphatases (RTP) are cell-surface proteins with a single TM region and intracellular phosphotyrosine phosphatase activity. Many family members exhibit constitutive activity in heterologous expression, dephosphorylating intracellular targets such as Src tyrosine kinase (SRC) to activate signalling cascades. Family members bind components of the extracellular matrix or cell-surface proteins indicating a role in intercellular communication.

| Nomenclature | RTP Type A | RTP Type B | RTP Type C | RTP Type D | RTP Type E | RTP Type F | RTP Type G |
|-----------------------------|-----------------------|-----------------------|--|--|-----------------------|--|---|
| HGNC, UniProt | <i>PTPRA</i> , P18433 | <i>PTPRB</i> , P23467 | <i>PTPRC</i> , P08575 | <i>PTPRD</i> , P23468 | <i>PTPRE</i> , P23469 | <i>PTPRF</i> , P10586 | <i>PTPRG</i> , P23470 |
| Putative endogenous ligands | – | – | galectin-1 (<i>LGALS1</i> , P09382) [244] | netrin-G3 ligand (<i>LRRC4B</i> , Q9NT99) [129] | – | netrin-G3 ligand (<i>LRRC4B</i> , Q9NT99) [129] | contactin-3 (<i>CNTN3</i> , Q9P232), contactin-4 (<i>CNTN4</i> , Q8IWW2), contactin-5 (<i>CNTN5</i> , O94779), contactin-6 (<i>CNTN6</i> , Q9UQ52) [18] |
| Inhibitors | – | – | – | – | – | illudalic acid (pIC ₅₀ 5.9) [142] | compound 1 (pK _i 5.6) [215] |

| Nomenclature | RTP Type H | RTP Type J | RTP Type K | RTP Type M | RTP Type N | RTP Type N2 | RTP Type O |
|-----------------------------|-----------------------|-----------------------|--|--|-----------------------|------------------------|-----------------------|
| HGNC, UniProt | <i>PTPRH</i> , Q9HD43 | <i>PTPRJ</i> , Q12913 | <i>PTPRK</i> , Q15262 | <i>PTPRM</i> , P28827 | <i>PTPRN</i> , Q16849 | <i>PTPRN2</i> , Q92932 | <i>PTPRO</i> , Q16827 |
| Putative endogenous ligands | – | – | galectin-3 (<i>LGALS3</i> , P17931), galectin-3 binding protein (<i>LGALS3BP</i> , Q08380) [122] | – | – | – | – |
| Inhibitors | – | – | – | compound 8a (pIC ₅₀ 5.2) [92] | – | – | – |

| Nomenclature | RTP Type Q | RTP Type R | RTP Type S | RTP Type T | RTP Type U | RTP Type Z1 |
|-----------------------------|------------------------------|------------------------------|--|------------------------------|------------------------------|--|
| HGNC, UniProt | <i>PTPRQ</i> , <i>Q9UMZ3</i> | <i>PTPRR</i> , <i>Q15256</i> | <i>PTPRS</i> , <i>Q13332</i> | <i>PTPRT</i> , <i>O14522</i> | <i>PTPRU</i> , <i>Q92729</i> | <i>PTPRZ1</i> , <i>P23471</i> |
| Putative endogenous ligands | – | – | chondroitin sulphate proteoglycan 3 (<i>NCAN</i> , <i>O14594</i>), netrin-G3 ligand (<i>LRRC4B</i> , <i>Q9NT99</i>) [129, 214] | – | – | contactin-1 (<i>CNTN1</i> , <i>Q12860</i>), pleiotrophin (<i>PTN</i> , <i>C9JR52</i>) (acts as a negative regulator) [18, 165] |
| Inhibitors | – | – | compound 7b (pIC ₅₀ 5.4) [84], 7-BIA (pIC ₅₀ 4.4) [239] | – | – | – |

Further reading on Receptor tyrosine phosphatase (RTP) family

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Tumour necrosis factor (TNF) receptor family

Catalytic receptors → Tumour necrosis factor (TNF) receptor family

Overview: Dysregulated TNFR signalling is associated with many inflammatory disorders, including some forms of arthritis and inflammatory bowel disease, and targeting TNF has been an effective therapeutic strategy in these diseases and for cancer immunotherapy [21, 22, 211].

| | | | | | | | |
|-------------------------|--|---|---|---|---------------------------------------|-------------------------------------|---|
| Nomenclature | tumor necrosis factor receptor 1 | tumor necrosis factor receptor 2 | lymphotoxin β receptor | OX40 | CD40 | Fas | decoy receptor 3 |
| Systematic nomenclature | TNFRSF1A | TNFRSF1B | TNFRSF3 | TNFRSF4 | TNFRSF5 | TNFRSF6 | TNFRSF6B |
| Common abbreviation | TNFR1 | TNFR2 | – | – | – | – | – |
| HGNC, UniProt | TNFRSF1A, P19438 | TNFRSF1B, P20333 | LTBR, P36941 | TNFRSF4, P43489 | CD40, P25942 | FAS, P25445 | TNFRSF6B, O95407 |
| Adaptor proteins | TRADD | TRAF1, TRAF2, TRAF5 | TRAF3, TRAF4, TRAF5 | TRAF1, TRAF2, TRAF3, TRAF5 | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 | FADD | – |
| Endogenous ligands | lymphotoxin- α (<i>LTA</i> , P01374), tumour necrosis factor membrane form (<i>TNF</i> , P01375), tumour necrosis factor shed form (<i>TNF</i> , P01375) | lymphotoxin- α (<i>LTA</i> , P01374), tumour necrosis factor membrane form (<i>TNF</i> , P01375) | LIGHT (<i>TNFSF14</i> , O43557), lymphotoxin $\beta_2\alpha_1$ heterotrimer (<i>LTA</i> <i>LTB</i> , P01374 Q06643) | OX-40 ligand (<i>TNFSF4</i> , P23510) | CD40 ligand (<i>CD40LG</i> , P29965) | Fas ligand (<i>FASLG</i> , P48023) | – |
| Ligands | – | – | – | compound 1 (Binding) (pIC ₅₀ 5.9) [219] | – | – | – |
| Comments | – | – | – | The OX40/OX40L pair is involved in late T-cell costimulatory signaling and both are transiently expressed following antigen recognition, and blocking OX40/OX40L is reported to prevent the development of disease in <i>in vivo</i> autoimmune and inflammatory disease models [248] | – | – | Decoy receptor for LIGHT (<i>TNFSF14</i> , O43557), TL1A (<i>TNFSF15</i> , O95150) and Fas ligand (<i>FASLG</i> , P48023). |

| | | | | | | | |
|-------------------------|------------------------------|---------------------------------------|--|-----------------------------------|---|--|--|
| Nomenclature | CD27 | CD30 | 4-1BB | death receptor 4 | death receptor 5 | decoy receptor 1 | decoy receptor 2 |
| Systematic nomenclature | TNFRSF7 | TNFRSF8 | TNFRSF9 | TNFRSF10A | TNFRSF10B | TNFRSF10C | TNFRSF10D |
| Common abbreviation | – | – | – | DR4 | DR5 | – | – |
| HGNC, UniProt | CD27, P26842 | TNFRSF8, P28908 | TNFRSF9, Q07011 | TNFRSF10A, O00220 | TNFRSF10B, O14763 | TNFRSF10C, O14798 | TNFRSF10D, Q9UBN6 |
| Adaptor proteins | TRAF2, SIVA | TRAF1, TRAF2, TRAF3, TRAF5 | TRAF1, TRAF2, TRAF3 | FADD | FADD | – | – |
| Endogenous ligands | CD70 (<i>CD70</i> , P32970) | CD30 ligand (<i>TNFSF8</i> , P32971) | 4-1BB ligand (<i>TNFSF9</i> , P41273) | TRAIL (<i>TNFSF10</i> , P50591) | – | – | – |
| Endogenous agonists | – | – | – | – | TRAIL (<i>TNFSF10</i> , P50591) [272] | – | – |
| Agonists | – | – | – | SC-67655 [88] | – | – | – |
| Antibodies | – | brentuximab vedotin (Inhibition) | – | – | tigatuzumab (Agonist) (pK _d ~ 8.5) [272] | – | – |
| Comments | – | – | – | – | – | Decoy receptor for TRAIL (<i>TNFSF10</i> , P50591). | Decoy receptor for TRAIL (<i>TNFSF10</i> , P50591). |

| | | | | | | | |
|-------------------------|--|---|--|--|---|--|--|
| Nomenclature | receptor activator of NF-kappa B | osteoprotegerin | death receptor 3 | TWEAK receptor | TACI | BAFF receptor | herpes virus entry mediator |
| Systematic nomenclature | TNFRSF11A | TNFRSF11B | TNFRSF25 | TNFRSF12A | TNFRSF13B | TNFRSF13C | TNFRSF14 |
| Common abbreviation | RANK | OPG | DR3 | – | – | BAFF-R | HVEM |
| HGNC, UniProt | TNFRSF11A , Q9Y6Q6 | TNFRSF11B , O00300 | TNFRSF25 , Q93038 | TNFRSF12A , Q9NP84 | TNFRSF13B , O14836 | TNFRSF13C , Q96RJ3 | TNFRSF14 , Q92956 |
| Adaptor proteins | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 | – | TRADD | TRAF1, TRAF2, TRAF3 | TRAF2, TRAF5, TRAF6 | TRAF3 | TRAF2, TRAF3, TRAF5 |
| Endogenous ligands | RANK ligand (TNFSF11, O14788) | – | TL1A (TNFSF15, O95150) | TWEAK (TNFSF12, O43508) | APRIL (TNFSF13, O75888) , BAFF (TNFSF13B, Q9Y275) | BAFF (TNFSF13B, Q9Y275) | B and T lymphocyte attenuator (BTLA, Q7Z6A9) , LIGHT (TNFSF14, O43557) , lymphotoxin-α (LTA, P01374) |
| Comments | – | Acts as a decoy receptor for RANK ligand (TNFSF11, O14788) and possibly for TRAIL (TNFSF10, P50591) . | The only known TNFSF ligand for DR3 is TNF-like protein 1A (TL1A) [245]. | – | – | – | – |

| | | | | | | |
|-------------------------|--|---|---|---|---|---|
| Nomenclature | nerve growth factor receptor | B cell maturation antigen | glucocorticoid-induced TNF receptor | toxicity and JNK inducer | RELT | death receptor 6 |
| Systematic nomenclature | TNFRSF16 | TNFRSF17 | TNFRSF18 | TNFRSF19 | TNFRSF19L | TNFRSF21 |
| Common abbreviation | – | BCMA | GITR | TAJ | – | DR6 |
| HGNC, UniProt | NGFR , P08138 | TNFRSF17 , Q02223 | TNFRSF18 , Q9Y5U5 | TNFRSF19 , Q9NS68 | RELT , Q969Z4 | TNFRSF21 , O75509 |
| Adaptor proteins | TRAF2, TRAF4, TRAF6 | TRAF1, TRAF2, TRAF3, TRAF5, TRAF6 | TRAF1, TRAF2, TRAF3, SIVA | TRAF1, TRAF2, TRAF3, TRAF5 | TRAF1 | TRADD |
| Endogenous ligands | NGF (NGF, P01138) (pIC ₅₀ 6) [112], BDNF (BDNF, P23560) , neurotrophin-3 (NTF3, P20783) , neurotrophin-4 (NTF4, P34130) | APRIL (TNFSF13, O75888) , BAFF (TNFSF13B, Q9Y275) | TL6 (TNFSF18, Q9UNG2) | lymphotoxin-α (LTA, P01374) | – | – |
| Comments | One of the two receptor types for the neurotrophins (factors that stimulate neuronal cell survival and differentiation). The other family of neurotrophin receptors are the Trk family of receptor tyrosine kinases. | – | – | Believed to be essential during embryonic development. | Abundant in hematologic tissues. Selective receptor for TNF receptor-associated factor 1 (TRAF1). Activates the NF- κ B pathway. | – |

| | | | | |
|-------------------------|---|---|---|--|
| Nomenclature | TNFRSF22 | TNFRSF23 | ectodysplasin A2 isoform receptor | ectodysplasin 1, anhidrotic receptor |
| Systematic nomenclature | – | – | TNFRS27 | – |
| HGNC, UniProt | – | – | EDA2R , Q9HAV5 | EDAR , Q9UNEO |
| Adaptor proteins | – | – | TRAF1, TRAF3, TRAF6 | TRAF1, TRAF2, TRAF3 |
| Endogenous ligands | – | – | ectodysplasin A2 (EDA, Q92838) [261] | ectodysplasin A1 (EDA, Q92838) [261] |
| Comments | Only identified in mouse to date. A potential decoy receptor for the cytotoxic ligand TNFSF10/TRAIL. Does not contain a cytoplasmic death domain so does not induce apoptosis, and does not activate the NF- κ B signalling pathway. | Only identified in mouse to date. A potential decoy receptor for the cytotoxic ligand TNFSF10/TRAIL. Does not contain a cytoplasmic death domain so does not induce apoptosis, and does not activate the NF- κ B signalling pathway. | Receptor for the EDA-A2 isoform of ectodysplasin encoded by the anhidrotic ectodermal dysplasia (EDA) gene. | Cell surface receptor for ectodysplasin A (a morphogen involved in the development of ectodermal tissues, including skin, hair, nails, teeth, and sweat glands). |

Comments: TNFRSF1A is preferentially activated by the shed form of TNF ligand, whereas the membrane-bound form of TNF serves to activate TNFRSF1A and TNFRSF1B equally. The neurotrophins nerve growth factor ([NGF \(NGF, P01138\)](#)), brain-derived neurotrophic factor ([BDNF \(BDNF, P23560\)](#)), [neurotrophin-3](#)

([NTF3, P20783](#)) (NTF3) and [neurotrophin-4 \(NTF4, P34130\)](#) (NTF4) are structurally unrelated to the TNF ligand superfamily but exert some of their actions through the “low affinity nerve growth factor receptor” (NGFR (TNFRSF16)) as well as through the [TRK family](#) of receptor tyrosine kinases. The endogenous

ligands for EDAR and EDA2R are, respectively, the membrane ([Q92838\[1-391\]](#)) and secreted ([Q92838\[160-391\]](#)) isoforms of Ectodysplasin-A (EDA, [Q92838](#)).

Further reading on Tumour necrosis factor (TNF) receptor family

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