THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: CATALYTIC RECEPTORS

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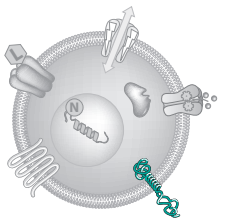

Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full.

Catalytic receptors are one of the seven major pharmacological targets into which the Guide is divided, with the others being G protein-coupled receptors, ligand-gated ion channels, ion channels, nuclear hormone receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors and Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and the Guide to Receptors and Channels, providing a permanent, citable, point-in-time record that will survive database updates.

An Introduction to Catalytic Receptors

Catalytic receptors are cell-surface proteins, usually dimeric in nature, which typically 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 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 generally 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 new group of catalytic receptors for the Guide is the integrins, which have roles in cell : cell communication, often associated with signalling in the blood.

Acknowledgements

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Conflict of interest

The authors state that there is no conflict of interest to disclose.

List of records presented

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 (FBNIII)-like domains, a transmembrane 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 structual 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.

IL-2 receptor family

Overview: The IL-2 receptor family consists of one or more ligand-selective subunits, and a common γ chain (γc): *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 [3].

Nomenclature	Interleukin-2 receptor	Interleukin-4 receptor type I	Interleukin-4 receptor type II	Interleukin-7 receptor	Interleukin-9 receptor
Subunits	Interleukin-2 receptor α subunit (Ligand-binding subunit), Interleukin-2 receptor β subunit (Ligand-binding subunit), Interleukin-2 receptor γ subunit (Other subunit)	Interleukin 4 receptor (Ligand-binding subunit), Interleukin-2 receptor γ subunit (Other subunit)	Interleukin 4 receptor (Ligand-binding subunit), Interleukin 13 receptor, α1 (Other subunit)	Interleukin 7 receptor (Ligand-binding subunit), Interleukin-2 receptor γ subunit (Other subunit)	Interleukin 9 receptor (Ligand-binding subunit), Interleukin-2 receptor γ subunit (Other subunit)
Endogenous agonists	IL-2 (*IL2*, P60568)	IL-4 (*IL4*, P05112)	IL-13 (*IL13*, P35225), IL-4 (*IL4*, P05112)	IL-7 (*IL7*, P13232)	IL-9 (*IL9*, P15248)
Endogenous antagonists	IL-1 receptor antagonist (*IL1RN*, P18510)	–	–	–	–
Selective antagonists	AF12198 [1], Ro264550 [3]	–	–	–	–

Nomenclature	Interleukin 13 receptor, α2	Interleukin-15 receptor	Interleukin-21 receptor	Thymic stromal lymphopoietin receptor
HGNC, UniProt	*IL13RA2*, Q14627	–	–	–
Subunits	–	Interleukin-2 receptor β subunit (Ligand-binding subunit), Interleukin 15 receptor, α subunit (Ligand-binding subunit), Interleukin-2 receptor γ subunit (Other subunit)	Interleukin 21 receptor (Ligand-binding subunit), Interleukin-2 receptor γ subunit (Other subunit)	Interleukin 7 receptor (Ligand-binding subunit), Cytokine receptor-like factor 2 (Other subunit)
Endogenous agonists	–	IL-15 (*IL15*, P40933)	IL-21 (*IL21*, Q9HBE4)	TSLP (*TSLP*, Q969D9)
Comment	Decoy receptor that binds IL-13 (*IL13*, P35225) as a monomer.	–	–	–

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.

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 (*IL3*, P08700)	IL-5 (*IL5*, P05113)	G-CSF (*CSF3*, P09919), GM-CSF (*CSF2*, P04141)
Selective antagonists	–	YM90709 [2]	–

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.

Nomenclature	Interleukin-6 receptor	Interleukin-11 receptor	Interleukin-31 receptor	Ciliary neutrophic factor 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-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
Endogenous agonists	IL-6 (*IL6*, P05231)	IL-11 (*IL11*, P20809)	IL-31 (*IL31*, Q6EBC2)	CNTF (*CNTF*, P26441), CRCF1/CLCF1 heterodimer (*CRLF1*, *CLCF1*, O75462, Q9UBD9)

Nomenclature	Leptin receptor	Leukemia inhibitory factor receptor	Oncostatin-M receptor	Interleukin-27 receptor
HGNC, UniProt	*LEPR*, P48357	–	–	–
Subunits	–	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)	Interleukin 27 receptor, alpha (Ligand-binding subunit), Interleukin-6 receptor, β subunit (Other subunit)
Endogenous agonists	leptin (*LEP*, P41159)	CTF1 (*CTF1*, Q16619), LIF (*LIF*, P15018), OSM (*OSM*, P13725)	OSM (*OSM*, P13725)	IL-27 (*IL27*, *EBI3*, Q14213, Q8NEV9)

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.

Subunits

Nomenclature	Interleukin-12 receptor, β2 subunit	Interleukin 23 receptor
HGNC, UniProt	*IL12RB2*, Q99665	*IL23R*, Q5VWK5

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	Eythropoietin receptor	Granulocyte colony-stimulating factor receptor	Growth hormone receptor	Prolactin receptor	Thrombopoietin receptor
HGNC, UniProt	*EPOR*, P19235	*CSF3R*, Q99062	*GHR*, P10912	*PRLR*, P16471	*MPL*, P40238
Endogenous agonists	erythropoietin (*EPO*, P01588)	G-CSF (*CSF3*, P09919)	growth hormone 1 (*GH1*, P01241), growth hormone 2 (*GH2*, P01242)	choriomammotropin (*CSH1*, *CSH2*, P01243), chorionic somatomammotropin hormone-like 1 (*CSHL1*, Q14406), prolactin (*PRL*, P01236)	thrombopoietin (*THPO*, P40225)

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.

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 genesencoding IFN-&ALPHA; subunits in a cluster on human chromosome 9p22: α1 (*IFNA1*, P01562), α2 (*IFNA2*, P01563), α4 (*IFNA4*, P05014), α5 (*IFNA5*, P01569), α6 (*IFNA6*, P05013), α7 (*IFNA7*, P01567), α8 (*IFNA8*, P32881), α10 (*IFNA10*, P01566), α13 (*IFNA13*, P01562), α14 (*IFNA14*, P01570), α16 (*IFNA16*, P05015), α17 (*IFNA17*, P01571) and α21 (*IFNA21*, P01568).

Nomenclature	Interferon-α/β receptor	Interferon-γ receptor
Subunits	interferon α/β receptor 1 (Ligand-binding subunit), Interferon α/β receptor 2 (Other subunit)	Interferon γ receptor 1 (Ligand-binding subunit), Interferon γ receptor 2 (Other subunit)
Endogenous agonists	IFN-α10 (*IFNA10*, P01566), IFN-α1/13 (*IFNA1*, *IFNA13*, P01562), 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*, Q9P0W0), IFN-ω (*IFNW1*, P05000)	IFN-γ (*IFNG*, P01579)

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; IL28RA/IL10RB responds to IL-28A, IL28B and IL-29.

Nomenclature	Interleukin-10 receptor	Interleukin-20 receptor	Interleukin-22α1/20β heteromer	Interleukin-22α1/10β heteromer	Interleukin-22 receptor α2	Interferon-λ receptor 1
HGNC, UniProt	–	–	–	–	*IL22RA2*, Q969J5	–
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)	–	Interferon-λ receptor 1 (Ligand-binding subunit), Interleukin 10 receptor, β subunit (Other 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)	–	IFN-λ1 (*IFNL1*, Q8IU54), IFN-λ2 (*IFNL2*, Q8IZJ0), IFN-λ3 (*IFNL3*, Q8IZI9)
Comment	–	–	–	–	Soluble decoy receptor that binds IL-22 (*IL22*, Q9GZX6) as a monomer	–

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.

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)	Interleukin 1 receptor, type II (Ligand-binding subunit), IL-1 receptor accessory protein (Other subunit)	Interleukin-18 1 (Ligand-binding subunit), IL-18 receptor accessory protein (Other subunit)
Endogenous agonists	IL-1α (*IL1A*, P01583), IL-1β (*IL1B*, P01584)	IL-33 (*IL33*, O95760)	IL-36α (*IL36A*, Q9UHA7), IL-36β (*IL36B*, Q9NZH7), IL-36γ (*IL36G*, Q9NZH8),	–	IL-18 (*IL18*, Q14116), IL-37 (*IL37*, Q9NZH6)
Endogenous antagonists	IL-1 receptor antagonist (*IL1RN*, P18510)	–	IL-36 receptor antagonist (*IL36RN*, Q9UBH0)	–	–
Selective antagonists	AF12198 [1]	–	–	–	–
Comment	–	–	IL-36 receptor antagonist (*IL36RN*, Q9UBH0) is a highly specific antagonist of the response to IL-36γ (*IL36G*, Q9NZH8)	Decoy receptor that binds IL-1α (*IL1A*, P01583), IL-1β (*IL1B*, P01584) and IL-1 receptor antagonist (*IL1RN*, P18510)	–

IL-17 receptor family

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

Nomenclature	Interleukin-17 receptor	Interleukin-25 receptor	Interleukin-17C receptor	Interleukin-17 receptor D
HGNC, UniProt	–	–	–	*IL17RD*, Q8NFM7
Subunits	Interleukin 17 receptor A (Ligand-binding subunit), interleukin 17 receptor C (Other subunit)	Interleukin 17 receptor B (Ligand-binding subunit), Interleukin 17 receptor A (Other subunit)	Interleukin 17 receptor E (Ligand-binding subunit), Interleukin 17 receptor A (Other subunit)	–
Endogenous agonists	IL-17A (*IL17A*, Q16552), IL-17A/IL-17F (*IL17F*, *IL17A*, Q16552, Q96PD4), IL-17F (*IL17F*, Q96PD4)	IL-17B (*IL17B*, Q9UHF5), IL-25 (*IL25*, Q9H293)	IL-17C (*IL17C*, Q9P0M4)	The endogenous agonist for this receptor is unknown

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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 (*NRTN*, Q99748), 197 aa); artemin (ARTN (*ARTN*, Q5T4W7), 237 aa) and PSPN (*PSPN*, O60542) (PSPN, 156 aa).

Nomenclature	GDNF family receptor α1	GDNF family receptor α2	GDNF family receptor α3	GDNF family receptor α4
Common abbreviation	GFRα1	GFRα2	GFRα3	GFRα4
HGNC, UniProt	*GFRA1*, P56159	*GFRA2*, O00451	*GFRA3*, O60609	*GFRA4*, Q9GZZ7
Potency order	GDNF (*GDNF*, P39905) > NRTN (*NRTN*, Q99748) > ARTN (*ARTN*, Q5T4W7)	NRTN (*NRTN*, Q99748) > GDNF (*GDNF*, P39905)	ARTN (*ARTN*, Q5T4W7)	PSPN (*PSPN*, O60542)
Radioligands (K_d)	[^{125}I]GDNF (rat) ($3x10^{-12}$ – $6.3x10^{-11}$ M) [4,6]	–	–	–

Comments: Inhibitors of other receptor tyrosine kinases, such as semaxinib, which inhibits VEGF receptor function, may also inhibit Ret function [5]. 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.

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Integrins

Overview: Integrins (provisional nomenclature) are heterodimeric entities, composed of α and β subunits, each 1TM 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 α1, α2, α10, α11, 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 Mg^{2+} atom 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.

Nomenclature	Subunits	Ligands	Selective inhibitors (pIC_{50})	Comment
α1β1	integrin, alpha 1 subunit, integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)	collagen, laminin	obtustatin (9.1) [11]	–
α2β1	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)	collagen, laminin, thrombospondin	TCI15 (7.9) [13]	–
αIIbβ3	integrin, alpha 2b subunit (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41), integrin, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61)	fibrinogen, fibronectin, von Willebrand factor, vitronectin, thrombospondin	abciximab, eptifibatide, G4120 [12], GR144053, Syk inhibitor III [14], tirofiban	–
α4β1	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)	fibronectin, VCAM-1, osteopontin, thrombospondin	natalizumab, TCS2314, BIO1211 (8.3 – 9.0) [9]	LDV-FITC is used as a probe at this receptor
αLβ2	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)	ICAM-1, ICAM-2	efalizumab, A286982 (7.4 – 7.5) [10]	–
αVβ3	integrin, alpha V subunit, integrin, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61)	vitronectin, fibronectin, fibrinogen, osteopontin, von Willebrand factor, thrombospondin, tenascin	etaracizumab, echistatin (11.7) [8], P11 (11.6) [8], cilengitide (8.5) [7]	–

Subunits

Nomenclature	HGNC, UniProt
integrin, alpha 1 subunit	*ITGA1*, P56199
integrin, alpha 2 subunit (CD49B, alpha 2 subunit of VLA-2 receptor)	*ITGA2*, P08514
integrin, alpha 2b subunit (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41)	*ITGA2B*, P17301
integrin, alpha 3 subunit (antigen CD49C, alpha 3 subunit of VLA-3 receptor)	*ITGA3*, P26006
integrin, alpha 4 subunit (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	*ITGA4*, P13612
integrin, alpha 5 subunit (fibronectin receptor, alpha polypeptide)	*ITGA5*, P08648
integrin, alpha 6 subunit	*ITGA6*, P23229
integrin, alpha 7 subunit	*ITGA7*, Q13683
integrin, alpha 8 subunit	*ITGA8*, P53708
integrin, alpha 9 subunit	*ITGA9*, Q13797
integrin, alpha 10 subunit	*ITGA10*, O75578
integrin, alpha 11 subunit	*ITGA11*, Q9UKX5
integrin, alpha D subunit	*ITGAD*, Q13349
integrin, alpha E subunit (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide)	*ITGAE*, P38570
integrin, alpha L subunit (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	*ITGAL*, P20701
integrin, alpha M subunit (complement component 3 receptor 3 subunit)	*ITGAM*, P11215
integrin, alpha V subunit	*ITGAV*, P06756
integrin, alpha X subunit (complement component 3 receptor 4 subunit)	*ITGAX*, P20702

Nomenclature	HGNC, UniProt
integrin, beta 1 subunit (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)	*ITGB1*, P05556
integrin, beta 2 subunit (complement component 3 receptor 3 and 4 subunit)	*ITGB2*, P05107
integrin, beta 3 subunit (platelet glycoprotein IIIa, antigen CD61)	*ITGB3*, P05106
integrin, beta 4 subunit	*ITGB4*, P16144
integrin, beta 5 subunit	*ITGB5*, P18084
integrin, beta 6 subunit	*ITGB6*, P18564
integrin, beta 7 subunit	*ITGB7*, P26010
integrin, beta 8 subunit	*ITGB8*, P26012

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 α1β1, α2β1, α10β1 and α11β1 recognise a range of triple-helical peptide motifs including GFOGER (O = hydroxyproline), a synthetic peptide.

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 α1β1, α2β1, α3,β1, α7β1 and α6β4 integrins10.

Fibrinogen 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 αIIbβ3; proteolysis by thrombin cleaves short peptides termed fibrinopeptides to generate fibrin, which polymerises as part of the blood coagulation cascade.

Fibronectin 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 (*FN1*, P02751) generates multiple isoforms.

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

Osteopontin forms an integral part of the mineralized matrix in bone (*SPP1*, P10451), where it undergoes extensive post-translation 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 αIIbβ3).

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Natriuretic peptide receptor family

Overview: Natriuretic peptide receptors (provisional nomenclature) are a family of homodimeric, catalytic receptors with a single TM domain and guanylyl cyclase (EC 4.6.1.2) activity on the intracellular domain of the protein sequence. Isoforms are activated by the peptide hormones atrial natriuretic peptide (ANP (*NPPA*, P01160)), brain natriuretic peptide (BNP (*NPPB*, P16860)) and C-type natriuretic peptide (CNP (*NPPC*, P23582)). Another family member is GC-C, the receptor for guanylin (*GUCA2A*, Q02747) and uroguanylin (*GUCA2B*, Q16661). 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 [25].

Nomenclature	NPR-A	NPR-B	NPR-C	guanylate cyclase 2C (heat stable enterotoxin receptor)
HGNC, UniProt	*NPR1*, P16066	*NPR2*, P20594	*NPR3*, P17342	*GUCY2C*, P25092
Potency order	ANP (*NPPA*, P01160) ≥ BNP (*NPPB*, P16860) >> CNP (*NPPC*, P23582) [27]	CNP (*NPPC*, P23582) >> ANP (*NPPA*, P01160) >> BNP (*NPPB*, P16860) [27]	ANP (*NPPA*, P01160) > CNP (*NPPC*, P23582) ≥ BNP (*NPPB*, P16860) [27]	uroguanylin (*GUCA2B*, Q16661) > guanylin (*GUCA2A*, Q02747)
Endogenous agonists	ANP (*NPPA*, P01160) (Selective) [26], BNP (*NPPB*, P16860) (Selective) [26]	CNP (*NPPC*, P23582) (Selective) [27]	osteocrin (*OSTN*, P61366) (Selective) [23]	–
Selective agonists	sANP [26]	–	cANF$^{4\text{-}23}$ [22]	*E. coli* heat-stable enterotoxin (ST_a), linaclotide [18]
Selective antagonists	anantin [29], A-71915 (pK_i 9.2 – 9.5) [15], [Asu7,23′]β-ANP-(7-28) (pK_i 7.5) [21]	monoclonal antibody 3G12 [17], [Ser^{11}](N-CNP,C-ANP)pBNP$^{2\text{-}15}$ [16]	M372049 [19], AP811 (pK_i 9.3) [28]	–
Radioligands (K_d)	[^{125}I]ANP	[^{125}I]CNP (human)	[^{125}I]ANP	[^{125}I]St_a

Comments: The polysaccharide obtained from fermentation of Aureobasidium species, HS142-1, acts as an antagonist at both NPR-A and NPR-B receptors [24]. *GUCY2D* (RetGC1, GC-E, Q02846) and *GUCY2F* (RetGC2, GC-F, P51841) are predominantly retinal guanylyl cyclase activities, which are inhibited by calcium ions acting through the guanylyl cyclase activating peptides GCAP1 (*GUCA1A*, 43080), GCAP2 (*GUCA1B*, Q9UMX6) and GCAP3 (*GUCA1C*, O95843) [20].

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Pattern Recognition receptors

Overview: Pattern recognition receptors (PRR, [42]) participate in the innate immune response to microbial agents, the stimulation of which leads to activation of intracellular enzymes and regulation of gene transcription. PRR include both cell-surface and intracellular proteins, including toll-like receptors (TLR), nucleotide-binding oligomerization domain-like receptors (NLR, also known as NOD-like receptors) and the mannose receptor family (ENSFM00250000004089). PRR may be divided into signalling-associated members, identified here, and endocytic members (such as the mannose receptor family), the function of which appears to be to recognise particular microbial motifs for subsequent cell attachment, internalisation and destruction. PRRs express multiple leucine-rich regions to bind a range of microbially-derived ligands, termed PAMPs or pathogen-associated molecular patterns, which includes peptides, carbohydrates, peptidoglycans, lipoproteins, lipopolysaccharides, and nucleic acids.

Toll-like receptor family

Overview: Members of this family 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, [43–44]). 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, it has been suggested that selected members of the family may be activated by endogenous ligands, such as hsp60 (*HSPD1*, P10809) [38].

Nomenclature	HGNC, UniProt	Agonists	Comment
TLR1	*TLR1*, Q15399	–	–
TLR2	*TLR2*, O60603	peptidoglycan [41,45]	–
TLR3	*TLR3*, O15455	polyIC [30]	–
TLR4	*TLR4*, O00206	LPS [39], taxol [36]	eritoran (E5564) is a lipid A analogue, which has been described as a TLR4 antagonist [35]
TLR5	*TLR5*, O60602	flagellin [31]	–
TLR6	*TLR6*, Q9Y2C9	–	–
TLR7	*TLR7*, Q9NYK1	imiquimod [33], loxoribine [32], R848 [33]	–
TLR8	*TLR8*, Q9NR97	imiquimod, R848 [33]	–
TLR9	*TLR9*, Q9NR96	CpG [34]	–
TLR10	*TLR10*, Q9BXR5	–	–
TLR11	–, Q6R5P0	–	Found in the mouse

NOD-like receptor family

Overview: Structural analysis has identified a common motif of a mid-peptide located nucleotide-binding and oligomerization (NACHT) domain, which allows division of NOD-like receptors into three subfamilies, NLRC (or NODs), NLRP (or NALP) and IPAF [40]. NLRC members are named on the basis of a sequence motif expressed at their N-termini, the caspase recruitment domain (CARD), while NLRP members have a pyrin domain. NLRs express C-terminal leucine-rich regions which have regulatory function and appear to recognize the microbial products to which the NLRs respond. NLRC family members 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. NLRP family members, upon activation, recruit adaptor proteins (*e.g.* ASC, also known as *PYCARD*, CARD5, TMS-1, Q9ULZ3). Activated NLRs associate in multiprotein complexes, known as inflammasomes [40], allowing the recruitment of caspases.

Nomenclature	HGNC, UniProt	Agonists	Comment
NLRC1	*NOD1*, Q9Y239	meso-DAP	–
NLRC2	*NOD2*, Q9HC29	muramyl dipeptide	–
NLRC3	*NLRC3*, Q7RTR2	–	–
NLRC5	*NLRC5*, Q86WI3	–	–
NLRX1	*NLRX1*, Q86UT6	–	–
CIITA	*CIITA*, P33076	–	–
NLRP1	*NLRP1*, Q9C000	muramyl dipeptide	–
NLRP2	*NLRP2*, Q9NX02	–	–
NLRP3	*NLRP3*, Q96P20	–	Multiple virus particles have been shown to act as agonists, including Sendai and influenza
NLRP4	*NLRP4*, Q96MN2	–	–
NLRP5	*NLRP5*, P59047	–	–
NLRP6	*NLRP6*, P59044	–	–
NLRP7	*NLRP7*, Q8WX94	–	–
NLRP8	*NLRP8*, Q86W28	–	–
NLRP9	*NLRP9*, Q7RTR0	–	–
NLRP10	*NLRP10*, Q86W26	–	–
NLRP11	*NLRP11*, P59045	–	–
NLRP12	*NLRP12*, P59046	–	–
NLRP13	*NLRP13*, Q86W25	–	–
NLRP14	*NLRP14*, Q86W24	–	–
IPAF	*NLRC4*, Q9NPP4	–	–
NAIP	*NAIP*, Q13075	–	–

Comments: NLRP3 has also been reported to respond to host-derived products, known as danger-associated molecular patterns, or DAMPs, including uric acid [37], ATP, L-glucose, hyaluronan and amyloid β (*APP*, P05067) [40].

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

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Receptor serine/threonine kinase (RSTK) family

Overview: Receptor serine/threonine kinases (RTSK), EC 2.7.11.30, respond to particular cytokines, the transforming growth factor β (TGFβ) 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 hetero-tetrameric, where where both subunits express serine/threonine kinase activity. The type I receptor serine/threonine kinases (ENSFM00250000000213) 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 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. 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. TGFβ 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 TGFβ/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 [47]. 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

Overview: The type I receptor serine/threonine kinases (ENSFM00250000000213) 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-like 1	activin A receptor, type I	bone morphogenetic protein receptor, type IA	activin A receptor, type IB	transforming growth factor, beta receptor 1	bone morphogenetic protein receptor, type IB	activin A receptor, type IC
Common abbreviation	ALK1	ALK2	BMPR1A	ALK4	TGFBR1	BMPR1B	ALK7
HGNC, UniProt	*ACVRL1*, P37023	*ACVR1*, Q04771	*BMPR1A*, P36894	*ACVR1B*, P36896	*TGFBR1*, P36897	*BMPR1B*, O00238	*ACVR1C*, Q8NER5

Type II receptor serine/threonine kinases

Nomenclature	activin A receptor, type IIA	activin A receptor, type IIB	anti-Mullerian hormone receptor, type II	bone morphogenetic protein receptor, type II (serine/threonine kinase)	transforming growth factor, beta receptor II (70/80kDa)
Common abbreviation	ActR2	ActR2B	MISR2	BMPR2	TGFBR2
HGNC, UniProt	*ACVR2A*, P27037	*ACVR2B*, Q13705	*AMHR2*, Q16671	*BMPR2*, Q13873	*TGFBR2*, P37173

Type III receptor serine/threonine kinases

Nomenclature	transforming growth factor, beta receptor III
Common abbreviation	TGFBR3
HGNC, UniProt	*TGFBR3*, Q03167

RSTK functional heteromers

Nomenclature	Transforming growth factor β receptor	Bone morphogenetic protein receptors	Growth/differentiation factor receptors	Activin receptors	Anti-Müllerian hormone receptors
Subunits	transforming growth factor, beta receptor 1 (Type I), transforming growth factor, beta receptor II (70/80kDa) (Type II), transforming growth factor, beta receptor III (Type III)	activin A receptor type II-like 1 (Type I), activin A receptor, type I (Type I), bone morphogenetic protein receptor, type IA (Type I), bone morphogenetic protein receptor, type IB (Type I), activin A receptor, type IIA (Type II), activin A receptor, type IIB (Type II), bone morphogenetic protein receptor, type II (serine/threonine kinase) (Type II)	bone morphogenetic protein receptor, type IA (Type I), activin A receptor, type IB (Type I), transforming growth factor, beta receptor 1 (Type I), bone morphogenetic protein receptor, type IB (Type I), activin A receptor, type IC (Type I), activin A receptor, type IIA (Type II), activin A receptor, type IIB (Type II), bone morphogenetic protein receptor, type II (serine/threonine kinase) (Type II)	activin A receptor, type IB (Type I), activin A receptor, type IC (Type I), activin A receptor, type IIA (Type II), activin A receptor, type IIB (Type II)	activin A receptor, type I (Type I), bone morphogenetic protein receptor, type IA (Type I), bone morphogenetic protein receptor, type IB (Type I), anti-Mullerian hormone receptor, type II (Type II)
Coupling	Smad2, Smad3 [48–49]	Smad1, Smad5, Smad8 [48–49]	Smad1, Smad5, Smad8 [48–49]	Smad2, Smad3 [49]	Smad1, Smad5, Smad8 [48–49]
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)	GDF1 (*GDF1*, P27539), GDF10 (*GDF10*, P55107), GDF9 (*GDF9*, O60383), GDF3 (*GDF3*, Q9NR23)	inhibin βA (*INHBA*, P08476), inhibin βB (*INHBB*, P09529)	Müllerian inhibiting substance (*AMH*, P03971)

Comments: A number of endogenous inhibitory ligands have been identified for RSTKs, including BMP3, inhibinα, inhibinβC and inhibinβE.

An appraisal of small molecule inhibitors of TGFβ and BMP signalling concluded that TGFβ pathway inhibitors were more selective than BMP signalling inhibitors [50]. The authors confirmed the selectivity of SB505124 to inhibit TGFβ signalling through ALK4, ALK5, ALK7 [46]. dorsomorphin inhibits BMP signalling through ALK2 and ALK3, it also inhibits AMP kinase [51].

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, UniProt	Other names
Smad1	*SMAD1*, Q15797	JV4-1, MADH1, MADR1
Smad2	*SMAD2*, Q15796	JV18-1, MADH2, MADR2
Smad3	*SMAD3*, P84022	HsT17436, JV15-2, MADH3
Smad4	*SMAD4*, Q13485	DPC4, MADH4
Smad5	*SMAD5*, Q99717	Dwfc, JV5-1, MADH5
Smad6	*SMAD6*, O43541	HsT17432, MADH6, MADH7
Smad7	*SMAD7*, O15105	MADH7, MADH8
Smad8	*SMAD9*, O15198	MADH6, MADH9

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Receptor tyrosine kinases

Overview: Receptor tyrosine kinases (RTKs, EC 2.7.10.1), 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 [55,65,82]. In the human genome, 58 RTKs have been identified, which fall into 20 families [70].

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 [82].

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

Overview: ErbB family receptors are Class I receptor tyrosine kinases [65]. ERBB2 (also known as HER-2 or NEU; *ERBB2*, P04626) appears to act as an essential partner for the other members of the family without itself being activated by a cognate ligand [66]. 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.

Nomenclature	Common abbreviation	HGNC, UniProt	Endogenous ligands
epidermal growth factor receptor	EGFR	*EGFR*, P00533	amphiregulin (AREG, AREGB, P15514), betacellulin (BTC, P35070), EGF (EGF, P01133), epigen (EPGN, Q6UW88), epiregulin (EREG, O14944), HB-EGF (HBEGF, Q99075), TGFα (TGFA, P01135)
v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 3	HER3	*ERBB3*, P21860	NRG-1 (NRG1, Q02297), NRG-2 (NRG2, O14511)
v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4	HER4	*ERBB4*, Q15303	betacellulin (BTC, P35070), epiregulin (EREG, O14944), HB-EGF (HBEGF, Q99075), NRG-1 (NRG1, Q02297), NRG-2 (NRG2, O14511), NRG-3 (NRG3, P56975), NRG-4 (NRG4, Q8WWG1)

Comments: [^{125}I]EGF (human) has been used to label the ErbB1 EGF receptor. The extracellular domain of ErbB2 can be targetted 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, [63]), gefitinib, erlotinib and tyrphostins AG879 and AG1478.

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 [65], 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	Insulin receptor-related receptor
Common abbreviation	InsR	IGF1R	IRR
HGNC, UniProt	*INSR*, P06213	*IGF1R*, P08069	*INSRR*, P14616
Endogenous ligands	insulin (INS, P01308)	IGF1 (*IGF1*, P05019), IGF2 (*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 II receptor), which lacks classical signalling capacity and appears to subserve a trafficking role [72]. INSRR, which has a much more discrete localization, being predominant in the kidney [69], currently lacks a cognate ligand or evidence for functional impact.

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

PQ401 inhibits the insulin-like growth factor receptor [56], while BMS-536924 inhibits both the insulin receptor and the insulin-like growth factor receptor [85].

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 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 polypeptide	platelet-derived growth factor receptor, beta polypeptide	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog	colony stimulating factor 1 receptor	fms-related tyrosine kinase 3
Common abbreviation	PDGFRα	PDGFRβ	Kit	CSFR	FLT3
HGNC, UniProt	*PDGFRA*, P16234	*PDGFRB*, P09619	*KIT*, P10721	*CSF1R*, P07333	*FLT3*, P36888
Endogenous ligands	PDGF	PDGF	SCF (*KITLG*, P21583)	G-CSF (*CSF3*, P09919), GM-CSF (*CSF2*, P04141), M-CSF (*CSF1*, P09603)	FLT3L (*FLT3LG*, P49771)
Comment	–	–	–	–	5′-fluoroindirubinoxime has been described as a selective FLT3 inhibitor [57]

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 [78]; 5′-fluoroindirubinoxime has been described as a selective FLT3 inhibitor [53].

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 variants 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 activate VEGFR1 homodimers, while VEGFC (*VEGFC*, P49767) and VEGFD (*FIGF*, O43915) activate VEGFR2/3 heterodimers and VEGFR3 homodimers, and, following proteolysis, VEGFR2 homodimers.

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

Comments: The VEGFR, as well as VEGF ligands, have been targeted by antibodies and tyrosine kinase inhibitors. DMH4 [62], Ki8751 [68] and ZM323881, a novel inhibitor of vascular endothelial growth factor-receptor-2 tyrosine kinase activity [84] 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

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 receptors 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 [61]. 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 [83].

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	*FGFR1*, P11362	*FGFR2*, P21802	*FGFR3*, P22607	*FGFR4*, P22455
Endogenous ligands	FGF-1 (*FGF1*, P05230), FGF-2 (*FGF2*, P09038), FGF-4 (*FGF4*, P08620) > FGF-5 (*FGF5*, P12034), FGF-6 (*FGF6*, P10767) [77]	FGF-1 (*FGF1*, P05230) > FGF-4 (*FGF4*, P08620), FGF-7 (*FGF7*, P21781), FGF-9 (*FGF9*, P31371) > FGF-2 (*FGF2*, P09038), FGF-6 (*FGF6*, P10767) [77]	FGF-1 (*FGF1*, P05230), FGF-2 (*FGF2*, P09038), FGF-9 (*FGF9*, P31371) > FGF-4 (*FGF4*, P08620), FGF-8 (*FGF8*, P55075) [77]	FGF-1 (*FGF1*, P05230), FGF-2 (*FGF2*, P09038), FGF-4 (*FGF4*, P08620), FGF-9 (*FGF9*, P31371) > FGF-6 (*FGF6*, P10767), FGF-8 (*FGF8*, P55075) [77]

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 [71,87]. PD161570 is an FGFR tyrosine kinase inhibitor [54], while PD173074 has been described to inhibit FGFR1 and FGFR3 [80].

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 κB (NF-κB) activation. Both trkA and trkB contain two leucine-rich regions and can exist in monomeric or dimeric forms.

Nomenclature	neurotrophic tyrosine kinase, receptor, type 1	neurotrophic tyrosine kinase, receptor, type 2	neurotrophic tyrosine kinase, receptor, type 3
Common abbreviation	trkA	trkB	trkC
HGNC, UniProt	*NTRK1*, P04629	*NTRK2*, Q16620	*NTRK3*, Q16288
Endogenous ligands	NGF (*NGF*, P01138) > NT-3 (*NTF3*, P20783)	BDNF (*BDNF*, P23560),NT-4 (*NTF4*, P34130) > NT-3 (*NTF3*, P20783)	NT-3 (*NTF3*, P20783)

Comments: [^{125}I]NGF (human) and [^{125}I]BDNF have been used to label the trkA and trkB receptor, respectively. p75 influences the binding of NGF (*NGF*, P01138) and NT-3 (*NTF3*, P20783) to trkA. The ligand selectivity of p75 appears to be dependent on the cell type; for example, in sympathetic neurones, it binds NT-3 (*NTF3*, P20783) with comparable affinity to trkC [60].

Small molecule agonists of trkB have been described, including LM22A4 [73], while ANA12 has been described as a non-competitive antagonist of BDNF binding to trkB [56]. GNF5837 is a family-selective tyrosine kinase inhibitor [52], while the tyrosine kinase activity of the trkA receptor can be inhibited by GW441756 ($p_{IC}50$= 8.7, [86]) and tyrphostin AG879 [76].

Type VIII RTKs: ROR family

Overview: Members of the ROR family (ENSFM00510000502747) 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 [67].

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

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, 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	macrophage stimulating 1 receptor (c-met-related tyrosine kinase)
Common abbreviation	Met	Ron
HGNC, UniProt	*MET*, P08581	*MST1R*, Q04912
Endogenous ligands	HGF (*HGF*, P14210)	MST1 (*MST1*, P09603)

Comments: PF04217903 is a selective Met tyrosine kinase inhibitor [58]. SU11274 is an inhibitor of the HGF receptor [79], with the possibility of further targets [53].

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

Overview: Members of this RTK family (ENSFM00500000269872) represented a novel structural motif, when sequenced. The ligands for this family, Gas6 (*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	c-mer proto-oncogene tyrosine kinase
Common abbreviation	Axl	Tyro3	Mer
HGNC, UniProt	*AXL*, P30530	*TYRO3*, Q06418	*MERTK*, Q12866
Endogenous ligands	Gas6 (*GAS6*, Q14393) [75], protein S (*PROS1*, P07225) [81]	Gas6 (*GAS6*, Q14393) [75], protein S (*PROS1*, P07225) [81]	Gas6 (*GAS6*, Q14393) [75]

Comments: AXL tyrosine kinase inhibitors have been described [74].

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 tyrosine kinase, endothelial
Common abbreviation	TIE1	TIE2
HGNC, UniProt	*TIE1*, P35590	*TEK*, Q02763
Endogenous ligands	–	angiopoietin-1 (*ANGPT1*, Q15389), angiopoietin-4 (*ANGPT4*, Q9Y264)

Type XIII RTKs: Ephrin receptor family

Overview: Ephrin receptors (ENSFM00250000000121) 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 (EFNA1 (*EFNA1*, P20827), EFNA2 (*EFNA2*, O43921), EFNA3 (*EFNA3*, P52797), EFNA4 (*EFNA4*, P52798) and EFNA5 (*EFNA5*, P52803)) and 1TM proteins for Ephrin B (ENSFM00250000002014: EFNB1 (*EFNB1*, P98172), EFNB2 (*EFNB2*, P52799) and EFNB3 (*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	EPH receptor A8	EPH receptor A10	EPH receptor B1	EPH receptor B2	EPH receptor B3	EPH receptor B4	EPH receptor B6
Common abbreviation	EphA1	EphA2	EphA3	EphA4	EphA5	EphA6	EphA7	EphA8	EphA10	EphB1	EphB2	EphB3	EphB4	EphB6
HGNC, UniProt	*EPHA1*, P21709	*EPHA2*, P29317	*EPHA3*, P29320	*EPHA4*, P54764	*EPHA5*, P54756	*EPHA6*, Q9UF33	*EPHA7*, Q15375	*EPHA8*, P29322	*EPHA10*, Q5JZY3	*EPHB1*, P54762	*EPHB2*, P29323	*EPHB3*, P54753	*EPHB4*, P54760	*EPHB6*, O15197

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

Comments: The tyrosine kinase inhibitors of DDR, imatinib and nilotinib, were identified from proteomic analysis [59].

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

Overview: The LTK family (ENSFM00500000270379) appear to lack endogenous ligands. LTK is subject to tissue-specific splice variation, which appears to generate products in distinct subcellular locations. Alk fusions derived from gene translocations are associated with large cell lymphomas and inflammatory myofibrilastic tumours.

Nomenclature	leukocyte receptor tyrosine kinase	anaplastic lymphoma receptor tyrosine kinase
Common abbreviation	LTK	ALK
HGNC, UniProt	*LTK*, P29376	*ALK*, Q9UM73
Comment	–	crizotinib appears to be a selective ALK inhibitor acting on the tyrosine kinase activity [64]

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Receptor tyrosine phosphatases (RTP)

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	HGNC, UniProt	Putative endogenous ligands
RTP Type A	*PTPRA*, P18433	–
RTP Type B	*PTPRB*, P23467	–
RTP Type C	*PTPRC*, P08575	galectin-1 (*LGALS1*, P09382) [93]
RTP Type D	*PTPRD*, P23468	netrin-G3 ligand (*LRRC4B*, Q9NT99) [90]
RTP Type E	*PTPRE*, P23469	–
RTP Type F	*PTPRF*, P10586	netrin-G3 ligand (*LRRC4B*, Q9NT99) [90]
RTP Type G	*PTPRG*, P23470	contactin-3 (*CNTN3*, Q9P232), contactin-4 (*CNTN4*, Q8IWV2), contactin-5 (*CNTN5*, O94779), contactin-6 (*CNTN6*, Q9UQ52) [88]
RTP Type H	*PTPRH*, Q9HD43	–
RTP Type J	*PTPRJ*, Q12913	–
RTP Type K	*PTPRK*, Q15262	galectin-3 (*LGALS3*, P17931), galectin-3 binding protein (*LGALS3BP*, Q08380) [89]
RTP Type M	*PTPRM*, P28827	–
RTP Type N	*PTPRN*, Q16849	–
RTP Type N2	*PTPRN2*, Q92932	–
RTP Type O	*PTPRO*, Q16827	–
RTP Type Q	*PTPRQ*, Q9UMZ3	–
RTP Type R	*PTPRR*, Q15256	–
RTP Type S	*PTPRS*, Q13332	chondroitin sulphate proteoglycan 3 (*NCAN*, O14594), netrin-G3 ligand (*LRRC4B*, Q9NT99) [90,92]
RTP Type T	*PTPRT*, O14522	–
RTP Type U	*PTPRU*, Q92729	–
RTP Type Z1	*PTPRZ1*, P23471	contactin-1 (*CNTN1*, Q12860), pleiotrophin (*PTN*, C9JR52) (acts as a negative regulator) [88,91]

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Tumour necrosis factor (TNF) receptor family

Overview: The TNF receptor superfamily (TNFRSF, provisional nomenclature) displays limited homology beyond an extracellular domain rich in cysteine residues and is activated by at least 18 different human homologues of TNF referred to as the TNF superfamily (TNFSF). Some homologues lacking transmembrane and cytoplasmic domains function as decoy receptors binding ligand without inducing cell signalling. Many of these receptors and ligands function as multimeric entities. Signalling through these receptors is complex and involves interaction with cytoplasmic adaptor proteins (such as TRADD and TRAF1). Several of these receptors contain cytoplasmic motifs known as 'death domains', which upon activation serve to recruit death domain- and death effector domain-containing proteins crucial for the initiation of an apoptotic response. Additional signalling pathways include the regulation of the nuclear factor κB or mitogen-activated protein kinase pathways. Pharmacological manipulation of these receptors is mainly enacted through chelating the endogenous agonists with humanised monoclonal antibodies (*e.g.* infliximab or adalimumab) or recombinant fusion proteins of IgG and soluble receptors (*e.g.* etanercept). Some mutated forms of TNF ligands are capable of selecting for different receptor subtypes.

Receptors

Nomenclature	Systematic nomenclature	Common abbreviation	HGNC, UniProt	Adaptor proteins	Endogenous ligands	Comment
tumor necrosis factor receptor 1	TNFRSF1A	TNFR1	*TNFRSF1A*, P19438	TRADD	TNFSF1 (*LTA*, P01374), TNF membrane form (*TNF*, P01375), TNF shed form (*TNF*, P01375)	–
tumor necrosis factor receptor 2	TNFRSF1B	TNFR2	*TNFRSF1B*, P20333	TRAF1, TRAF2, TRAF5	TNFSF1 (*LTA*, P01374), TNF membrane form (*TNF*, P01375)	–
lymphotoxin β receptor	TNFRSF3	–	*LTBR*, P36941	TRAF3, TRAF4, TRAF5	LIGHT (*TNFSF14*, O43557), lymphotoxin $\beta_2\alpha_1$ heterotrimer (*LTA*, *LTB*, Q06643, P01374)	–
OX40	TNFRSF4	–	*TNFRSF4*, P43489	TRAF1, TRAF2, TRAF3, TRAF5	OX-40 ligand (*TNFSF4*, P23510)	–
CD40	TNFRSF5	–	*CD40*, P25942	TRAF1, TRAF2, TRAF3, TRAF5, TRAF6	CD40 ligand (*CD40LG*, P29965)	–
Fas	TNFRSF6	–	*FAS*, P25445	FADD	Fas ligand (*FASLG*, P48023)	–
CD27	TNFRSF7	–	*CD27*, P26842	TRAF2, SIVA	CD70 (*CD70*, P32970)	–
CD30	TNFRSF8	–	*TNFRSF8*, P28908	TRAF1, TRAF2, TRAF3, TRAF5	CD30 ligand (*TNFSF8*, P32971)	–
4-1BB	TNFRSF9	–	*TNFRSF9*, Q07011	TRAF1, TRAF2, TRAF3	4-1BB ligand (*TNFSF9*, P41273)	–
death receptor 4	TNFRSF10A	DR4	*TNFRSF10A*, O00220	FADD	TRAIL (*TNFSF10*, P50591)	–
death receptor 5	TNFRSF10B	DR5	*TNFRSF10B*, O14763	FADD	TRAIL (*TNFSF10*, P50591)	–
receptor activator of NF-kappa B	TNFRSF11A	RANK	*TNFRSF11A*, Q9Y6Q6	TRAF1, TRAF2, TRAF3, TRAF5, TRAF6	RANK ligand (*TNFSF11*, O14788)	–
osteoprotegerin	TNFRSF11B	OPG	*TNFRSF11B*, O00300	–	–	Acts as a decoy receptor for RANK ligand (*TNFSF11*, O14788) and possibly for TRAIL (*TNFSF10*, P50591)
death receptor 3	TNFRSF25	DR3	*TNFRSF25*, Q93038	TRADD	TL1A (*TNFSF15*, O95150)	–
TWEAK receptor	TNFRSF12A	–	*TNFRSF12A*, Q9NP84	TRAF1, TRAF2, TRAF3	TWEAK (*TNFSF12*, O43508)	–
TACI	TNFRSF13B	–	*TNFRSF13B*, O14836	TRAF2, TRAF5, TRAF6	APRIL (*TNFSF13*, O75888), BAFF (*TNFSF13B*, Q9Y275)	–

Nomenclature	Systematic nomenclature	Common abbreviation	HGNC, UniProt	Adaptor proteins	Endogenous ligands	Comment
BAFF receptor	TNFRSF13C	BAFF-R	*TNFRSF13C*, Q96RJ3	TRAF3	BAFF (*TNFSF13B*, Q9Y275)	–
herpes virus entry mediator	TNFRSF14	HVEM	*TNFRSF14*, Q92956	TRAF2, TRAF3, TRAF5	BTLA (*BTLA*, Q7Z6A9), LIGHT (*TNFSF14*, O43557), TNFSF1 (*LTA*, P01374)	–
nerve growth factor receptor	TNFRSF16	–	*NGFR*, P08138	TRAF2, TRAF4, TRAF6	BDNF (*BDNF*, P23560), NT-3 (*NTF3*, P20783), NT-4 (*NTF4*, P34130), NGF (*NGF*, P01138)	–
B cell maturation antigen	TNFRSF17	BCMA	*TNFRSF17*, Q02223	TRAF1, TRAF2, TRAF3, TRAF5, TRAF6	APRIL (*TNFSF13*, O75888), BAFF (*TNFSF13B*, Q9Y275)	–
glucocorticoid-induced TNF receptor	TNFRSF18	GITR	*TNFRSF18*, Q9Y5U5	TRAF1, TRAF2, TRAF3, SIVA	TL6 (*TNFSF18*, Q9UNG2)	–
toxicity and JNK inducer	TNFRSF19	TAJ	*TNFRSF19*, Q9NS68	TRAF1, TRAF2, TRAF3, TRAF5	TNFSF1 (*LTA*, P01374)	–
RELT	TNFRSF19L	–	*RELT*, Q969Z4	TRAF1	–	–
death receptor 6	TNFRSF21	DR6	*TNFRSF21*, O75509	TRADD	–	–
ectodysplasin A2 isoform receptor	TNFRS27	–	*EDA2R*, Q9HAV5	TRAF1, TRAF3, TRAF6	ectodysplasin A2 (*EDA*, Q92838) [94]	–

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), P01138), brain-derived neurotrophic factor (BDNF (*BDNF*, P23560), P23560), NT-3 (*NTF3*, P20783) (NTF3, P20783) and NT-4 (*NTF4*, P34130) (NTF4, P34130) 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).

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