

Cytokine Receptors (Interleukin-1 Receptor/TIR Family)

Key References

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Overview

The interleukin-1/TIR family in animals comprises three subgroups of proteins; of these, two are type I integral membrane receptor proteins and the third is a group of intracellular proteins. All family members are characterized by the presence of a domain of ca. 200 amino residues referred to as the TIR (toll – interleukin-1 resistance) domain. Detailed sequence comparisons of a large number of TIR domains have revealed the presence of three conserved regions among the different members of the family; box 1 (FDAFISY), box 2 (GYKLC-RD-PG), and box 3 (a conserved W surrounded by basic residues). Crystal structures of the TIR domains of human TLR-1 and TLR-2 revealed that the domain is a compact globular structure composed of a series of α helices surrounding a core of β strands. Box 1 and 2 lie close together in space and form a composite site with box 2 projecting as a loop from the domain. Box 3 forms the core of the long C-terminal α helix. This suggests that these three sequences may have been conserved because they are important for protein-protein interactions rather than for the overall structural stability of the domain.

In the IL-1 receptor-like subfamily, the TIR domain is C-terminal to a single transmembrane sequence, and the N-terminal region of the protein is composed of three immunoglobulin-like regions. The N-terminal region is extracellular, is composed of either one (SIGGR) or three immunoglobulin domains and binds ligands. In the TLR (toll-like receptor) subfamily, the TIR domain is C-terminal to a single transmembrane sequence. The N-terminal region is extracellular, is composed of a variable number of leucine rich repeats that form a large flat, but concave surface that appears capable of accommodating a wide range

of ligand structures. The third subfamily, not tabulated here because they are not receptors, are intracellular protein adaptors containing minimally one TIR domain, usually linked to one or more other protein interaction domains such as a death domain. The prototype for this group of proteins is myD88 that binds to the site on the receptor TIR domains formed by Box-1 and 2, via a homotypic TIR-TIR interaction, and couples the receptors to downstream signaling mechanisms.

The IL-1 receptor-like subfamily of receptors are conventional polypeptide hormone receptors for cytokines of the IL-1 family (IL-1 α (IL-1F1), IL-1 β α (IL-1F2), IL-1ra α (IL-1F3), IL-18 (IL-1F4) and IL-1F5-10). The ligand receptor pairings for IL-1F1-4 are well defined and supported by good receptor pharmacology. However, while receptor-selective, functional effects have been found for several other IL-1Fs, high affinity receptor binding has not been detected. The well characterized functional receptors (IL-1R and IL-18R) are heterodimers (IL-1R/IL-1AcP and IL-18R/IL-1RAcPL) and it is possible therefore that the low affinity of binding so far detected is due to lack of the appropriate heterodimers.

The finding that tolls were the long sought after receptors for bacterial agonists such as gram negative LPS was triggered by the break through observation that flies conditionally mutated in the toll-1 gene, a gene known only to have a role in embryonic development prior to that time, became uniquely sensitive to fungal infection when subject to gene inactivation as adults. Subsequent to that observation large amount of literature documented the role played by animal TLRs as receptors for a wide range of bacterial and viral products, broadly

termed pathogen associated molecular patterns (PAMPs). This recent and rapidly moving field is still, unsurprisingly, full of gaps. Thus, there are few convincing radio-ligand binding studies for any TLR/ligand pair with most data on specificity being derived from functional studies. In addition, there is increasing evidence that most TLRs function in the context of multi-component complexes at the cell surface, with many diverse proteins present, well characterized examples being the TLR1/TLR2/CD14 or TLR6/TLR2/CD14 complexes that mediate responses to lipotechoic acid.

Cytokine Receptors (Interleukin-1 Receptor/TIR Family)

Cytokines - Interleukin-1 Receptor/TIR Family ^a

RECEPTOR	Type I IL-1 Receptor (10654)	Type II IL-1 Receptor (18148)	ST2	IL-18 Receptor	IL-1Rrp2	TIGIRR-1	TIGIRR-2
CURRENTLY ACCEPTED NAME	IL-1RI	IL-1RII	ST2	IL-18 Receptor	IL-1Rrp2	TIGIRR -1	TIGIRR-2
ALTERNATIVE NAME	—	—	T2, Fit-1	IL-1 R7	—	IL-1R9	OP4 IL1RAPL
SUBUNIT COMPOSITION	IL1RI/IL1R AcP	IL1RII	ST2	IL18R/IL18RAcP	IL1Rrp2/IL1RAcP	TIGIRR -1	Not known
SELECTIVE AGONISTS ^b	IL-1 α (12778), IL-1 β (19401)	None, receptor does not signal	Not known	IL-18 (10531(r))	IL-F6, IL1F8, IL1F9	Not known	Not known
SELECTIVE ANTAGONISTS	IL-1ra	Not applicable	Not known	Not known	Not known	Not known	Not known
SIGNAL TRANSDUCTION MECHANISMS	SAPKs NF κ B	SAPKs NF κ B(?)	SAPKs NF κ B	SAPKs NF κ B	SAPKs NF κ B	Not known	Not known
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-IL-1 α [¹²⁵ I]-IL-1 β [¹²⁵ I]-IL-1ra	[¹²⁵ I]-IL-1 α [¹²⁵ I]-IL-1 β	[¹²⁵ I]-ST2 binding protein	[¹²⁵ I]-IL-18	Not known	Not known	Not known
TISSUE EXPRESSION	All tissues	Leukocytes	Leukocytes	Lymphocytes	Epithelia	Brain, muscle, placenta	Widespread
PHYSIOLOGICAL FUNCTION	Host defense	Host defense	Not known	T cell regulation	Inflammation	Not known	Not known
DISEASE RELEVANCE	Inflammation	Inflammation	Not known	Autoimmunity	Inflammation	Not known	Mental retardation

Cytokines - Interleukin-1 Receptor/TIR Family ^a (continued)

RECEPTOR	IL-1RAcP	SIGIRR	IL-18RAcP
CURRENTLY ACCEPTED NAME	IL-1RAcP	SIGIRR	IL-18RAcP
ALTERNATIVE NAME	—	—	
SUBUNIT COMPOSITION	IL1RI/IL1R AcP	Not known	IL18R/IL18RAcP
SELECTIVE AGONISTS ^a	IL-1 α (12778), IL-1 β (19401)	Not known	IL-18
SELECTIVE ANTAGONISTS	IL-1ra	Not known	Not known
SIGNAL TRANSDUCTION MECHANISMS	SAPKs NF κ B	Not known Not known	SAPKs NF κ B
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-IL-1 α [¹²⁵ I]-IL-1 β [¹²⁵ I]-IL-1ra	Not known Not known	[¹²⁵ I]-IL-18
TISSUE EXPRESSION	All tissues	Epithelial	Lymphocytes
PHYSIOLOGICAL FUNCTION	Host defense	TIR signaling inhibitor	T cell regulation
DISEASE RELEVANCE	Inflammation	Inflammatory bowel disease	Autoimmunity, allergy

Cytokine Receptors (Interleukin-1 Receptor/TIR Family)

Cytokines - Interleukin-1 Receptor/TIR Family ^c

RECEPTOR	TLR-1	TLR -2	TLR -3	TLR -4	TLR -5	TLR -6	TLR -7	TLR -8
CURRENTLY ACCEPTED NAME	Toll-1	Toll-2	Toll-3	Toll-4	Toll-5	Toll-6	Toll-7	Toll-8
ALTERNATIVE NAME	Toll-1 RSC786	Toll-2	Toll-3	Toll-4	Toll-5	Toll-6	Toll-7	Toll-8
SUBUNIT COMPOSITION	Toll-1/Toll-2/CD14	Toll-1/Toll-2/CD14	Not known	(Tlr4)2CD14	Not known	Toll-6/Toll-2/CD14	Not known	Not known
SELECTIVE AGONISTS	Bacterial extracts, MD2	Bacterial extracts, MD2	dsRNA	LPS (L3012, L4391), (gram -ve) MD2	Flagellin	Bacterial extracts, MD2	dsRNA	CPG DNA
SELECTIVE ANTAGONISTS	LTA (L3265, L2515, L4015, L3140)	LTA (L3265, L2515, L4015, L3140)	Not known	Not known	Not known	LTA (L3265, L2515, L4015, L3140)	R848	R848
SIGNAL TRANSDUCTION MECHANISMS	SAPKs, NFκB	SAPKs, NFκB	Not known	SAPKs NFκB ??	SAPKs, NFκB	Not known	Not known	SAPKs, NFκB
RADIOLIGANDS OF CHOICE	—	—	—	—	—	—	—	—
TISSUE EXPRESSION	Leukocytes	Leukocytes	Leukocytes	Leukocytes	Leukocytes	Leukocytes	Leukocytes	Leukocytes
PHYSIOLOGICAL FUNCTION	LTA receptor	LTA receptor	PAMP receptor	LPS receptor	PAMP receptor	LTA receptor	Not known	Not known
DISEASE RELEVANCE	Lyme disease	Infections	Infections	Meningitis	Infections	Infections	Infections	Infections

FOOTNOTES

Cytokine Receptors (Interleukin-1 Receptor/TIR Family)

Cytokines - Interleukin-1 Receptor/TIR Family ^c (continued)

RECEPTOR	TLR -9	TLR-10	TLR-11
CURRENTLY ACCEPTED NAME	Toll-9	Toll-10	Toll-11
ALTERNATIVE NAME	Toll-9	Toll-10	Toll-11
SUBUNIT COMPOSITION	Not known	Not known	Not known
SELECTIVE AGONISTS	Not known	Not known	Not known
SELECTIVE ANTAGONISTS	CpG islands	Not known	LPS(?) (L3012, L4391)
SIGNAL TRANSDUCTION MECHANISMS	SAPKs, NFκB	SAPKs, NFκB	SAPKs, NFκB
RADIOLIGANDS OF CHOICE	Not known	Not known	Not known
TISSUE EXPRESSION	Leukocytes	Leukocytes	Bladder
PHYSIOLOGICAL FUNCTION	PAMP receptor	PAMP receptor	PAMP receptor
DISEASE RELEVANCE	Infections	Infections	Urological infections

FOOTNOTES

a There are at least five Interleukin-1 like cytokines encoded in the human genome. These presumably are the ligands for the four orphan receptors that are IL-1R related (three Ig domains out/TIR domain cytoplasmic).

b Product numbers refer to the human cytokine. For other species, please visit our website at www.sigma-aldrich.com and use our Product Search.

c The Tolls have recently been found to be receptors for pathogen associated molecular patterns (PAMPs), such as that embodied in gram negative lipopolysaccharide. More recently, two reports have shown that Tolls can heterodimerize to form receptors, the specificity of which is created combinatorially. In addition, a small family of secreted cytokine-like molecules have been described, which may be the mammalian homologs of the fly spatzle proteins. However, to date, these have been found to be required for PAMP activation of Tolls rather than to be agonists when present alone. Finally, the Toll naming convention used here is for human Tolls.