T1/ST2 Signaling Establishes It as a Member of an Expanding Interleukin-1 Receptor Family*

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Through data base searches, we have discovered new proteins that share homology with the signaling domain of the type I interleukin-1 receptor (IL-1RI): human "randomly sequenced cDNA 786" (rsc786), murine MyD88, and two partial Drosophila open reading frames, MstProx and STSdM224S. Comparisons between these new proteins and known IL-1RI homologous proteins such as Toll, 18-Wheeler, and T1/ST2 revealed six clusters of amino acid similarity. We tested the hypothesis that sequence similarity between the signaling domain of IL-1RI and the three mammalian family members might indicate functional similarity. Chimeric IL-1RI receptors expressing the putative signaling domains of T1/ST2, MyD88, and rsc786 were assayed by three separate IL-1 responsive assays, NF-κB, phosphorylation of an epidermal growth factor receptor peptide, and an interleukin 8 promoter-controlled reporter construct, for their ability to transduce an IL-1-stimulated signal. All three assays were positive in response to the T1/ST2 chimera, while the MyD88 and rsc786 chimeras failed to respond. These data indicate that the sequence homology between IL-1RI and T1/ST2 indicates a functional homology as well.

Interleukin-1 (IL-1) is an important component of the mammalian inflammatory response and is produced by many different types of cells following tissue injury and infection (1). The receptors and ligands of the IL-1 pathway have been well defined (for review see Refs. 2 and 3). Three ligands, IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra) bind three forms of IL-1 receptor, an 80-kDa type I IL-1 receptor (IL-1RI) (4), a 68-kDa type II IL-1 receptor (IL-1RII) (5), and a soluble form of the type II IL-1R (sIL-1RII) (6). The cytoplasmic or signaling domain of the human IL-1RI consists of 213 amino acids and has been shown to be essential for cellular responses to IL-1 in vivo (7), while the type II receptor has a cytoplasmic domain of only 29 residues and does not appear to transduce a signal (8). The interactions between the ligands and receptors play an essential role in the stimulation and regulation of the IL-1-mediated host response to injury and infection. Cells expressing IL-1RI and treated with IL-1α or IL-1β respond in several specific ways, including stimulating nuclear localization of the rel-related transcription factor, NF-κB (for review, see Ref. 9), activation of protein kinases of the mitogen-activated protein kinase superfamily that phosphorylate residue threonine 669 (Thr-669) of the epidermal growth factor receptor (EGFR) (10–12), and stimulation of transcription of the IL-8 gene (13).

We explore the possibility of another level of complexity in IL-1 signaling, the existence of IL-1R-like proteins and their role in IL-1 and IL-1-like signal transduction pathways.

The IL-1RI cytoplasmic (signaling) domain shares significant homology to the cytoplasmic region of the Drosophila melanogaster transmembrane protein Toll (14). Toll is a transmembrane protein involved in establishment of dorsal/ventral polarity in the Drosophila embryo. Site-directed mutagenesis and deletion analysis have demonstrated that the cytoplasmic domain of IL-1RI and, in particular, residues conserved between IL-1RI and Toll are essential for transduction of intracellular IL-1-stimulated signals (7, 15, 16).

In addition to Toll, four other characterized cDNAs have been recognized as homologous to the cytoplasmic domain of the type I IL-1 receptor. These include T1/ST2 (17–19), the IL-1 receptor accessory protein (IL-1R AcP) (20), the tobacco N gene (21), and the Drosophila protein 18-Wheeler (22). T1/ST2 is a transmembrane protein that has been characterized as a novel primary response gene expressed in BALB/c-3T3 cells. The IL-1R AcP is also a transmembrane protein and was identified through a monoclonal antibody that blocked the binding of IL-1β to IL-1RI but recognized a protein distinct from the receptor itself. Both T1/ST2 and IL-1R AcP share homology to IL-1RI intracellularly and extracellularly. The tobacco N gene encodes a protein with an amino-terminal domain that has significant homology to the cytoplasmic domain of Toll and IL-1RI. Interestingly, tobacco plants carrying the N gene are resistant to tobacco mosaic virus by means of a "hypersensitive response" that resembles a localized inflammatory response similar to that induced by IL-1 in mammalian cells. 18-Wheeler has not been extensively characterized but is thought to encode a heterophilic cell adhesion molecule required for morphogenesis.

Recognizing this growing family, we conducted data base searches to identify other cDNAs with sequence homology to IL-1RI and found four. We then asked whether the sequence similarity observed in these novel proteins and in the previously identified T1/ST2 protein indicates a similarity in signaling function as well.

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1 The abbreviations used are: IL-1, interleukin 1; IL-1RI, type I interleukin 1 receptor; rsc786, randomly sequenced cDNA 786; IL-1R AcP, interleukin 1 receptor accessory protein; ORF, open reading frame; EGFR, epidermal growth factor receptor.
**T1/ST2 Signaling**

**EXPERIMENTAL PROCEDURES**

Chimeric Constructions—All native receptor and chimeric receptor constructs were cloned into pCD304, a variant of pCD302 (23). To construct the chimeric receptors, we first introduced a Bgl II site into the murine IL-1RI (except for the MyD88-E construct (see Fig. 2), which was cloned into a natural Hind III site in the murine IL-1RI). All constructs were confirmed by sequencing.

Transient Transfections—Transfections were by the DEAE/Dextran method, followed by chloroquine treatment as described (24) into COS7 cells. Expression levels of the various chimeras were determined by a radioimmunoassay. Transfected cells were bound with a rat monoclonal antibody 2A3 (24) with gentle rocking. Cells were washed once with 5% MBM and incubated with 1 ng/ml of the mouse anti-IL-2R antibody 2A3 (24) with gentle rocking. Cells were washed with 5% MBM and twice with phosphate-buffered saline. Wells were stripped by the addition of 1 ml of 0.5% NaOH, and total counts were determined. Results are expressed as total cpm averaged over two duplicate wells.

Cloning of MstProx—A 220-base pair polymerase chain reaction product from the IL-1RI homologous region of MST84D was generated using Drosophila genomic DNA as template, and oligonucleotides with the following sequences were used: 5'-GACCTTTCCAGAGAGAA-3' (121) and 5'-ATATCCCGGGACGTAG-3'. The polymerase chain reaction product was radiolabeled and used to screen 100,000 clones of a Drosophila genomic library (Clontech). Five hybridizing clones were purified to homogeneity. The clone with the largest insert (about 15 kilobases) was sequenced until the limits of the MstProx ORF were reached.

Stimulation of Cells—2 days post-transfection, confluent transfected COS7 cells were stimulated with 10 ng/ml huIL-1α for 30 min for NF-κB assay. For the Thr-669 kinase assay, stimulation was with 10.0 ng/ml of the mouse anti-IL-2R antibody 2A3 (24) with gentle rocking. Cells were washed with 5% MBM and twice with phosphate-buffered saline. Wells were stripped by the addition of 1 ml of 0.5% NaOH, and total counts were determined. Results are expressed as total cpm averaged over two duplicate wells.

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**RESULTS**

By base data searching, we have discovered two new mammalian members of the IL-1R-like family (see alignment in Fig. 1): a murine protein, MyD88 (27), and a novel human gene, rsc786.
The genomic library and isolated and sequenced clones encoding probe derived from this sequence, we screened a 1RI-like ORF proximal to the rest of these sequences (we referred to sequences containing short ORFs of unknown function that show a "sequence-tagged site," GenBank accession no. G01378). Both of these sequences contain short ORFs of unknown function that show homology to the IL-1RI cytoplasmic domain and a signal sequence. The region of homology to the IL-1RI cytoplasmic domain is restricted to the carboxy-terminal 150 residues of MyD88. The biology of human rsc786 has not yet been investigated, but the nucleotide sequence predicts a transmembrane protein with a cytoplasmic domain of about 175 residues that shows homology to IL-1RI. The extracellular portion of rsc786 does not resemble IL-1RI but contains leucine-rich repeats similar to those of Toll and 18-Wheeler.

In addition to the mammalian proteins, our data base searches also identified two additional Drosophila IL-1RI homologs. These new IL-1RI family members are the genomic fragment MstProx (Ref. 31 and GenBank accession nos. X67703, S74217, and S74219) and STSdM2245 ("sequence-tagged site," GenBank accession no. G01378). Both of these sequences contain short ORFs of unknown function that show homology to the IL-1RI cytoplasmic domain. MstProx also encodes several sperm proteins in addition to the partial IL-1RI-like ORF proximal to the rest of the sequences (we refer to this ORF as MstProx for "proximal to the Mst locus"). Using a probe derived from this sequence, we screened a Drosophila genomic library and isolated and sequenced clones encoding the MstProx gene. We found that MstProx did indeed contain an ORF encoding a transmembrane receptor protein similar both extracellularly and cytoplasmically to Toll and 18-Wheeler and, of the mammalian family members, most closely related to rsc786. The portion of MstProx homologous to the cytoplasmic domain of IL-1RI is shown in Fig. 1.

An amino acid multiple sequence alignment of the IL-1RI-like portion of the IL-1RI family members is shown in Fig. 1. Comparison of the homologous portions of these proteins reveals six distinct regions of conservation ranging in size from 8 to 16 residues within the IL-1RI cytoplasmic domain of 213 residues (see Fig. 1 and "Discussion").

To investigate whether the sequence conservation observed among these genes also reflects a functional conservation with regard to IL-1 signaling, we constructed IL-1RI chimeric receptors for three of the mammalian IL-1RI family members and tested the chimeric receptors for their ability to transduce an IL-1-mediated signal in vivo.

Assay System—Construction of IL-1RI chimeric receptors allowed us to assay for response to a known ligand, IL-1. The structures of the chimeric receptors are shown in Fig. 2. They consist of the extracellular and transmembrane portions of the murine IL-1RI but have the IL-1RI cytoplasmic domain replaced by the IL-1RI homologous domains of T1/ST2, MyD88, or rsc786. Since the T1/ST2 sequence shares a high degree of homology with the IL-1RI, it was relatively clear where to make the junction point between the IL-1RI and T1/ST2 sequences (see Fig. 2). However, for MyD88 and rsc786, it was not obvious where the best junction points would be, so several different chimeric constructs were made for each. These constructs varied the junction point and/or inserted additional arginine residues to create different geometry and spacing between the putative signaling domain and the membrane-spanning region of the chimeric receptor (Fig. 2).

The chimeric receptors were tested for their ability to transduce an IL-1 signal in vivo in a transient transfection system. COS7 cells transfected with the chimeric constructs were pre-treated with a polyclonal antibody (P3) to the human IL-1RI to block IL-1 binding to the endogenous primate IL-1R and then assayed for IL-1 response via the transfected chimeric receptors. We utilized a different species (murine) of IL-1RI for the extracellular and transmembrane portions of our chimeric receptors, which is not prevented from binding and responding to IL-1 by the polyclonal antibody (see data below). Expression levels of the various chimeras were determined by radioimmunoassay (see "Experimental Procedures" and Table I). The ability of the various chimeric receptors to mediate activation of NF-κB, Thr-669 phosphorylation, or induction of the IL-8 reporter construct through IL-1 stimulation is compared in each assay with that of the non-chimeric native murine IL-1RI transfected into COS7 cells in parallel.

NF-κB Assays—In cells stimulated with IL-1, activated NF-κB protein complex translocates to the nucleus and binds its cognate recognition sequence. Fig. 3 shows the results of NF-κB gel shift assays using nuclear extracts from cells transfected with empty vector, murine full-length receptor, or a chimeric construct. In Fig. 3, panel A, the first four lanes are the vector-transfected controls showing that stimulation by IL-1 results in a substantial NF-κB signal that is successfully blocked by pretreatment with the sheep anti-human IL-1RI antibody, P3 (Fig. 3A, compare lanes 3 and 4). Cells transfected with full-length murine IL-1RI, pretreated with P3, and then stimulated with IL-1 (human IL-1α, 1.0 ng/ml) served as our positive control. Clearly, even in the presence of P3, a significant NF-κB signal is observed, indicating an IL-1 response through the transfected murine IL-1RI (Fig. 3A, compare lanes 4 and 8).

When the T1/ST2 chimeric receptor was transfected into COS7 cells and stimulated with IL-1 in the presence of P3 antibody, a clear NF-κB response was obtained (see Fig. 3A, lane 6), indicating that the T1/ST2 cytoplasmic domain is capable of activating NF-κB DNA binding activity in response to IL-1 approximately as well as the full-length murine IL-1RI (Fig. 3A, compare lanes 6 and 8). Therefore, by functional conservation as well as sequence homology, T1/ST2 is clearly a
member of the IL-1R family.

We also tested several chimeric constructs for MyD88 and rsc786. Lanes 7–16 of the gel in Fig. 3B are samples transfected with five different MyD88 chimeric receptors (see Fig. 2 for structures). Although some MyD88 chimeras appear to stimulate NF-κB to a small degree in response to IL-1, none of these stimulations were significant in comparison to those observed by the T1/ST2 chimera or native murine IL-1RI nor were they consistently reproducible. It should be pointed out that the MyD88 chimeric receptors were expressed at a lower level than the native IL-1RI and the T1/ST2 chimeras (Table I). All of the rsc786 chimeric receptors shown in Fig. 2 were tested for their ability to stimulate NF-κB in response to IL-1, but all failed to activate NF-κB (data not shown). All expressed as well or better than the IL-1R positive control (data not shown).

Thr-669 Kinase—IL-1 treatment of cells leads to multiple serine-threonine phosphorylation events (10). One readily measured kinase activity is that which phosphorylates residue threonine 669 (Thr-669) of the EGFR. This phosphorylation is carried out by members of the mitogen-activated protein kinase superfamily (11, 12). Activation of Thr-669 kinase by IL-1 has been shown to occur via a different signal transduction pathway after IL-1 stimulation. Thus, this second type of assay, Thr-669 kinase activation, also provides functional evidence that the T1/ST2 protein is a member of the IL-1R family.

To investigate the Thr-669 kinase activity stimulated by IL-1 in transfected cells, we measured the phosphorylation of a synthetic peptide consisting of residues 663–673 of EGFR (12). Cytoplasmic extracts from IL-1-stimulated or unstimulated cells transfected with empty vector, full-length murine IL-1RI, or chimeric receptors were assayed. Extracts were incubated with EGFR peptide as substrate for activated Thr-669 kinase in the presence of [γ-32P]ATP. Results are expressed as the ratio of Thr-669 kinase activity detected in cells after IL-1 stimulation to the value observed in unstimulated cells. Fig. 4A shows the results of Thr-669 kinase assays from cells transfected with empty vector, full-length murine IL-1RI, and the T1/ST2 chimeric receptor. Open bars indicate samples treated with the P3 antiserum alone, and shaded bars indicate pre-treatment with P3 followed by a 10-min stimulation with IL-1 (human IL-1α, 10 ng/ml). Though the presence of P3 alone induces a slight increase in the Thr-669 kinase activity above the background value of untreated cells, treatment with IL-1 in the absence of antibody produces a significantly elevated level of Thr-669 kinase activity. Pretreatment with P3 followed by stimulation with IL-1 reduces the Thr-669 kinase activity in vector-transfected cells to a value comparable with P3 alone (Fig. 4A, sample 1), indicating that stimulation via endogenous COS7 receptors is blocked. Fig. 4A, sample 2, shows that cells transfected with full-length murine IL-1R receptor respond to IL-1 via activated Thr-669 kinase despite pretreatment with the P3 antiserum.

The results with the T1/ST2 chimera are given in Fig. 4A, sample 3. Cells transfected with this chimera, pretreated with P3 antiserum and then stimulated with IL-1, respond to IL-1 with a 3-fold increase in Thr-669 kinase activity (a typical level of response) (26), clearly indicating that the transfected T1/ST2 chimeric receptor is capable of activating the Thr-669 kinase pathway after IL-1 stimulation. Thus, this second type of assay, Thr-669 kinase activation, also provides functional evidence that the T1/ST2 protein is a member of the IL-1R family.

In Fig. 4B (samples 3 through 6) we show that pretreatment with P3 followed by IL-1 stimulation of cells transfected with our various MyD88 chimeric receptor constructs does not in-

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**Table I**

| Transfected construct | Raw cpm | Corrected cpm | Expression level relative to murine full-length |
|-----------------------|---------|---------------|-----------------------------------------------|
| Vector only           | 218.4   | 0             | 0.0                                           |
| MuIL-1RI              | 7374.6  | 7156.2        | 100.0                                         |
| T1/ST2                | 3959.8  | 3741.4        | 52.3                                          |
| MyD88-A               | 1189.0  | 970.6         | 13.6                                          |
| MyD88-B               | 1359.0  | 1140.6        | 15.9                                          |
| MyD88-C               | 3574.7  | 3356.3        | 46.9                                          |
| MyD88-D               | 382.6   | 164.2         | 2.3                                           |

**Fig. 3.** Activation of NF-κB by IL-1 in COS7 cells transfected with receptor chimeras. A, NF-κB gel shift assays using nuclear extracts harvested from cells transfected with empty vector (lanes 1–4), T1/ST2 chimeric receptor (lanes 5 and 6), and murine IL-1RI (lanes 7 and 8) as shown above each lane. Presence of the polyclonal serum P3 at a 1:100 dilution (raised against human IL-1R type I) and/or huIL-1α (final concentration = 1.0 ng/ml) is indicated by a “+” above the lane. Lane 9 is the same as lane 3 except 200 ng of cold double-stranded synthetic oligonucleotide NF-κB probe was included as competitor. Lane 10 is a binding reaction without nuclear extract (probe only). B, NF-κB gel shift assays using nuclear extracts harvested from cells transfected as shown above each lane empty vector (lanes 1–4), murine IL-1RI (lanes 5 and 6), and five different MyD88 chimeric receptors (lanes 7 and 8, MyD88-A; 9 and 10, MyD88-B; 11 and 12, MyD88-C; 13 and 14, MyD88-D; 15 and 16, MyD88-E). For details of constructs, see Fig. 2. Lanes 17 and 19 are identical to lane 3 except 200 ng of cold double-stranded synthetic oligonucleotide NF-κB probe was included as competitor in the sample run in lane 19. Lane 18 is a binding reaction without nuclear extract (probe only).
IL-1 stimulation does not activate the IL-8 reporter construct in cells expressing MyD88 and rsc786 chimeric receptors (Fig. 5, data not shown).

Many proteins from diverse systems show homology to the cytoplasmic domain of the IL-1RI. This expanding IL-1RI-like family includes murine and human proteins, Drosophila proteins, and a plant (tobacco) protein. We have identified two new mammalian members and two new Drosophila members. The new mammalian family members include a murine protein MyD88 (27) and a human gene, rsc786 (28). MyD88 was originally isolated and characterized as a myeloid differentiation primary response gene, involved in terminal differentiation of M1D+ cells (differentiation inducible myeloblastic leukemia cell line) to macrophages upon IL-6 stimulation. rsc786 is essentially uncharacterized. Another murine member, T1ST2, was previously characterized as a novel primary response gene expressed in BALB/c-3T3 cells (17–19). The transmembrane protein muIL-1R AcP (20) has homology to both the type I and type II IL-1R. IL-1R AcP has recently been shown to increase the affinity of IL-1RI for IL-1β and may be involved in mediating the IL-1 response.

The D. melanogaster members of the IL-1RI family include the transmembrane protein Toll (32, 33). The IL-1RI homologous portion of Toll has been shown to be required for its role in establishing the dorsal/ventral polarity of the embryo during Drosophila development (14, 33). Stimulation of Toll by its presumptive ligand, Spatzle, causes nuclear localization of a Drosophila homolog of NF-xB, Dorsal, and activation of the serine/threonine protein kinase, Pelle (34, 35). It has also been shown that the portion of Toll with homology to IL-1RI is necessary and sufficient for activating the pathway that results in nuclear localization of Dorsal in Schneider cells (36). Clearly, the sequence homology observed between Toll and IL-1RI and the homologous components of their respective signal transduction pathways also reflects an evolutionarily conserved functional similarity. Here, we also present two additional Drosophila family members, MstProx and STSDm2245, both Drosophila genomic fragments that contain partial ORFs capable of encoding proteins homologous to the signaling domain of IL-1RI. Cloning and sequencing more of the MstProx ORF has confirmed that it is a new member of the IL-1RI family (see Fig. 1).

Besides the mammalian and Drosophila proteins there is also a noteworthy plant member of the IL-1RI family, the tobacco N gene. The N gene encodes a protein with an amino-terminal domain that has significant homology to Toll and the cytoplasmic domain of the IL-1RI (21). Introduction of the N gene into tobacco mosaic virus-sensitive strains of tobacco confers resistance to tobacco mosaic virus via the ability to mount a hypersensitive response to the virus at the site of infection (21) similar to the acute inflammatory response pathway stimulated by injury and mediated by IL-1 in mammals.

We have investigated whether the sequence similarities observed between four of the mammalian members of the family indicate functional similarities (the muIL-1R AcP sequence was published after these studies were completed). A homology line-up of selected IL-1R family members is shown in Fig. 1. Comparison of the homologous portions of these proteins reveals six distinct regions of conservation ranging in size from 8 to 16 residues within the IL-1RI cytoplasmic domain of 213 residues. The most COOH-terminal of the homology domains has been defined by deletion analysis and site-directed mutagenesis of the native IL-1RI to be essential for certain IL-1-mediated signals (15). Two of the residues in this domain, Phe-530 and Trp-531, that were defined as essential in the human IL-1RI by site-directed mutagenesis are also conserved in all members of the family (see Fig. 1). The significance of...
these homologies is unknown, but it is possible that sequence similarities in certain domains indicate that these domains are conserved because they must interact with some of the same components of the signal transduction pathway as the IL-1RI.

In addition to activation of signal transduction pathways, these interactions might alternatively provide regulatory roles such as amplification or abrogation of the IL-1 signal.

We have shown that a chimeric receptor consisting of the extracellular and transmembrane portions of the murine IL-1RI and the cytoplasmic domain of T1/ST2 is indeed capable of transmitting an IL-1-mediated signal to the cell as assayed by activation of NF-\( \kappa \)B, Thr-669 kinase, and an IL-8 promoter-controlled reporter construct. Activation of NF-\( \kappa \)B and Thr-669 kinase indicates that the T1/ST2 cytoplasmic domain is capable of activating at least two separate signaling pathways that respond to IL-1 (26). This demonstrates that the sequence homology observed between the cytoplasmic domain of the IL-1RI and the T1/ST2 protein is functionally significant.

It is not clear why MyD88 and rsc786 were incapable of transmitting a significant IL-1-mediated signal via their IL-1RI chimeric receptors as assayed by NF-\( \kappa \)B, Thr-669 kinase, and IL-8 promoter activation. One possibility might be that the chimeric receptors, in the context of the MyD88 and rsc786 proteins, were simply not functional constructs. Though we did address this possibility by making several versions of each of these chimeras, none of them signaled in our assays in any significant way. Another explanation is that the MyD88 and rsc786 chimeric receptors are activating the cell in response to IL-1 but not through the NF-\( \kappa \)B, Thr-669 kinase, or IL-8 promoter pathways. MyD88 and rsc786 may interact with some of the same proteins that the native IL-1RI and the T1/ST2 protein do but may stimulate these proteins to signal in subtly different ways not detected in our assays. Perhaps one or more of the factors responsible for interacting with and signaling from the IL-1RI-like domain of MyD88 and rsc786 are not found in COS7 cells. We find this unlikely since these cells are IL-1 responsive, and interspecies conservation is sufficient enough to allow signaling through transfected murine IL-1RI and the murine T1/ST2 chimeric receptor. A further possibility is suggested by the recent report of an IL-1 receptor accessory protein (20). Perhaps a similar protein, capable of interacting with the extracellular portion of rsc786 or the amino-terminal domain of MyD88, is required for signaling by these proteins. Such an accessory protein, even if present in COS cells, would not be expected to interact with the extracellular portion of the IL-1R, and it is possible that the endogenous COS cell IL-1R AcP might not be able to complement the rsc786 and MyD88 signaling domains for signaling function. It is also possible that MyD88 and rsc786 do not serve in a signaling capacity. Instead, they may function to abrogate IL-1 signaling by forming non-productive complexes with components of the IL-1 signaling pathway, serving to inhibit or regulate the cell's ability to respond to IL-1. Interestingly, T1/ST2, the family member most closely related to the IL-1RI in sequence as well as function, also maps to the same chromosomal location (37, 38), while rsc786 is more distantly related in sequence, does not appear to be functionally conserved as indicated by our investigation, and also maps to a separate linkage group than IL-1RI.4

Clearly, the IL-1RI homologous portion of T1/ST2 (when present as part of a chimeric IL-1 receptor) is capable of producing an IL-1 response similar to that produced by the native IL-1RI. The specificity of this signal could be regulated through expression patterns of native T1/ST2 receptor and its cognate ligand that may differ from the expression patterns of IL-1RI and IL-1\( \alpha \) and -\( \beta \). It remains to be shown how the signals transduced by T1/ST2 and other possible signals (as yet uncharacterized) transduced by IL-1RI family members such as MyD88 and rsc786 fit into the overall scheme of IL-1 signal transduction.

4 T. Taguchi, J. Mitcham, S. Dower, J. Sims, and J. Testa, submitted for publication.
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