Molecular Neurobiology

ISSN0893-7648/03/27(3): 239–248/$25.00

The Expanding Interleukin-1 Family and Its Receptors

Do Alternative IL-1 Receptor/Signaling Pathways Exist in the Brain?

Herve Boutin,[1] Ian Kimber,[2] Nancy J. Rothwell,[1] and Emmanuel Pinteaux*,[1]

[1]School of Biological Sciences, University of Manchester, Oxford Road, Manchester M13 9PT, UK; [2]Syngenta, Central Toxicology Laboratory, Alderley Park, Macclesfield SK10 4TJ, UK

Abstract

Interleukin-1 (IL-1) has been implicated in neuroimmune responses and has pleiotropic actions in the brain. Compelling evidence has shown that IL-1 is a major mediator of inflammation and the progression of cell death in response to brain injury and cerebral ischemia. Its expression is strongly increased in these pathological conditions, and central administration of exogenous IL-1 significantly exacerbates ischemic brain damage. In contrast, inhibiting IL-1 actions (by intracerebroventricular [icv] injection of IL-1ra, neutralizing antibody to IL-1 or caspase-1 inhibitor) significantly reduces ischemic brain damage. IL-1 acts by binding to the IL-1 type-I receptor (IL-1RI), which is to date, the only known functional receptor for IL-1. However, our recent investigations suggest that IL-1 can act independently of IL-1RI, raising the possibility that additional, as yet undiscovered, receptor(s) for IL-1 exist in the brain. The recent characterization of putative, new IL-1 ligands and new IL-1 receptor-related molecules leads to the hypothesis that there might be alternative IL-1 signaling pathway(s) in the central nervous system (CNS).

Index Entries: Interleukin-1; IL-1F; new ligands; novel receptor; signaling; CNS.

Introduction

Inflammation is a complex biological process that occurs in response to tissue injury and/or infection, and is characterized by a rapid influx and activation of leukocytes (including monocytes/macrophages and neutrophils) from the circulating blood, with the ultimate goal of elimination of invading pathogens and the repair of the injured tissue. The central nervous system (CNS) has historically been viewed as an immune-privileged tissue, since immune responses were thought to be constrained by the tight junctions between endothelial cells of

Received September 6, 2002; Accepted October 29, 2002
* Author to whom all correspondence and reprint requests should be addressed. Email: emmanuel.pinteaux@man.ac.uk

the blood–brain barrier that limits access of peripheral immune cells. However it is now clear that immune responses do indeed occur in the brain, and have been implicated in many neuropathological conditions, including acute brain injury, stroke, and chronic neurodegenerative disorders (*see [1,2]* for review).

Stroke is the third greatest cause of mortality in the western world. It is characterized by occlusion of a cerebral artery resulting in reduction of blood supply to the brain. This leads to the development of a core, that is a region of injury in which extensive neuronal-cell death occurs, surrounded by a penumbra, a hypoperfused region, in which an inflammatory response is accompanied by mild-cell death (*see [3,4]* for review). The main molecular mechanisms involved in the progression of the infarction is the release of excitatory amino acids and the generation of highly neurotoxic molecules such as reactive oxygen species, as well as the development of an inflammatory response. Inflammation of the brain is characterized by early infiltration of leukocytes, activation of resident cells (e.g., microglia, astrocytes, and endothelial cells) and production of cytokines, of which IL-1, IL-6, and tumor necrosis factor α (TNFα) are the most important *(5,6).* This report focuses on the role of IL-1 in cerebral ischemia and reviews accumulating evidence for new IL-1 receptor(s) and/or alternative signaling pathway(s) in the brain.

Interleukin-1 Family

IL-1 is a member of the interleukin family of cytokines, a group of structurally and functionally distinct soluble proteins secreted by different cell types of the immune system and other nonimmune cells. IL-1 has attracted much interest since it was discovered, almost 20 years ago *(7):* it is produced by many cell types, participates in diverse cellular processes including cell activation, differentiation, proliferation, and cell-to-cell interactions, and is a pivotal regulator of the immune responses to infection and inflammation *(8).* More interestingly, IL-1 has been found to play important roles in the development of the inflammatory responses of the brain to acute injury, chronic neurodegenerative diseases, and infection *(1,2).* The IL-1 family of cytokines includes two agonists, IL-1α and β, that are the products of separate genes, with high-sequence homology and are believed to share similar biological functions *(8).* Both agonists are synthesized as 32 kDa precursor proteins. Pro-IL-1α is active and can be cleaved to a 17 kDa mature form by membrane-bound calpain. In contrast, pro-IL-1β is inactive and requires cleavage to a 17 kDa mature form by IL-1β converting enzyme (ICE), also known as caspase-1, and this mature IL-1β is the main form released from cells. A third member of the IL-1 family is the naturally occurring IL-1 receptor antagonist (IL-1ra) that acts as a competitive inhibitor of IL-1α and β actions by binding to the IL-1 receptor without inducing an intracellular signal *(8).*

IL-1α and β trigger their intracellular actions by binding to a specific 80 kDa plasma-membrane receptor, the IL-1 type-I receptor (IL-1RI) *(9),* which then associates with the 66 kDa IL-1 receptor-accessory protein (IL-1RAcP) to initiate an intracellular signal *(10).* Both IL-1RI and IL-1RAcP have extracellular domains of approx 320 amino acids, which contain three immunoglobulin(Ig)-like domains that are critical for ligand binding, and therefore these receptors are members of the immunoglobulin superfamily. Their 220 amino acid intracellular domains include a conserved region of 200 amino acids, that is also found in the intracellular domain of the Toll receptor *(11)* and 18-wheeler *(12),* involved in antifungal defence in adult flies and in the establishment of dorsoventral polarity in the developing embryo respectively. This conserved region has therefore been named the Toll/IL-1R related (TIR) domain and is also present in the intracellular domain of mammalian homologs of Toll called the Toll-like receptors (TLR) (*see [13]* for review). A second, 68 kDa receptor for IL-1 has

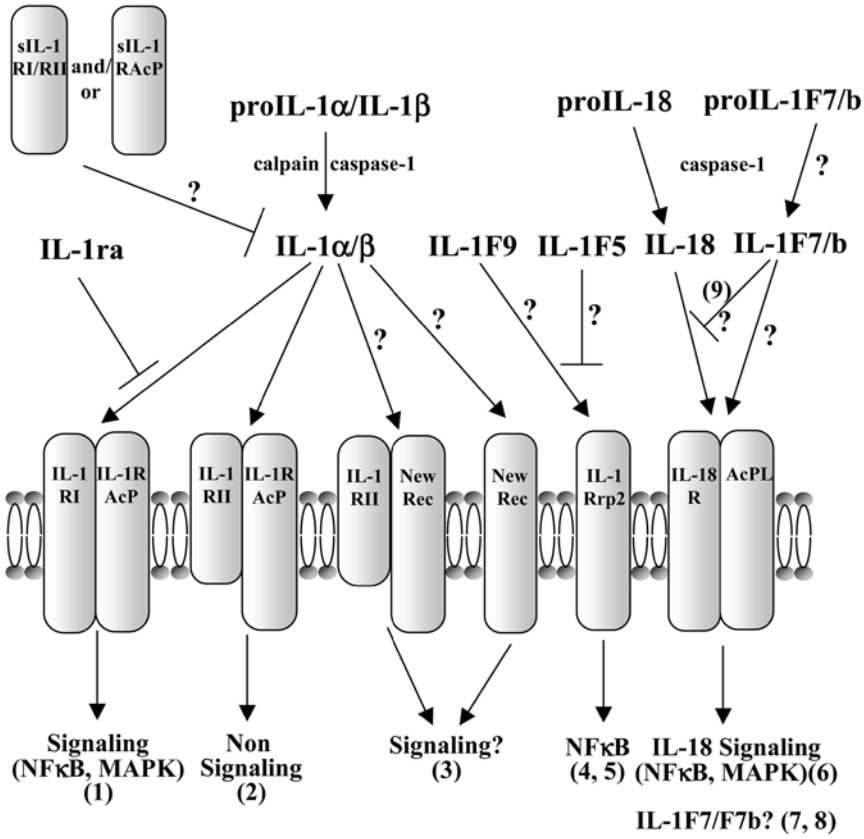

Fig. 1. Representation of the classical IL-1 signaling pathway and possible existence of novel IL-1β receptor(s) and/or alternative IL-1 signaling pathway(s) exist in the brain, based on previous published studies as cited: (1) Parker et al., 2002; (2) Malinowsky et al., 1998; (3) Touzani et al., 2001; (4) Debets et al., 2001; (5) Lovenberg et al., 1996; (6) Wheeler et al., 2000; (7) Pan et al., 2001; (8) Kumar et al., 2002; (9) Bufler et al., 2002. Abbreviations: IL, interleukin; IL-1F, interleukin-1 family; IL-R, interleukin receptor; IL-1RAcP, interleukin-1-receptor accessory protein; AcPL, accessory protein-like; IL-1Rrp2 interleukin-1-receptor related protein 2; MAPK mitogen-activated protein kinase; NFκB, nuclear factor-kappa B.

been identified and termed the IL-1 type-II receptor (IL-1RII). This receptor also possesses three Ig-like extracellular domains but lacks the entire cytoplasmic tail, and is therefore unable to transduce a signal. Consequently, IL-1RII has been proposed to act as a decoy receptor by sequestering excess ligands *(14).* IL-1RII also interacts with IL-1RAcP *(15),* suggesting that this receptor sequesters not only IL-1β, but also IL-1RAcP away from IL-1RI.

IL-1RI, IL-1RII, and IL-1RAcP also exist as soluble proteins (sIL-1RI, sIL-1RII, sIL-1RAcP) formed by proteolytic cleavage of the extracellular domains of the membrane-bound receptors, and soluble splice variants for IL-1RII and IL-1RAcP have been reported *(16,17).* The function of these soluble proteins is still unclear, but they may also act as soluble-decoy receptors, possibly as heterodimeric soluble complexes, that inhibit the actions of released IL-1.

Binding of IL-1α or β to IL-1RI induces association of the receptor with the IL-1RAcP and the formation of a high-affinity tri-complex, which can initiate signal transduction.

Downstream signaling elements, including the adaptor MyD88 *(18)*, the IL-1 receptor associated kinase (IRAK) *(19)* and/or IRAK-2 *(20)*, are recruited and activated. The IRAKs then activate the TNF receptor associated factor 6 (TRAF6) *(21)*, which induces distinct intracellular-signaling pathways culminating in the activation of nuclear factor-kappa B (NFκB) and mitogen-activated protein kinases (MAPKs) p38, the extracellular signal-regulated kinase p42/44 (ERK1/2), and the c-Jun N-terminal kinase (JNK) (reviewed in *[22]*). This leads to initiation of transcription of the genes for other inflammatory mediators such as IL-6, TNFα, and prostaglandin E_2 (PGE_2).

Pathology of IL-1 in the Brain

The IL-1 family and its receptors are expressed in the brain, albeit at very low levels under physiological conditions. IL-1 immunoreactivity has been detected in normal brain tissue *(23)* and in cerebrospinal fluid *(24)*. Low-level expression of IL-1RI and IL-1RII has been detected in restricted areas of the brain, particularly in the hippocampus, the choroid plexus, and the cerebellum, predominantly on neuronal and vascular cells *(25,26)*. In contrast, IL-1RAcP is highly expressed in many brain regions including the cortex, the hippocampus and the hypothalamus *(27)*. The high level of IL-1RAcP in regions where IL-1RI has not been detected suggests that IL-1RAcP may interact with an additional new receptor for IL-1 and/or have additional distinct functions. At the cellular level, expression of IL-1RI, IL-1RII, and IL-1RAcP has also been reported on glial cells, predominantly on astrocytes *(28–30)* and oligodendrocytes *(31,32)*.

In contrast to normal conditions, increased expression of IL-1α and β has been detected in the brain after acute injury, infection, and during neurodegenerative disorders including Alzheimer's and Parkinson's diseases, multiple sclerosis, and Down's syndrome (*see [1,2]* for review). Elevated levels of IL-1β in the brain are, in all cases, associated with neuronal-cell death. In stroke, IL-1β levels are increased at an early stage (from 0 to 3 h post-ischemia) *(5,33)*, and sustained during the development of the infarction (until 72 h post-ischemia) *(34)*. The main source of brain IL-1β following cerebral ischemia appears to be microglia *(35)*, although later expression has been detected in astrocytes *(36,37)*. In addition, expression of IL-1β has also been reported in oligodendrocytes *(32)* and neurones *(37)*. Expression of both IL-1RI and IL-1RII is also increased in response to cerebral ischemia *(38,39)*, but only a slight increase in the expression of IL-1RAcP is observed at 4 and 24 h after ischemia *(40)*. Additional evidences strongly implicate IL-1 as a major factor in the progression of the inflammation and brain damage caused by cerebral ischemia. Intracerebroventricular (icv) injection of IL-1 dramatically exacerbates ischemic-brain damage, whereas inhibition of endogenous IL-1 (by icv injection of IL-1ra, a neutralizing antibody to IL-1, or specific caspase-1 inhibitor) significantly reduces ischemic injury *(41–43)*. Furthermore, mice lacking caspase-1, or expressing a negative mutant of caspase-1, show a significant reduction of infarct volume compared with wild-type mice *(44,45)*, and deletion of IL-1α and β reduces ischemic-brain damage by about 80% *(46)*. These observations strongly implicate IL-1 as an important mediator of the progression of acute-brain injury. However, several recent publications suggest that IL-1 could act in the brain via an alternative receptor(s) and/or via activation of alternative signaling pathway(s).

Recent Extension of the IL-1 and IL-1 Receptors Families

During the last 5 yr the sequencing of the human genome and the use of homology searches of human genomic sequence databases has led to the discovery of putative genes (and related proteins) with homology to the known members of the IL-1 family and their receptors.

The first IL-1 related cytokine discovered was IL-18, originally named IL-1γ or interferon-γ-inducing factor (IGIF) as it was reported to induce production of interferon-γ from peripheral immune cells *(47).* IL-18 shares several features with the IL-1 family since it is produced as a precursor protein that is cleaved to a mature 18 kDa protein by caspase-1. IL-18 binds to a plasma-membrane receptor complex formed by the association of the IL-18 receptor (IL-18R) (originally discovered as the IL-1 receptor related protein (IL-1Rrp) *[48]*) *(49),* and the IL-18 accessory protein (AcPL) *(50).* These two proteins share high-sequence homology with IL-1RI and IL-1RAcP since they possess three Ig-like domains and a TIR domain in their extracellular and intracellular regions respectively. In addition, binding of IL-18 to its receptor complex induces the recruitment and activation of similar downstream elements to that of IL-1 (including MyD88, IRAK1/2, and TRAF6), leading to activation of similar intracellular pathways (NFκB and MAPKs).

More recently, additional gene sequences encoding six putative new ligands homolog of the IL-1 family have been identified *(51–56).* These new genes are clustered on the long arm of chromosome 2q in humans, where genes for IL-1α, IL-1β and IL-1ra are also localized, suggesting that they arose by a series of tandem gene duplications from a common ancestral gene. A unifying nomenclature for the new IL-1 genes has therefore been proposed (IL-1F1-IL-1F10) (reviewed in *[57]*). These new ligands share 21 to 37% amino acid homology with IL-1β and IL-1ra (reviewed in *[57]*), with the exception of IL-1F5, which shares 52% homology with IL-1ra. In addition, the tertiary structure of IL-1F5 is similar to that of IL-1ra *(57),* suggesting that IL-1F5 may be another endogenous antagonist that inhibits the actions of either IL-1α/β or other IL-1Fs.

New members of the IL-1 receptor family have also been discovered. These include T1/ST2 *(58),* the IL-1 receptor related protein 2 (IL-1Rrp2) *(59),* TIGIRR-1 *(60,61),* the IL-1 receptor accessory protein-like (IL1RAPL) molecule *(60,62),* and SIGIRR *(63),* bringing the number of IL-1 receptor-related genes to ten. With the exception of SIGIRR, which contains only one extracellular Ig-like domain, all the new receptors possess three extracellular Ig-like domains and an intracellular TIR domain, suggesting that they are theoretically capable of binding IL-1 (or a related protein) and transducing intracellular signals. However, the functions of these orphan receptors remain unknown and none of them has been shown to bind IL-1β, IL-1α, or IL-1ra.

IL-1F5 and IL-1F9 are highly expressed in epithelial cells of the skin, lung, and stomach and their expression, as well as IL-1Rrp2 expression, is increased in lesional psoriasis in skin *(64).* IL-1F5 and IL-1F9 are also expressed in activated monocytes and B-cells, and IL-1F5 has been found in activated dentritic cells *(52).* Interestingly, IL-1F9 activates NFκB in Jurkat cells transfected with IL-1Rrp2, and this action is antagonized by IL-1F5 *(64),* but neither IL-1F5 nor IL-1F9 activates NFκB via binding to IL-1RI. These results suggest that IL-1F9/F5 and IL-1Rrp2 may act as an independent novel IL-1 signaling system that is analogous to the classical one of IL-1αβ/IL-1ra and IL-1RI.

IL-1F7 has been shown to bind the IL-18R *(55),* and recently Kumar and coworkers have reported that IL-1F7b, a splice variant of IL-1F7, possesses a prodomain and a caspase-1 cleavage site, and cleavage at the predicted site generates the mature form of the ligand *(65).* They also showed that both the pro- and mature- forms of IL-1F7b bind the soluble IL-18-α-Fc fusion protein, although with a significantly lower affinity than IL-18. Consistent with this latter result, they also showed that IL-18, but not IL-1F7b, induces IFNγ production. A very recent report showed that after binding to the IL-18 binding protein (IL-18BP), an endogenous inhibitor of IL-18, IL-1F7b forms a complex that binds to AcPL *(66).* This leads to inhibition of the formation of a functional receptor complex between AcPL and the IL-18R, suggesting that IL-1F7b acts as an antagonist of IL-18 activity.

Do Novel IL-1 Receptor(s) and/or Alternative IL-1 Signaling Pathway(s) Exist in the Brain?

In recent years, we have investigated whether the expanding IL-1 family of cytokines and their receptors trigger alternative actions in the brain, via binding of either one of the classical ligands, IL-1α or IL-1β to a new, as yet unidentified receptor, or of one of the recently discovered ligands to IL-1RI, IL-1RII or one to the recently discovered new receptors.

IL-18 was the first IL-1-related protein discovered and this cytokine, its receptor complex, and IL-18BP are all expressed constitutively in rat brain *(67).* IL-18 is upregulated in the late stages of focal cerebral ischemia in rats *(68)* and during the acute phase of experimental autoimmune encephalomyelitis in rats *(69).* These observations suggest a role for IL-18 in inflammatory responses of the brain, but its actions in the CNS are not yet known. In contrast to IL-1, IL-18 is not pyrogenic *(70)* and although expression of IL-18 has been reported in microglia *(71),* its actions on glial cells have not been elucidated. Thus, further investigations are needed to identify the precise functions of IL-18 in the CNS.

We have shown that icv injection of IL-1α or β dramatically exacerbates ischemic-brain damage in mice, while icv injection of IL-1ra significantly reduces ischemic injury *(42,72).* In contrast, mice lacking IL-1RI exhibit similar brain damage to their wild-type counterparts and icv injection of IL-1β exacerbates ischemic-brain damage to the same extent in wild-type and IL-1RI–/– mice, whereas IL-1ra does not confer any neuroprotection in mice lacking IL-1RI *(40).* In IL-1RI–/– mice, IL-1 fails to induce changes in body weight or to reduce food intake. Furthermore these animals fail to exhibit normal inflammatory and host-defence responses to IL-1 *(73),* indicating that IL-1RI is required for these actions of IL-1 but not for its effects on ischemic-brain damage *(74).* These observations strongly suggest that IL-1 can specifically modify ischemic-brain damage independently of IL-1RI. It is not know if other receptor(s) are induced specifically in the absence of IL-1RI or if they participate in brain damage in normal mice. However, we have observed that deletion of IL-1α and β reduces ischemic-brain damage to a much greater extent than a maximal dose of IL-1ra. It was suggested that either IL-1RII may acquire signaling activity in the absence of IL-1RI, probably by interacting with a second subunit, or that IL-1β binds to a novel functional receptor. Previous studies suggest that IL-1RII could be a functional receptor for IL-1 since an antibody to IL-1RII significantly reduces the pyrogenic responses to icv injection of IL-1β *(75).* IL-1RII-deficient mice would provide a useful tool to study the specific role of this receptor in the modulation of IL-1 actions. However, generation of these mice has not yet been successful; even so, this may suggest the extreme importance of IL-1RII during either the development or physiological conditions.

The actions of IL-1 in ischemic-brain damage of IL-1RI–/– mice has prompted us to perform other studies using IL-1RI–/– mixed glial-cell cultures in order to identify signaling pathways that might be activated by IL-1β in the absence of IL-1RI *(76).* We found that IL-1β induces substantial release of IL-6 and PGE_2, and activates NFκB and the MAPKs p38, JNK, and ERK1/2 in mixed glial-cell cultures from wildtype mice, but not in cells prepared from IL-1RI–/– mice. These results suggest that the actions of IL-1 observed in IL-1RI–/– mice in vivo are mediated by alternative signaling pathway(s) and further investigations are being conducted to identify these pathways.

The discovery of new IL-1 ligands and new IL-1 receptor-related genes points to the possibility of alternative IL-1 signaling pathways in the brain. This hypothesis has became more tenable since some of the new ligands (i.e., IL-1F5 and IL-1F6) have been reported to be expressed in the brain *(51,52).* In addition, some of the new IL-1 receptors, such as

T1/ST2 *(77),* IL-1Rrp2 *(59),* and IL1RAPL *(60)* have also been identified in the CNS. Particular interest is focused on a possible alternative IL-1 pathway involving IL-1F5, IL-1F9, and IL-1Rrp2, since IL-1F9 has been shown to activate NFκB via binding to IL-1Rrp2, which is blocked by IL-1F5 *(64).* IL-1Rrp2 is highly expressed in the meninges, choroid plexus, and cerebral cortex where high expression of IL-1RI is also detected *(59),* and we have recently detected expression of IL-1F5 mRNA in cerebral cortex (unpublished data). These observations suggest that IL-1F9/IL-1F5 may trigger specific functions in the brain through IL-1Rrp2. Our recent published data have shown that despite constitutive expression of IL-1Rrp2 mRNA in glial cell cultures, recombinant mouse IL1F9 failed to induce any of the classical IL-1β responses *(78)*. These observations do not however rule out the possibility of IL-1F9 to activate alternative pathway(s). Finally, IL-18R is expressed in the brain *(67),* and since IL-1F7 and its splice variant IL-1F7b bind to this receptor *(55,65),* these ligands may play an important role in the CNS. Alternatively, binding of IL-1F7b to the IL-18BP could inhibit IL-18 actions in the brain by blocking formation of a functional IL-18 receptor complex *(66).*

Conclusion

These recent observations are intriguing, but leave many questions unanswered regarding the actions of IL-1 in the brain and the existence of an unidentified IL-1 receptor in the CNS. Future studies will focus on the identification of the signaling pathway(s) activated by IL-1β in the brains of IL-1RI-deficient mice. The development of specific antibodies and/or the generation of mice deficient for one of these new ligands/receptors will provide powerful tools to study their specific roles and functions in the brain.

Acknowledgments

Funded by grants from MRC and Syngenta PLC grants. The authors would like to thank Dr. Rosemary Gibson for critically reviewing this manuscript.

References

1. Rothwell N. J. and Luheshi G. N. (2000) Interleukin 1 in the brain: biology, pathology and therapeutic target. *Trends Neurosci.* **23,** 618–625.
2. Allan S. M. and Rothwell N. J. (2001) Cytokines and acute neurodegeneration. *Nat. Rev. Neurosci.* **2,** 734–744.
3. Fisher M. and Garcia J. H. (1996) Evolving stroke and the ischemic penumbra. *Neurology* **47,** 884–888.
4. Touzani O., Roussel S., and MacKenzie E. T. (2001) The ischaemic penumbra. *Curr. Opin. Neurol.* **14,** 83–88.
5. Saito K., Suyama K., Nishida K., Sei Y., and Basile A. S. (1996) Early increases in TNF-alpha, IL-6 and IL-1 beta levels following transient cerebral ischemia in gerbil brain. *Neurosci. Lett.* **206,** 149–152.
6. Touzani O., Boutin H., Chuquet J., and Rothwell N. (1999) Potential mechanisms of interleukin-1 involvement in cerebral ischaemia. *J. Neuroimmunol.* **100,** 203–215.
7. Schmidt J. A. (1984) Purification and partial biochemical characterization of normal human interleukin 1. *J. Exp. Med.* **160,** 772–787.
8. Dinarello C. A. (1996) Biologic basis for interleukin-1 in disease. *Blood* **87,** 2095–2147.
9. Sims J. E., Gayle M. A., Slack J. L., et al. (1993) Interleukin 1 signaling occurs exclusively via the type I receptor. *Proc. Natl. Acad. Sci. USA* **90,** 6155–6159.
10. Wesche H., Korherr C., Kracht M., Falk W., Resch K., and Martin M. U. (1997) The interleukin-1 receptor accessory protein (IL-1RAcP) is essential for IL-1-induced activation of interleukin-1 receptor-associated kinase (IRAK) and stress-activated protein kinases (SAP kinases). *J. Biol. Chem.* **272,** 7727–7731.
11. Lemaitre B., Nicolas E., Michaut L., Reichhart J. M., and Hoffmann J. A. (1996) The dorsoventral

regulatory gene cassette spatzle/Toll/cactus controls the potent antifungal response in Drosophila adults. *Cell* **86,** 973–983.
12. Eldon E., Kooyer S., D'Evelyn D., Duman M., Lawinger P., Botas J., and Bellen H. (1994) The Drosophila 18 wheeler is required for morphogenesis and has striking similarities to Toll. *Development* **120,** 885–899.
13. O'Neill L. A. (2000) The interleukin-1 receptor/Toll-like receptor superfamily: signal transduction during inflammation and host defense. *Sci. STKE.* **2000,** RE1.
14. McMahan C. J., Slack J. L., Mosley B., et al. (1991) A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. *EMBO J.* **10,** 2821–2832.
15. Malinowsky D., Lundkvist J., Laye S., and Bartfai T. (1998) Interleukin-1 receptor accessory protein interacts with the type II interleukin-1 receptor. *FEBS Lett.* **429,** 299–302.
16. Liu C., Hart R. P., Liu X. J., Clevenger W., Maki R. A., and De Souza E. B. (1996) Cloning and characterization of an alternatively processed human type II interleukin-1 receptor mRNA. *J. Biol. Chem.* **271,** 20,965–20,972.
17. Jensen L. E., Muzio M., Mantovani A., and Whitehead A. S. (2000) IL-1 signaling cascade in liver cells and the involvement of a soluble form of the IL-1 receptor accessory protein. *J. Immunol.* **164,** 5277–5286.
18. Wesche H., Henzel W. J., Shillinglaw W., Li S., and Cao Z. (1997) MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. *Immunity* **7,** 837–847.
19. Cao Z., Henzel W. J., and Gao X. (1996) IRAK: a kinase associated with the interleukin-1 receptor. *Science* **271,** 1128–1131.
20. Muzio M., Ni J., Feng P., and Dixit V. M. (1997) IRAK (Pelle) family member IRAK-2 and MyD88 as proximal mediators of IL-1 signaling. *Science* **278,** 1612–1615.
21. Cao Z., Xiong J., Takeuchi M., Kurama T., and Goeddel D. V. (1996) TRAF6 is a signal transducer for interleukin-1. *Nature* **383,** 443–446.
22. O'Neill L. A. and Greene C. (1998) Signal transduction pathways activated by the IL-1 receptor family: ancient signaling machinery in mammals, insects, and plants. *J. Leukoc. Biol.* **63,** 650–657.
23. Breder C. D., Dinarello C. A., and Saper C. B. (1988) Interleukin-1 immunoreactive innervation of the human hypothalamus. *Science* **240,** 321–324.
24. Lue F. A., Bail M., Jephthah-Ochola J., Carayanniotis K., Gorczynski R., and Moldofsky H. (1988) Sleep and cerebrospinal fluid interleukin-1-like activity in the cat. *Int. J. Neurosci.* **42,** 179–183.
25. Ban E., Milon G., Prudhomme N., Fillion G., and Haour F. (1991) Receptors for interleukin-1 (alpha and beta) in mouse brain: mapping and neuronal localization in hippocampus. *Neuroscience* **43,** 21–30.
26. French R. A., VanHoy R. W., Chizzonite R., et al. (1999) Expression and localization of p80 and p68 interleukin-1 receptor proteins in the brain of adult mice. *J. Neuroimmunol.* **93,** 194–202.
27. Liu C., Chalmers D., Maki R., and De Souza E. B. (1996) Rat homolog of mouse interleukin-1 receptor accessory protein: cloning, localization and modulation studies. *J. Neuroimmunol.* **66,** 41–48.
28. Tomozawa Y., Inoue T., and Satoh M. (1995) Expression of type I interleukin-1 receptor mRNA and its regulation in cultured astrocytes. *Neurosci. Lett.* **195,** 57–60.
29. Zetterstrom M., Lundkvist J., Malinowsky D., Eriksson G., and Bartfai T. (1998) Interleukin-1-mediated febrile responses in mice and interleukin-1 beta activation of NFkappaB in mouse primary astrocytes, involves the interleukin-1 receptor accessory protein. *Eur. Cytokine Netw.* **9,** 131–138.
30. Pousset F., Cremona S., Dantzer R., Kelley K. W., and Parnet P. (2001) Dexamethasone upregulates type II IL-1 receptor in mouse primary activated astrocytes. *J. Neurochem.* **76,** 901–909.
31. Brogi A., Strazza M., Melli M., and Costantino-Ceccarini E. (1997) Induction of intracellular ceramide by interleukin-1 beta in oligodendrocytes. *J. Cell Biochem.* **66,** 532–541.
32. Blasi F., Riccio M., Brogi A., Strazza M., et al. (1999) Constitutive expression of interleukin-1beta (IL-1beta) in rat oligodendrocytes. *Biol. Chem.* **380,** 259–264.
33. Buttini M., Sauter A., and Boddeke H. W. (1994) Induction of interleukin-1 beta mRNA after focal cerebral ischaemia in the rat. *Brain Res. Mol. Brain Res.* **23,** 126–134.
34. Hillhouse E. W., Kida S., and Iannotti F. (1998) Middle cerebral artery occlusion in the rat causes a biphasic production of immunoreactive interleukin-1beta in the cerebral cortex. *Neurosci. Lett.* **249,** 177–179.

35. Giulian D., Baker T. J., Shih L. C., and Lachman L. B. (1986) Interleukin 1 of the central nervous system is produced by ameboid microglia. *J. Exp. Med.* **164,** 594–604.
36. Davies C. A., Loddick S. A., Toulmond S., Stroemer R. P., Hunt J., and Rothwell N. J. (1999) The progression and topographic distribution of interleukin-1beta expression after permanent middle cerebral artery occlusion in the rat. *J. Cereb. Blood Flow Metab.* **19,** 87–98.
37. Pearson V. L., Rothwell N. J., and Toulmond S. (1999) Excitotoxic brain damage in the rat induces interleukin-1beta protein in microglia and astrocytes: correlation with the progression of cell death. *Glia* **25,** 311–323.
38. Sairanen T. R., Lindsberg P. J., Brenner M., and Siren A. L. (1997) Global forebrain ischemia results in differential cellular expression of interleukin-1beta (IL-1beta) and its receptor at mRNA and protein level. *J. Cereb. Blood Flow Metab.* **17,** 1107–1120.
39. Wang X., Barone F. C., Aiyar N. V., and Feuerstein G. Z. (1997) Interleukin-1 receptor and receptor antagonist gene expression after focal stroke in rats. *Stroke* **28,** 155–161.
40. Touzani O., Boutin H., LeFeuvre R., Parker L., Miller A., Luheshi G., and Rothwell N. (2002) Interleukin-1 influences ischemic brain damage in the mouse independently of the interleukin-1 type I receptor. *J. Neurosci.* **22,** 38–43.
41. Loddick S. A., MacKenzie A., and Rothwell N. J. (1996) An ICE inhibitor, z-VAD-DCB attenuates ischaemic brain damage in the rat. *Neuroreport* **7,** 1465–1468.
42. Relton J. K. and Rothwell N. J. (1992) Interleukin-1 receptor antagonist inhibits ischaemic and excitotoxic neuronal damage in the rat. *Brain Res. Bull.* **29,** 243–246.
43. Yamasaki Y., Matsuura N., Shozuhara H., Onodera H., Itoyama Y., and Kogure K. (1995) Interleukin-1 as a pathogenetic mediator of ischemic brain damage in rats. *Stroke* **26,** 676–680.
44. Schielke G. P., Yang G. Y., Shivers B. D., and Betz A. L. (1998) Reduced ischemic brain injury in interleukin-1 beta converting enzyme-deficient mice. *J. Cereb. Blood Flow Metab.* **18,** 180–185.
45. Friedlander R. M., Gagliardini V., Hara H., et al. (1997) Expression of a dominant negative mutant of interleukin-1 beta converting enzyme in transgenic mice prevents neuronal cell death induced by trophic factor withdrawal and ischemic brain injury. *J. Exp. Med.* **185,** 933–940.
46. Boutin H., Lefeuvre R. A., Horai R., Asano M., Iwakura Y., and Rothwell N. J. (2001) Role of IL-1alpha and IL-1beta in ischemic brain damage. *J. Neurosci.* **21,** 5528–5534.
47. Ushio S., Namba M., Okura T., et al. (1996) Cloning of the cDNA for human IFN-gamma-inducing factor, expression in *Escherichia coli*, and studies on the biologic activities of the protein. *J. Immunol.* **156,** 4274–4279.
48. Parnet P., Garka K. E., Bonnert T. P., Dower S. K., and Sims J. E. (1996) IL-1Rrp is a novel receptor-like molecule similar to the type I interleukin-1 receptor and its homologues T1/ST2 and IL-1R AcP. *J. Biol. Chem.* **271,** 3967–3970.
49. Torigoe K., Ushio S., Okura T., et al. (1997) Purification and characterization of the human interleukin-18 receptor. *J. Biol. Chem.* **272,** 25,737–25,742.
50. Born T. L., Thomassen E., Bird T. A., and Sims J. E. (1998) Cloning of a novel receptor subunit, AcPL, required for interleukin-18 signaling. *J. Biol. Chem.* **273,** 29,445–29,450.
51. Mulero J. J., Pace A. M., Nelken S. T., Loeb D. B., Correa T. R., Drmanac R., and Ford J. E. (1999) IL1HY1: A novel interleukin-1 receptor antagonist gene. *Biochem. Biophys. Res. Commun.* **263,** 702–706.
52. Smith D. E., Renshaw B. R., Ketchem R. R., Kubin M., Garka K. E., and Sims J. E. (2000) Four new members expand the interleukin-1 superfamily. *J. Biol. Chem.* **275,** 1169–1175.
53. Busfield S. J., Comrack C. A., Yu G., Chickering T. W., Smutko J. S., Zhou H., Leiby K. R., Holmgren L. M., Gearing D. P., and Pan Y. (2000) Identification and gene organization of three novel members of the IL-1 family on human chromosome 2. *Genomics* **66,** 213–216.
54. Kumar S., McDonnell P. C., Lehr R., et al. (2000) Identification and initial characterization of four novel members of the interleukin-1 family. *J. Biol. Chem.* **275,** 10,308–10,314.
55. Pan G., Risser P., Mao W., et al. (2001) IL-1H, an interleukin 1-related protein that binds IL-18 receptor/IL-1Rrp. *Cytokine* **13,** 1–7.
56. Lin H., Ho A. S., Haley-Vicente D., et al. (2001) Cloning and characterization of IL-1HY2, a novel interleukin-1 family member. *J. Biol. Chem.* **276,** 20,597–20,602.
57. Dunn E., Sims J. E., Nicklin M. J., and O'Neill L. A. (2001) Annotating genes with potential roles

in the immune system: six new members of the IL-1 family. *Trends Immunol.* **22,** 533–536.
58. Mitcham J. L., Parnet P., Bonnert T. P., et al. (1996) T1/ST2 signaling establishes it as a member of an expanding interleukin-1 receptor family. *J. Biol. Chem.* **271,** 5777–5783.
59. Lovenberg T. W., Crowe P. D., Liu C., et al. (1996) Cloning of a cDNA encoding a novel interleukin-1 receptor related protein (IL 1R-rp2). *J. Neuroimmunol.* **70,** 113–122.
60. Born T. L., Smith D. E., Garka K. E., Renshaw B. R., Bertles J. S., and Sims J. E. (2000) Identification and characterization of two members of a novel class of the interleukin-1 receptor (IL-1R) family. Delineation of a new class of IL-1R-related proteins based on signaling. *J. Biol. Chem.* **275,** 29,946–29,954.
61. Sana T. R., Debets R., Timans J. C., Bazan J. F., and Kastelein R. A. (2000) Computational identification, cloning, and characterization of IL-1R9, a novel interleukin-1 receptor-like gene encoded over an unusually large interval of human chromosome Xq22.2-q22.3. *Genomics* **69,** 252–262.
62. Carrie A., Jun L., Bienvenu T., et al. (1999) A new member of the IL-1 receptor family highly expressed in hippocampus and involved in X-linked mental retardation. *Nat. Genet.* **23,** 25–31.
63. Thomassen E., Renshaw B. R., and Sims J. E. (1999) Identification and characterization of SIGIRR, a molecule representing a novel subtype of the IL-1R superfamily. *Cytokine* **11,** 389–399.
64. Debets R., Timans J. C., Homey B., et al. (2001) Two novel IL-1 family members, IL-1 delta and IL-1 epsilon, function as an antagonist and agonist of NF-kappa B activation through the orphan IL-1 receptor-related protein 2. *J. Immunol.* **167,** 1440–1446.
65. Kumar S., Hanning C. R., Brigham-Burke M. R., et al. (2002) Interleukin-1F7b (IL-1H4/IL-1F7) is processed by caspase-1 and mature IL-1F7b binds to the IL-18 receptor but does not induce IFN-gamma production. *Cytokine* **18,** 61–71.
66. Bufler P., Azam T., Gamboni-Robertson F., Reznikov L. L., Kumar S., Dinarello C. A., and Kim S. H. (2002) A complex of the IL-1 homologue IL-1F7b and IL-18-binding protein reduces IL-18 activity. *Proc. Natl. Acad. Sci. USA* **99,** 13,723–13,728.
67. Wheeler R. D., Culhane A. C., Hall M. D., Pickering-Brown S., Rothwell N. J., and Luheshi G. N. (2000) Detection of the interleukin 18 family in rat brain by RT-PCR. *Brain Res. Mol. Brain Res.* **77,** 290–293.
68. Jander S., Schroeter M., and Stoll G. (2002) Interleukin-18 expression after focal ischemia of the rat brain: association with the late-stage inflammatory response. *J. Cereb. Blood Flow Metab.* **22,** 62–70.
69. Jander S. and Stoll G. (1998) Differential induction of interleukin-12, interleukin-18, and interleukin-1beta converting enzyme mRNA in experimental autoimmune encephalomyelitis of the Lewis rat. *J. Neuroimmunol.* **91,** 93–99.
70. Gatti S., Beck J., Fantuzzi G., Bartfai T., and Dinarello C. A. (2002) Effect of interleukin-18 on mouse core body temperature. *Am. J. Physiol Regul. Integr. Comp. Physiol.* **282,** R702–R709.
71. Conti B., Park L. C., Calingasan N. Y., Kim Y., Kim H., Bae Y., Gibson G. E., and Joh T. H. (1999) Cultures of astrocytes and microglia express interleukin 18. *Brain Res. Mol. Brain Res.* **67,** 46–52.
72. Loddick S. A., Liu C., Takao T., Hashimoto K., and De Souza E. B. (1998) Interleukin-1 receptors: cloning studies and role in central nervous system disorders. *Brain Res. Brain Res. Rev.* **26,** 306–319.
73. Glaccum M. B., Stocking K. L., Charrier K., et al. (1997) Phenotypic and functional characterization of mice that lack the type I receptor for IL-1. *J. Immunol.* **159,** 3364–3371.
74. Labow M., Shuster D., Zetterstrom M., et al. (1997) Absence of IL-1 signaling and reduced inflammatory response in IL-1 type I receptor-deficient mice. *J. Immunol.* **159,** 2452–2461.
75. Luheshi G., Hopkins S. J., Lefeuvre R. A., Dascombe M. J., Ghiara P., and Rothwell N. J. (1993) Importance of brain IL-1 type II receptors in fever and thermogenesis in the rat. *Am. J. Physiol.* **265,** E585–E591.
76. Parker L. C., Luheshi G. N., Rothwell N. J., and Pinteaux E. (2002) IL-1beta signalling in glial cells in wildtype and IL-1RI deficient mice. *Br. J. Pharmacol.* **136,** 312–320.
77. Kumar S., Tzimas M. N., Griswold D. E., and Young P. R. (1997) Expression of ST2, an interleukin-1 receptor homologue, is induced by proinflammatory stimuli. *Biochem. Biophys. Res. Commun.* **235,** 474–478.
78. Berglöf E., Andre R., Renshow B. R., et al. (2003) IL-1Rrp2 expression and IL-1F9 (IL-1H1) actions in brain cells. *J. Immunol.* **139,** 36–43.