The Interleukin-1 Receptor/Toll-Like Receptor Superfamily

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A reader's guide to the revised STKE Review
"The Interleukin-1 receptor/Toll-like receptor superfamily:
Signal transduction during inflammation and host defense,"
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Since the publication of the original review 2 years ago, there has been an explosion in information regarding the interleukin-1 receptor/Toll-like receptor (IL-1R/TLR) superfamily. The most significant advances to date are the expansion of the superfamily to include an adaptor subgroup, identification of various bacterial and endogenous products that serve as TLR ligands, and elucidation of the signal transduction pathways activated by these effectors. Details are also emerging as to why distinct signaling pathways are activated by the different receptor types. These advances are highlighted in the current review either as additions to the original material or as entirely new sections. The figures have also been updated to provide the reader with an overall view of this ever-advancing area. Some highlights of the updated review are listed below, organized by the sections that contain the most detail about these topics.

Adaptor Subgroup

- A cytosolic adapter protein homologous to MyD88 has been identified (*1*, *2*). The protein termed Mal (also known as TIRAP) plays an essential role in the signaling pathway shared by TLR-2 and TLR-4 (*3*, *4*).
- The latest addition to the adaptor subgroup, Toll-IL-1 receptor (TIR) domain-containing adaptor inducing IFN-β (TRIF), preferentially activates the interferon-β (IFN-β) promoter in response to TLR-3 activation (*5*).

Toll

- Activation of *Drosophila* Toll by Spätzle during immune responses requires the presence of a novel serine protease, Persephone (*6*).
- Genetic screens for fly mutations that block antimicrobial gene expression have identified two probable pattern recognition receptors, the peptidoglycan recognition proteins PGRP-SA and PGRP-LC (*7*, *8*).

TLR-2 and TLR-4 as Signaling Receptors for Microbial Products

- Differences in the patterns of immune and inflammatory genes induced in response to different pathogen-associated molecular patterns (PAMPs) are emerging (*9*).
- A molecular basis for why different types of lipopolysaccharide (LPS) are recognized by different TLRs has been suggested (*10*).

Other Members of the TLR Family

- The repertoire of ligands for the TLR family has been extended to include viral and endogenous products, as well as additional bacterial products (*11*, *12*).

Signal Transduction

- A novel IL-1R-associated kinase (IRAK) family member, IRAK-4, lies upstream of IRAK-1 and is indispensable for IL-1R/TLR-dependent signaling (*13*).
- IRAK-M is a negative regulator of TLR-dependent signaling (*14*).
- Ubiquitination of specific signaling components leads to their activation rather than degradation (*15*, *16*).

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References

1. K. A. Fitzgerald, E. M. Palsson-McDermott, A. G. Bowie, C. A. Jefferies, A. S. Mansell, G. Brady, E. Brint, A. Dunne, P. Gray, M. T. Harte, D. McMurray, D. E. Smith, J. E. Sims, T. A. Bird, L. A. O'Neill, Mal (MyD88-adapter-like) is required for Toll-like receptor-4 signal transduction. *Nature* **413**, 78-83 (2001).
2. T. Horng, G. M. Barton, R. Medzhitov, TIRAP: An adapter molecule in the Toll signaling pathway. *Nat. Immunol.* **9**, 835-841 (2001).
3. M. Yamamoto, S. Sato, H. Hemmi, H. Sanjo, S. Uematsu, T. Kaisho, K. Hoshino, O. Takeuchi, M. Kobayashi, T. Fujita, K. Takeda, S. Akira, Essential role for TIRAP in activation of the signalling cascade shared by TLR-2 and TLR-4. *Nature* **420**, 324-329 (2002).
4. T. Horng, G. M. Barton, R. Flavell, R. Medzhitov, The adaptor molecule TIRAP provides signalling specificity for Toll-like receptors. *Nature* **420**, 329-333 (2002).
5. M. Yamamoto, S. Sato, K. Mori, K. Hoshino, O. Takeuchi, K. Takeda. S. Akira, A novel Toll/IL-1 receptor domain-containing adapter that preferentially activates the IFN-β promoter in the toll-like receptor signaling. *J. Immunol.* **169**, 6668-6672 (2002).
6. P. Ligoxygakis, N. Pelte, J. A. Hoffmann, J. M. Reichhart, Activation of *Drosophila* Toll during fungal infection by a blood serine protease. *Science* **297**, 114-116 (2002).
7. T. Michel, J. Reichhart, J. A. Hoffmann, J. Royet, *Drosophilia* Toll is activated by Gram-positive bacteria through a circulating peptidoglycan recognition protein. *Nature* **414**, 756-759 (2001).
8. M. Gottar, V. Gobert, T. Michel, M. Belvin, G. Duck, J. A. Hoffmann, D. Ferrandon, J. Royet, The *Drosophilia* immune response against Gram-negative bacteria is mediated by a peptidoglycan recognition protein. *Nature* **416**, 640-643 (2002).
9. F. Re, J. L. Strominger, Toll-like receptor 2 (tlr2) and tlr4 differentially activate human dendritic cells. *J. Biol. Chem.* **276**, 37692-37699 (2001).
10. M. G. Netea, M. van Deuren, B. J. Kullberg, J. M. Cavaillon, J. W. Van der Meer, Does the shape of lipid A determine the interaction of LPS with toll-like receptors? *Trends Immunol.* **23**, 135-139 (2002).
11. L. Alexopoulou, A. Czopik-Holt, R. Medzhitov, R. Flavell, Recognition of double stranded RNA and activation of NF-κB by toll-like receptor 3. *Na-*

ture **413**, 696-712 (2001).
12. Y. Okamura, M. Watari, E. S. Jerud, D. W. Young, S. T. Ishizaka, J. Rose, J. C. Chow, J. F. Strauss 3rd, The extra domain A of fibronectin activates Toll-like receptor 4. *J. Biol. Chem.* **276**, 10229-10233 (2001).
13. S. Li, A. Strelow, E. J. Fontana, H. Wesche, IRAK-4: A novel member of the IRAK family with the properties of an IRAK-kinase. *Proc. Nat. Acad. Sci. U.S.A.* **99**, 5567-5572 (2002).
14. K. Kobayashi, L. D. Hernandez, J. E. Galan, C. A. Janeway Jr., R. Medzhitov, R. A. Flavell, IRAK-M is a negative regulator of Toll-like signaling. *Cell* **110**, 191-202 (2002).
15. L. Deng, C. Wang, E. Spencer, L. Yang, A. Braun, J. You, C. Slaughter, C. Pickart, Z. J. Chen, Activation of the IκB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. *Cell* **103**, 351-361 (2000).
16. C. Wang, L. Deng, M. Hong, G. R. Akkaraju, J. Inoue Z. J. Chen, TAK1 is a ubiquitin-dependent kinase of MKK and IKK. *Nature* **412**, 346-351 (2001).

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