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MACROPHAGE DIFFERENTIATION MARKER MyD88 IS A MEMBER OF THE *Toll*/IL-1 RECEPTOR FAMILY

Dan Hultmark

Department of Molecular Biology, Stockholm University, S-106 91 Stockholm, Sweden

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The interleukin-1 receptor in mammals and the product of the *Toll* gene in *Drosophila* are related transmembrane receptors, involved in the activation of transcription factors of the *rel* family. Whereas the interleukin-1 receptor mediates the effects of interleukin-1 in the immune system, *Toll* is part of the system that determines dorsoventral polarity in the *Drosophila* embryo, although *Toll* may also have a function in the immune response in the fly. Here, I demonstrate that the open reading frame of MyD88, a gene induced in myeloid differentiation, is related to the cytoplasmic domains of the interleukin-1 receptor and the *Toll* gene product. The three related proteins define a family of signal transmitters, the original function of which may be to mediate responses in the immune system.

Some remarkable similarities have recently been discovered between the signaling pathways that generate dorsoventral polarity in the fruitfly, *Drosophila*, and those that mediate the effects of interleukin-1 (IL-1) in the mammalian immune system. External signals that determine the ventral pole of the *Drosophila* embryo are received by the *Toll* gene product, a membrane protein that is related to the interleukin-1 receptor (1, 2). In both cases the receptors activate transcription factors of the *rel* family: *dorsal* and NF-κB, respectively (see 3, 4). When activated, both transcription factors dissociate from their respective cytoplasmic inhibitors, *cactus* and IκB, and become localized in the nucleus.

In addition to its function in embryogenesis, *Toll* may also play a role in the immune response in *Drosophila*. A *dorsal*-related transcription factor, *Dif*, was recently found to mediate the induction of bactericidal cecropins in infected

Abbreviations: IL-1, interleukin-1; IL-1R, interleukin-1 receptor.

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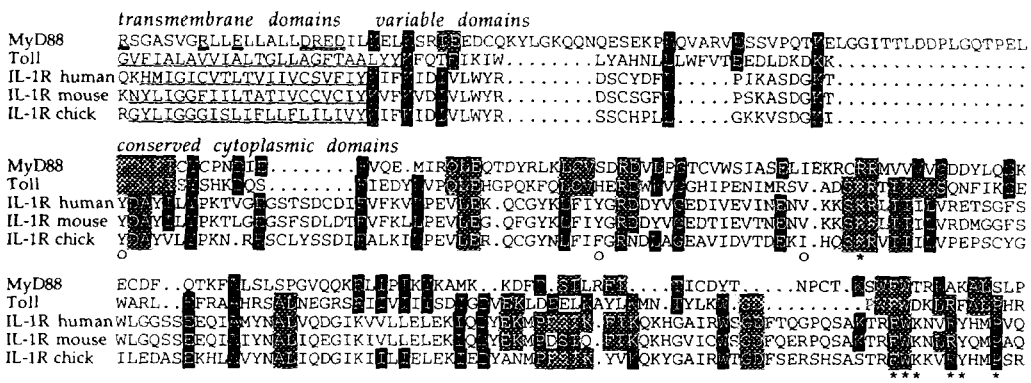

Fig. 1. Alignment of the conserved parts of MyD88, Toll and three different type I interleukin-1 receptors. Sequence identities between at least two of the three classes of molecules are in black boxes. The hydrophobic putative transmembrane domains are underlined. The corresponding region in MyD88 includes charged residues (thick underlining). Residues found to affect function in *Toll* mutants (2), or in the human interleukin-1 receptor (8), are marked (o) or (*), respectively. Excluded from the alignment are the extracellular domains and short carboxy-terminal extensions in *Toll* and the IL–1 receptors. Also excluded are the amino terminal 27 residues in MyD88. Sequence analysis was aided by the GCG Package, Version 7 (Genetics Computer Group, Madison, Wisconsin, USA). Sequence accession numbers: P22366, P08953, P14778, P13504, M81846.

flies, and this factor becomes translocalized to the nucleus in a *Drosophila* mutant that has the *Toll*-encoded receptor constitutively activated (5).

In a computer analysis of the similarities between *Toll* and the IL-1 receptor, I noticed what appears to be a previously unrecognized third member of the same family, MyD88 (Fig. 1). This gene was originally isolated as an early transcript in IL-6-induced differentiating myeloid cells (6), and it has been postulated to be a mediator of macrophage differentiation (7). The similarities between *Toll* and the IL-1 receptor are restricted to the cytoplasmic domain, and a similar domain is also present in MyD88. This part of MyD88 is most closely related to the *Toll* gene product, with 27% amino acid sequence identity, compared to 18% for the IL-1 receptor. Out of the 136-157 residues in the cytoplasmic domain, 14 are absolutely conserved in all members of the family. They include three of the residues shown by *in vitro* mutagenesis to be essential in the human IL-1 receptor (8) (Fig. 1).

It is uncertain whether MyD88 could be an integral membrane protein, like the *Toll* and IL-1 receptors. MyD88 has a stretch of hydrophobic amino acids approximately at the position where the transmembrane domains are found in *Toll* and the IL-1 receptor (Fig. 1), but this stretch is interrupted by charged amino acids, and it does not conform to the consensus for a transmembrane segment. MyD88 is shorter than its homologs, and it lacks the long extracellular domains of *Toll* and the IL-1 receptor.

Whether MyD88 is a membrane-bound receptor or not, its similarity to the cytoplasmic parts of *Toll* and the IL-1 receptor strongly suggests that MyD88 is also part of an intracellular signalling pathway. This would certainly be compatible with its suggested function in the initiation of macrophage differentiation. Together with *Toll* and the IL-1 receptor, MyD88 may define a family of signal transducing molecules with an ancestral function in the activation of the immune defense.

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