Gene name: **MYD88**

External Ids for MYD88 Gene: HGNC: 7562 NCBI Gene: 4615 Ensembl: ENSG00000172936 OMIM®: 602170 UniProtKB/Swiss-Prot: Q99836

NCBI Gene Summary: This gene encodes a cytosolic adapter protein that **plays a central role in the innate and adaptive immune response**. This protein functions as an essential signal transducer in the interleukin-1 and Toll-like receptor signaling pathways. These pathways regulate that activation of numerous proinflammatory genes. The encoded protein consists of an N-terminal death domain and a C-terminal Toll-interleukin1 receptor domain. Patients with defects in this gene have an increased susceptibility to pyogenic bacterial infections. Alternate splicing results in multiple transcript variants.

GeneCards Summary: MYD88 (MYD88 Innate Immune Signal Transduction Adaptor) is a Protein Coding gene. Diseases associated with MYD88 include Immunodeficiency 68 and Macroglobulinemia, Waldenstrom 1. Among its related pathways are Toll Like Receptor 7/8 (TLR7/8) Cascade and Diseases of Immune System. Gene Ontology (GO) annotations related to this gene include *identical protein binding* and *death receptor binding*.

UniProtKB/Swiss-Prot Summary: Adapter protein involved in the Toll-like receptor and IL-1 receptor signaling pathway in the innate immune response (PubMed:15361868, 18292575, 33718825, 37971847). Acts via IRAK1, IRAK2, IRF7 and TRAF6, leading to NF-kappa-B activation, cytokine secretion and the inflammatory response (PubMed:15361868, 19506249, 24316379). Increases IL-8 transcription (PubMed:9013863). Involved in IL-18-mediated signaling pathway. Activates IRF1 resulting in its rapid migration into the nucleus to mediate an efficient induction of IFN-beta, NOS2/INOS, and IL12A genes. Upon TLR8 activation by GU-rich single-stranded RNA (GU-rich RNA) derived from viruses such as SARS-CoV-2, SARS-CoV and HIV-1, induces IL1B release through NLRP3 inflammasome activation (PubMed:33718825). MyD88-mediated signaling in intestinal epithelial cells is crucial for maintenance of gut homeostasis and controls the expression of the antimicrobial lectin REG3G in the small intestine (By similarity). (MYD88_HUMAN,Q99836)

Cellular localization: mainly cytosol, endosome, nucleus, plasma membrane.
Full Name: *Myeloid Differentiation Primary Response 88*
Protein Type: Intracellular adaptor protein
Key Role: Acts as a central signal transducer for many Toll-like receptors (TLRs) and Interleukin-1 receptors (IL-1Rs).

🔬 Biological Function of MYD88

- MYD88 is critical for initiating innate immune responses.
- After pathogen detection by surface receptors (especially TLRs like TLR2, TLR4), MYD88 assembles a multi-protein signaling complex (called the Myddosome).
- This complex triggers downstream signaling that leads to:
    - Activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells).
    - Activation of MAPKs (mitogen-activated protein kinases).
    - Rapid production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β.

🛠️ How MYD88 Works Mechanistically:

- When a TLR or IL-1R is activated by a pathogen, it recruits MYD88 through TIR domains (Toll/IL-1 receptor domains).
- MYD88 then recruits IRAK family kinases (IRAK1, IRAK4).
- This leads to activation of TRAF6, culminating in the activation of NF-κB and AP-1 transcription factors.
- These transcription factors initiate expression of inflammatory cytokines.

🦠 MYD88's Role in Sepsis

- MYD88 is absolutely central in sepsis because it controls the first wave of cytokine production in response to bacterial, fungal, and viral infections.
- In early sepsis:
    - MYD88-mediated signaling ensures rapid pathogen recognition and immune activation.
    - Necessary for bacterial clearance and survival during early infection.
- In severe or late-stage sepsis:
    - Overactivation of MYD88 signaling leads to cytokine storm, excessive inflammation, and organ failure.
    - Uncontrolled MYD88 activation is implicated in systemic inflammatory response syndrome (SIRS) seen in sepsis.

📈 Clinical Relevance of MYD88 in Sepsis

Diagnostic:

- MYD88 pathway gene expression (MYD88 itself, or its downstream targets like IL1B, TNF) is often upregulated early in septic patients.
- Some transcriptomic panels for sepsis diagnosis indirectly reflect MYD88 activity through its target genes.

Prognostic:

- Hyperactivation of MYD88 pathways correlates with worse outcomes (higher SOFA scores, ICU mortality).
- In contrast, in immune-paralysis states (very late sepsis), defective MYD88 signaling may lead to inability to clear infections, contributing to secondary infections and death.

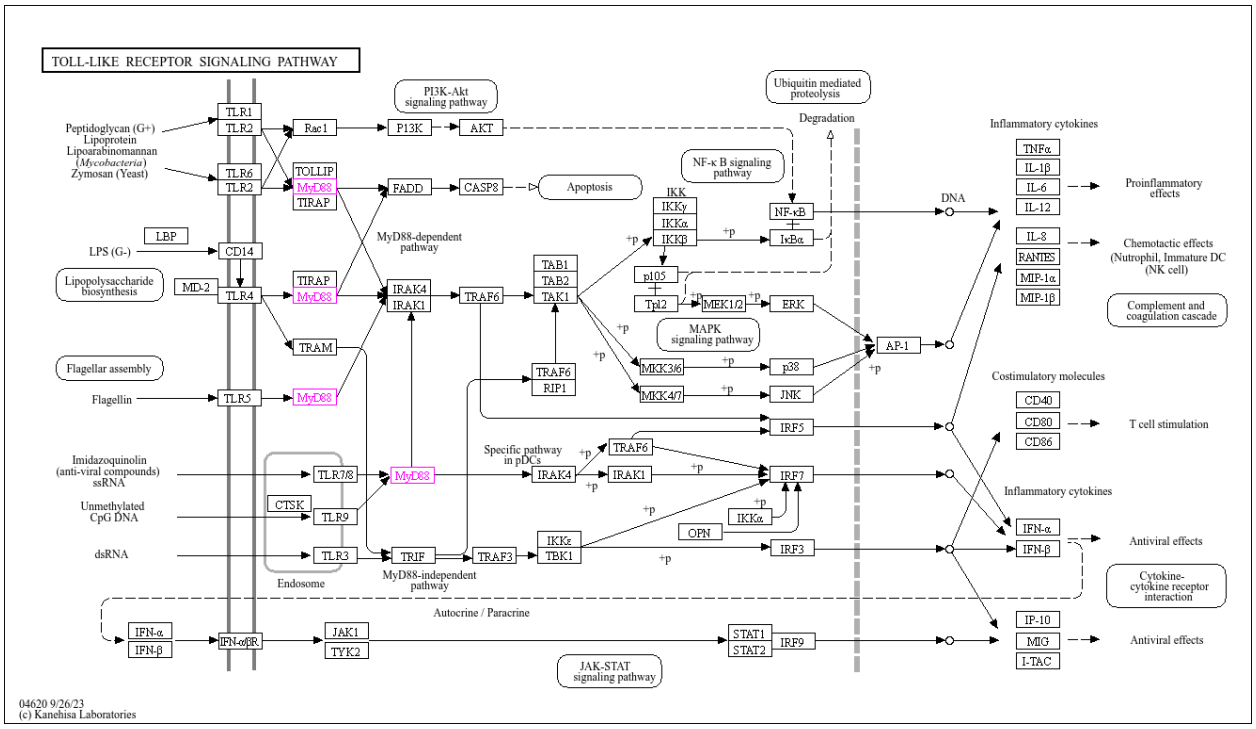
Therapeutic Target:

- Experimental inhibitors of MYD88 or its downstream adaptors (IRAK4 inhibitors) are being developed to reduce hyperinflammation in severe sepsis and cytokine storm syndromes.

🧪 Supporting Literature

doi: 10.1371/journal.pone.0037584.
doi: 10.1189/jlb.0807528
doi: 10.1097/ALN.0b013e31822a22f7.

KEGG:



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