Uncovering the TREM-1-TLR connection

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The innate immune system has several large genetically encoded receptor families that interact during the detection and elimination of pathogens. The Toll-like receptor (TLR) family recognizes a diverse group of evolutionarily conserved molecules including lipopolysaccharide (LPS), peptidoglycan, and nucleic acids. Engagement of these receptors results in proinflammatory signaling. Another family of innate immune receptors, triggering receptors expressed on myeloid cells (TREM), is capable of altering the downstream signaling potential of the TLR molecules. The TREM family contains both inhibitory and activating receptors that act to fine-tune the inflammatory response mediated by TLR. The novel report (Ornatowska and colleagues, 15) expand our understanding of the potential mechanism of TREM-1 modulation on TLR4 signaling. Using siRNA silencing of TREM-1 and pathway-specific microarray analysis, they show that TREM-1 silencing in macrophage results in decreased transcription of key proteins in the TLR4 signaling pathway. This downregulation of adaptor proteins during TREM-1 silencing suggests that TREM-1 may be impacting cytokine and chemokine production by increasing the availability of downstream signaling molecules in the setting of acute inflammation.

In their recent article, Ornatowska et al. (15) expand our understanding of the potential mechanism of TREM-1 modulation on TLR4 signaling. Using siRNA silencing of TREM-1 and pathway-specific microarray analysis, they show that TREM-1 silencing in macrophage results in decreased transcription of key proteins in the TLR4 signaling pathway. This downregulation of adaptor proteins during TREM-1 silencing suggests that TREM-1 may be impacting cytokine and chemokine production by increasing the availability of downstream signaling molecules in the setting of acute inflammation.

When TLR4 binds, MD2/LPS Toll/IL-1R homology (TIR) domain containing adaptor molecules are recruited. These molecules can trigger two main signaling pathways: MyD88-dependent and TRIF-dependent (MyD88-independent) pathways. Signal transduction through both of these pathways will result in activation of NF-κB and mitogen-activated protein kinase cascades leading to inflammatory cytokine production. However, only TRIF-dependent pathways result in interferon (INF) and INF-inducible gene expression (16). Because adaptor recruitment dictates downstream cytokine expression, an understanding of the molecular events that control adaptor molecule recruitment is an area of intense investigation. Macrophage can utilize MyD88, TRIF, TRAM, or MAL/TIRAP adaptors following TLR4 ligation. TLR4 recruitment of TRIF results in INF production, whereas MyD88 recruitment leads to NF-κB-mediated responses that include TNF, IL-1, IL-12, IL-8, and MIP-1α production. Clearly, alterations in either selective adaptor recruitment or adaptor availability allow the immune system to tailor the output of the response following TLR ligation.

TREM-1 silencing did not alter TRIF-mediated expression of INF indicating that TREM-1 may not play a significant role in amplifying this TLR signaling pathway. However, the impact of TREM-1 silencing on MyD88, CD14, and other downstream signaling molecules could be the explanation for the decreased proinflammatory signaling observed both in vitro and in vivo following TREM-1 silencing. These authors noted significant decreases in MyD88 and CD14 transcripts as well as decreases in downstream molecules in the NF-κB pathway [IkBα, precursor to p50 (p100), CEBP-B] following LPS stimulation in the setting of TREM-1 silencing. These data suggest that TREM-1 may be impacting cytokine and chemokine production by increasing the availability of downstream signaling molecules in the setting of acute inflammation.
provide an explanation for how TREM-1 is able to amplify the output of the TLR4 response. It would be interesting to examine whether TREM-1 silencing in the in vivo models results in decreased levels of these signaling molecules as is noted in decreased in vitro studies.

Another intriguing question is whether different TREM-1 ligands can potentially cause alterations in TLR4 recruitment of adaptor proteins that ultimately control whether MYD88-dependent or -independent pathways are favored. Indeed, it seems that TREM-1 molecules, like many other innate immune receptors, may have the ability to bind multiple ligands. TREM-1 binding to platelets, serum, and viruses has been described, although no ligands have been identified (7, 13, 18). Recent structural data from TLR4/MD-2/LPS cocrystals reveal that TLR4’s interaction with LPS is not a direct interaction but is in fact mediated via MD2 (8). Whether TREM-1 ligands are similar multimeric complexes awaits discovery.

As functional genomic approaches enable us to identify overlapping signal pathways, the relationship between TREM-1 and TLR downstream signaling molecules will provide a more complete picture of the pathways involved in inflammation and identify potential therapeutic targets to alter these responses.

REFERENCES


