

Toll-Like Receptor Function

Indications for Ordering

Assist in diagnosis of innate immunodeficiencies when genetic defects of the innate immune system are suspected in individuals negative for other immunodeficiencies (eg, no detectable abnormality of antibody function, complement activity, neutrophil function, or cell-mediated immunity)

Test Description

- Mononuclear cells are isolated from anticoagulated whole blood and incubated with toll-like receptor (TLR) ligands and media alone
- TLR-specific ligands utilized
 - TLR2-TLR1 – Pam3CSK4 synthetic bacterial lipopeptide
 - TLR6-TLR2 – zymosan cell wall particles from *Saccharomyces cerevisiae*
 - TLR3 – polyinosinic-polycytidylic acid (poly[I:C])
 - Synthetic analog of dsRNA
 - TLR4 – lipopolysaccharide (LPS), ultrapure, from *Salmonella minnesota* mutant R595
 - TLR5 – flagellin from *Salmonella typhimurium*
 - TLR7-TLR8 – CL097 derivative of imidazoquinoline compound R848
- Peripheral blood mononuclear cell (PBMC) production of tumor necrosis factor alpha (TNF α), interleukin 1 beta (IL-1 β), and interleukin 6 (IL-6) are measured by multiplex bead assay for TLR1-8
- PBMC production of chemokine CXCL10 is measured for TLR3
 - Increases specificity

Tests to Consider

Typical testing strategy

- Screen for more common immunodeficiencies
 - Immunoglobulin levels
 - Complement testing
 - Cell-mediated immunity testing
 - Neutrophil function testing
- If other screens are normal, consider
 - TLR testing, IRAK4/MYD88 deficiency testing

Primary test

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- Ascertain TLR function and indicate a possible molecular defect in the innate immune system that is related to TLR function

Disease Overview

Incidence

- IRAK4 deficiency – rare
- MYD88 deficiency – rare
- TLR3 deficiency – 1/250,000

Symptoms

- Recurrent pyogenic bacterial infections
- IRAK4/MYD88 deficiency
 - Normal appearance
 - Clinically indistinguishable between the 2 deficiencies
 - Particular susceptibility to *Streptococcus pneumoniae*, *Shigella sonnei*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*
 - All invasive infections occur before age 14
 - Spontaneous improvement for most after age 14
- TLR3/UNC93B1 deficiency – selective susceptibility to herpes simplex 1 encephalitis

Pathophysiology

- TLRs enable innate immunity to prevent infection
 - Function as recognition factors for microbial and viral ligands
 - TLRs 1, 2, and 4-8 signal through an MYD88- and IRAK4-dependent pathway
 - TLR3 and endosomal TLR4 signaling are independent of MYD88 or IRAK4
 - Induce appropriate cytokine pathways by stimulating interferons, TNF α , IL-1 β , IL-6, and CXCL10
- Impaired innate immunity
 - Associated with disruptions to the signaling pathways
 - Suspected genetic associations
 - *IRAK4*, *MYD88*, *TLR3* genes

Test Interpretation

Results

- Interpretation provided by the medical director
 - Compares individual's results to client's normal control, as well as the laboratory control
- Positive – lack of or marginal response to specific TLR ligands
 - Suggests a possible molecular defect in the innate immune system related to TLR function or other components of the signaling pathway, such as IRAK4 or MYD88
- Negative – normal cytokine responses
 - Suggests normal TLR function

Limitations

- Results should be interpreted in conjunction with the individual's clinical status
- Defects in *TLR3* gene associated with herpes simplex encephalitis may not be detected in this assay based on the report of a patient with compound heterozygous mutations in *TLR3* leading to decreased cytokine production in response to poly I:C in fibroblasts but not PBMCs (Guo, 2011)

Reference

Guo Y, Audry M, et al. Herpes simplex virus encephalitis in a patient with complete TLR3 deficiency: TLR3 is otherwise redundant in protective immunity. *J Exp Med*. 2011;208(10):2083-2098