Seminar 4002: Ordering TLR-Receptor Testing in Patients with Recurrent Infections

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Toll-Like Receptor (TLR) Combinations and Ligands (Liew FY et al. Nat Rev Imm 5:446 (2005)):


Major Infectious Susceptibilities in patients with TLR pathway defects:

<table>
<thead>
<tr>
<th>IRAK4, MyD88</th>
<th>Invasive pneumococcal infections</th>
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</thead>
<tbody>
<tr>
<td>TLR3, TRIF, TRAF3, Unc93B</td>
<td>Herpes encephalitis</td>
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<tr>
<td>Dectin1, CARD9</td>
<td>Candida</td>
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<tr>
<td>NEMO, IκBα</td>
<td>Bacterial, Mycobacterial, and Viral</td>
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Known Human Defects in TLR Signaling (Suhir & Etzioni Clin Rev Allergy Imm 24:490 (2011)):

- Red = Single gene mutations associated with specific immunodeficiencies
- Blue = Polymorphisms that affect infectious susceptibility

Toll-Like Receptor (TLR) Function Assay

**FOR EVALUATION OF PATIENTS WITH RECURRENT INFECTION WHO MAY HAVE GENETIC DEFECTS RELATED TO TLR FUNCTION**

**Test Highlights**
- This assay can be used to evaluate a patient with recurrent infections who is suspected of having genetic defects of the innate immune system.
- Mononuclear cells are isolated from anticoagulated whole blood and incubated with Toll-like receptor (TLR) ligands for TLR 1, 2, 3, 4, 5, 6, 7, 8, and 9, and in non-blood donors, followed by measurement of TNF-alpha, IL-10, and IL-6.
- A lack of response to specific TLR ligands may suggest a possible molecular defect in the innate immune system related to TLR function or other components of the signaling pathway such as IRAK or MyD88.

**TLR Function**

- **TEST CODE:** 63091
- **Tests Included in this Panel:** TLR 1, 2, 3, 4, 5, 6, 7, 8, and 9
- **CPT CODE:** 85063

**Clinical Utility**
This test would be indicated in a patient with symptoms of immune deficiency when the routine immunological assessments have not been instructive.

**Procedure**
Heparinized whole blood is stimulated with TLR ligands in 96-well plates (as background) and the cultured cells are incubated at 37°C. Following the stimulation phase, the plate is measured and analyzed for TNF-alpha using a Modular AxSym Analyzer. This test has not been cleared or approved for diagnostic use by the U.S. Food and Drug Administration.

**TLR Toll-Like Receptor Defect Screening Assay**

**Notes**
- Binding of TLRs to their cognate ligands initiates a signaling cascade that results in an inflammatory response to contain and combat infection. TLR alpha (heterogeneous factor alpha) is one of the key cytokines produced. This assay measures the ability of a patient peripheral blood mononuclear cells to produce TNF-alpha in response to stimulation with 9 different ligands - each specific for a single TLR. These 9 ligands identify all but TLR 10 whose ligand is as yet undefined.