

Toll-Like Receptor Defect Screening Assay

Clinical Background

The importance of human Toll-like receptors (TLR) to the etiology of Primary Immunodeficiency Disease has only recently been appreciated. The TLR family consists of ten receptors that are critical for innate immune responses as well as the generation of adaptive immune responses. TLRs are pattern recognition molecules that sense invading pathogens and respond by inducing a signaling cascade that culminates in an appropriate effector response. Mutations or polymorphisms in TLRs and associated adaptor molecules lead to increased susceptibility to certain pathogens (see the table below)

TLR	Disease Association	Reference
TLR2	<i>M. tuberculosis</i> , <i>S. aureus</i> and other gram positive infections	(1, 2)
TLR3	Herpes simplex virus	(3)
TLR4	RSV	(4)
TLR9	HIV progression	(5)
IRAK-4 (adaptor molecule)	Invasive bacterial diseases, generally <i>S. pneumoniae</i> , <i>S. aureus</i>	(6)

What is the assay?

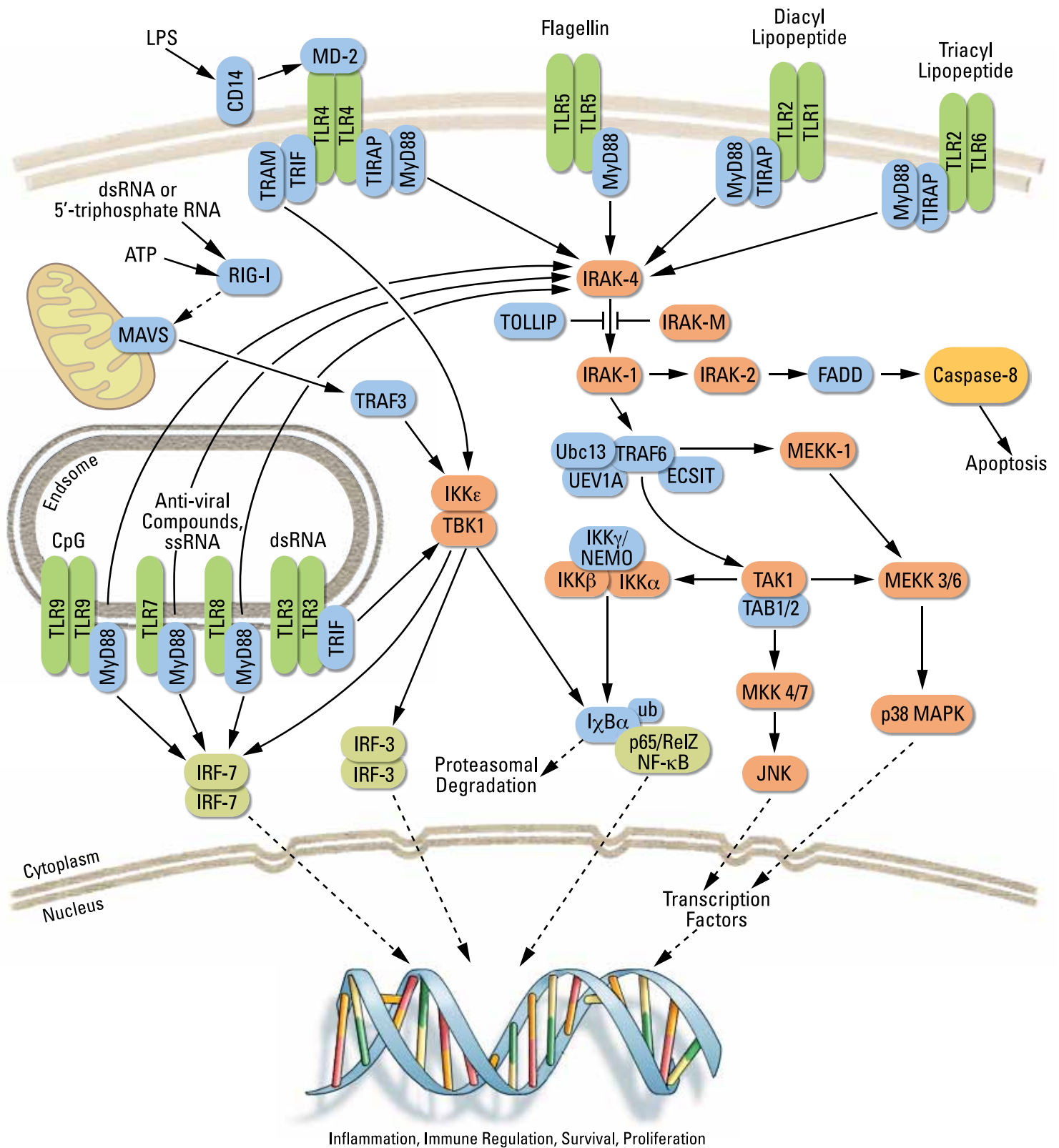
Binding of TLRs to their cognate ligands initiates a signaling cascade that results in an inflammatory response to contain and combat infection. TNF α (tumor necrosis factor alpha) is one of the key cytokines produced. The assay measures the ability of a patient's peripheral blood mononuclear cells to produce TNF α 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.

Test Information

Test code:	TLR
Method:	Lymphocyte stimulation followed by quantitative immunoassay for TNF α
Reference range:	By report
Specimen requirements:	10 ml of heparinized whole blood
Transport requirements:	10 ml heparinized whole blood (green top tube), room temperature, within 30 hrs of draw
Turn around time:	14 days
CPT code:	86353 (x9), 83520 (x9)

Contact Us
800.550.6227

NJlabs.org



References:

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2. Yim, J. J., et al. 2006. The association between microsatellite polymorphisms in intron II of the human Toll-like receptor 2 gene and tuberculosis among Koreans. *Genes Immun* 7:150-155.
3. Zhang, S. Y., et al. 2007. TLR3 deficiency in patients with herpes simplex encephalitis. *Science* 317:1522-1527.
4. Tal, G., et al. 2004. Association between common Toll-like receptor 4 mutations and severe respiratory syncytial virus disease. *J Infect Dis* 189:2057-2063.
5. Bochud, P. Y., et al. 2007. Polymorphisms in Toll-like receptor 9 influence the clinical course of HIV-1 infection. *AIDS* 21:441-446.
6. Ku, C. L., et al. 2007. Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. *J Exp Med* 204:2407-2422.