

Innate Immunity & Inflammation

The innate immune system is an evolutionally conserved mechanism that provides an early and effective response against invading microbial pathogens. It relies on a limited set of pattern recognition receptors (PRRs) that recognize specific pathogen-associated molecular patterns (PAMPs) commonly present in microbes but not in host. Upon detection of PAMPs, some PRRs trigger an inflammatory response leading to efficient destruction of the invading pathogens. Three main families of PRRs have been shown to initiate proinflammatory signaling pathways: the **Toll-like receptors (TLRs)**, the **NOD-like receptors (NLRs)** and **RIG-I-like receptors (RLRs)**.

Toll Like Receptors (TLRs) TLRs are the first identified and best characterized receptors among the signaling PRRs. They initiate key inflammatory responses and also shape adaptative immunity. They recognize a variety of PAMPs from bacteria, fungi, parasites, and viruses, such as lipopolysaccharide (LPS), flagellin, and CpG DNA. TLRs initiate shared and distinct signaling pathways leading to the activation of various transcription factors, such as NF- κ B and AP-1, and the subsequent production of pro-inflammatory cytokines.

Nod-Like Receptors (NLRs) NLRs (also known as CATERPILLERS) constitute a recently identified family of intracellular PRRs, which contains more than 20 members in mammals. Although the ligands and functions of many of these receptors are not known, their primary role is to recognize cytoplasmic PAMPs and/or endogenous danger signal, inducing immune responses. NLRs have been grouped into several subfamilies on the basis of their effector domains: NODs, NALPs, CIITA, IPAF, and NAIPs.

RIG-I-Like Receptors (RLRs) RLRs constitute a family of cytoplasmic RNA helicases that are critical for host antiviral responses. RIG-I (retinoic-acid-inducible protein 1) and MDA-5 (melanoma-differentiation-associated gene 5) sense double-stranded RNA (dsRNA), a replication intermediate for RNA viruses, leading to production of type I interferons (IFNs) in infected cells. A third RLR has been described: laboratory of genetics and physiology 2 (LGP2), that acts as a negative feedback regulator of RIG-I and MDA-5.

Inflammasomes The nucleotide-binding oligomerization domain-like receptor (NLR) family of proteins is involved in the regulation of innate immunity responses. Certain members of the NLR family sense pathogen-associated molecular patterns (PAMPs) in the cytosol and induce the assembly of large caspase-1-activating complexes called inflammasomes.

Other Pathogen Sensors Besides TLRs, NLRs and RLRs, other receptors can also recognize molecules present on pathogenic organisms. Those receptors include members of the PGRP (peptidoglycan recognition proteins) and C-type lectin families. C-type lectins, also called C-type lectin receptors (CLRs), encompass a large family of proteins that act as phagocytic receptors that bind carbohydrate moieties of various pathogens. This family comprises MBL, Dectin1, DC-SIGN and the structurally related receptors SIGNRs.

Danger Signal - DAMPS PRRs detect not only PAMPs, but also molecules released by stressed cells undergoing necrosis called damage-associated molecular patterns (DAMPs) or alarmins. These DAMPs act as endogenous danger signals to alert and activate innate immune cells. The major DAMPs are HMGB1 (high mobility group box protein-1), S100A8/A9, heat-shock proteins, uric acid and DNA.

Toll-Like Receptors

InvivoGen offers a large set of tools to study **Toll-Like Receptors (TLRs) pathways**: TLR and related genes, TLR expressing cell lines, TLR Detection products, antibodies against TLR, TLR inhibitors, a large choice of TLR ligands and antagonist.

Introduction



Toll-Like Receptors (TLRs) play a critical role in the early innate immune response to invading pathogens by sensing microorganisms. These evolutionarily conserved receptors, homologues of the *Drosophila* Toll gene, recognize highly conserved structural motifs only expressed by microbial pathogens, called pathogen-associated microbial patterns (PAMPs).

TLR & TLR-Related Genes



InvivoGen offers the largest collection of human and mouse genes involved in the TLR pathways. The entire open reading frames (ORFs) of these genes are provided in an expression plasmid and are fully sequenced. The genes are available native, tagged or modified to act as dominant negative mutants.

TLR Expressing Cell lines



InvivoGen provides an expanding collection of TLR expressing cells. These cells enable efficient monitoring of TLR activity using ELISA analysis such as IL-8 titration or reporter-based systems that monitor the activation of NF- κ B.

TLR Detection



InvivoGen offers a comprehensive set of tools designed for the detection of Toll-like receptors. These tools include primers to detect the expression of the TLRs at the mRNA or protein level, fusions between the TLRs and a fluorescent protein to study their localization and a family of inducible plasmids to monitor TLR activation.

TLR Antibodies



- **TLR antibodies** include a selection of IgA chimeric monoclonal antibodies, IgG monoclonal antibodies and IgG polyclonal antibodies. Most of these antibodies can be used in neutralization experiments, but also for other applications such as flow cytometry, immunochemistry and Western blotting.

- **Anti-HA antibody** is provided to detect the expression of TLR proteins fused to the HA tag by Western blot or immunoprecipitation.

TLR Ligands



InvivoGen offers the largest choice of ligands known to activate specific TLRs, that can serve as controls in genetic and pharmaceutical studies on TLRs. The ligands are available individually or in kits.

TLR Inhibition



InvivoGen provides a number of tools that should prove useful to help elucidate the molecular mechanisms involved in TLR signaling. These tools include dominant negative TLRs, short hairpin RNAs (shRNAs) that silence TLR and adaptor genes and inhibitors of TLR signaling.

TLR Ligand Detection



Endotoxin Detection: InvivoGen provides the HEK-Blue™ LPS Detection Kit, a simple, rapid and reliable system to detect the presence of lipopolysaccharides in your samples.
TLR Ligand Screening: InvivoGen has developed an innovative method to determine whether a compound is recognized by TLRs and acts either as an agonist or antagonist.

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TLR Ligands

The Largest Collection of TLR Agonists

Toll-like receptors recognize a wide variety of ligands, called pathogen-associated molecular patterns (PAMPs), discriminating gram-positive and gram-negative bacteria from fungi and other pathogens. InvivoGen offers the most comprehensive choice of ligands known to activate specific TLRs, that can serve as controls in genetic and pharmaceutical studies on TLRs. InvivoGen strives to provide TLR ligands of the highest quality. All ligands are tested for induction on TLRs and endotoxin levels. TLR ligands are provided individually or as TLR Agonist kits

TLR2 Ligands : TLR2 is involved in the recognition of a wide array of microbial molecules representing broad groups of species such as Gram-positive and Gram-negative bacteria, as well as mycoplasma and yeast.

TLR3 Ligand : TLR3 recognizes double-stranded RNA (dsRNA), a molecular pattern associated with viral infection. Polyinosine-polycytidylic acid (poly(I:C)), a synthetic analog of dsRNA, is the ligand of choice for TLR3.

TLR4 Ligands : TLR4 is the receptor for Gram-negative lipopolysaccharide (LPS) and lipid A, its toxic moiety. InvivoGen offers LPS from various bacteria and monophosphoryl lipid A.

TLR5 Ligands : TLR5 recognizes flagellin, the major component of the bacterial flagellar filament, from both Gram+ and Gram- bacteria. InvivoGen provides flagellin purified from *B.subtilis* (Gram+) and *S.typhimurium* (Gram-) bacteria and a new recombinant form.

TLR7/8 Ligands: TLR7 and TLR8 are involved in the response to viral infection. They recognize GU-rich short single-stranded RNA as well as small synthetic molecules such as imidazoquinolines and nucleoside analogues.

TLR9 Ligands : TLR9 recognizes specific unmethylated CpG-ODN sequences that distinguish microbial DNA from mammalian DNA. Three types of stimulatory ODNs have been described: type A, B and C. InvivoGen also provides inhibitory ODNs as well as control ODNs.

Labeled TLR Ligands: Labeled ligands are useful to study their cellular uptake and localization. InvivoGen offers CpG-ODNs that are labeled with FITC at their 3' terminus and *E.coli* lipopolysaccharide labeled with biotin.

NOD Ligands: NOD1 and NOD2 are intracellular pathogen-recognition molecules that sense bacterial peptidoglycan (PGN). InvivoGen provides insoluble and soluble PGNs from Gram- and Gram+ bacteria and bioactive fragments of PGN such as iE-DAP and MDP.

IFN Inducer: Double-stranded B DNA is a very potent inducer of type I interferons that is obtained by complexing the synthetic double-stranded DNA, poly(dAdT)•poly(dT-dA), with cationic lipids.

NF-κB Activators: InvivoGen provides two known activators of the transcription factor NF-κB: Tumor Necrosis Factor alpha (TNF-α) and Phorbol Myristate Acetate (PMA).



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TLR Agonist kits : The TLR agonist kits represent convenient and economical tools to study the stimulation of the TLRs. Each kit contains several known agonists for a given TLR and allows to perform 100 tests (100 μ l in a 96-well plate).

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