

## Toll-like receptors: Inflammation's missing link

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**New London, N.H.** — New insights regarding the regulation of inflammation are leading researchers to evaluate toll-like receptors (TLRs) as potential targets for the development of new therapies in chronic inflammatory disease.

The biochemical mechanisms behind TLR activity are a passion of Alberto Visintin, Ph.D., assistant professor of medicine at the University of Massachusetts School of Medicine. Presenting at the Gordon Research Conference on Tissue Repair and Regeneration in 2005, Dr. Visintin gave an overview of the role of TLRs in inflammatory response and an update on his research specific to the recognition of gram negative pathogens.

Signals causing the activation of inflammation come from chemical mediators such as cytokines and molecular signatures found on invading organisms, such as gram negative lipopolysaccharides (LPS). CD14, a pattern-recognition receptor (PRR) that binds LPS, is critically involved in mediating LPS responses. However, CD14 lacks a transmembrane domain, and the mechanism by which LPS to CD14 binding induces cell activation and pro-inflammatory cytokine production was a mystery for many years.

Enter the discovery of toll-like receptors (TLRs) around six years ago; this ultimately bridged that gap in understanding. This family of type I transmembrane PRRs is essential in the recognition of the pathogen-associated molecular patterns (PAMPs) that are unique to microbes. Ten TLRs have been described in humans to date, each one recognizing a specific class or classes of PAMPs.

TLRs are expressed primarily in cell types that are involved in the first line of defense, such as dendritic cells, macrophages, neutrophils, mucosal epithelial cells and dermal endothelial cells. Most of these receptors, and in particular TLR2 and TLR4, have been implicated in innate immunity and inflammation.

### Immunities

The somewhat dual nature of a vertebrate's immune system is able to optimize the body's response to unwanted intrusions. Innate immunity is the first line of defense,

initiating early response to pathogen invasion by providing a first level of self/non-self recognition.

Adaptive (acquired) immunity is mediated by B- and T-cells after exposure to antigens and shows enhanced specificity (by producing high affinity extracellular adaptors, the antibodies, which bridge the pathogens and the host's effector functions) and memory.

TLRs mediate innate immune responses that are specific to the type of invading pathogen. This is critical not only for providing the host with immediate protection, but also for initiating adaptive responses that are appropriate for the type of infection.

When infection occurs, dendritic cells capture the pathogen, exit the site of infection and migrate to the lymph nodes. During migration, the cells undergo a maturation process that is initiated through TLRs engagement. This implements an immediate increase in scavenging activities (phagocytosis and macropinocytosis) by macrophages and dendritic cells, enhancing their ability to take up pathogens and process them as antigens. All these events prepare dendritic cells for their role in T-cell stimulation, leading to adaptive immunity activation.

### **A look at TLR4**

The potent inflammatory properties of gram negative bacterial LPS, for example, can be ascribed largely to cellular recognition by TLR4, the signaling receptor that is the focus of Dr. Visintin's work.

"In particular, I study MD-2, which is a soluble extracellular adapter between LPS and TLR4. Without a physical association with MD-2, TLR4 cannot signal the presence of LPS," he explains. "This was confirmed in a variety of ways, but the most convincing was using a generation of knockout mice for both TLR4 and MD-2, which are phenocopies and completely blind to LPS."

According to Dr. Visintin, it works this way: To form stable receptor complexes, MD-2 must be bound to the extracellular domain of TLR4. Together, TLR4 and MD-2 transduce a signal upon binding LPS. Supernatants from MD-2-transfected cells can then confer signaling function on TLR4-expressing cells.

### **TLRs and the skin**

The importance of TLRs to the skin, Dr. Visintin says, is clear. The primary function of the skin is to provide a barrier between the body and the outer world, and specialized dendritic cells, like Langerhans cells, can start the inflammatory response almost immediately upon exposure to stressful stimuli such as UV light, a mechanical injury or biotic injury.

"The biotic injury is most interesting, I think, because these cells process parts of the bugs that are invading and then bring all the packets of information to the lymph nodes to show what they have in the context of a danger signal," Dr. Visintin tells

**Dermatology Times.** "Tolls are responsible for alerting the immune system to a danger."

**Disclosure:** Dr. Visintin reports no conflicts of interest.