Toll-like receptors (TLRs) are important components of the innate immune system, the evolutionary ancient response system consisting of pattern recognition proteins that recognize pathogen-associated molecular patterns (PAMPs). TLRs are a series (10 in humans) of cell surface or intracellular receptor proteins that contain signaling motifs that are structurally similar to the mammalian interleukin (IL)–1 receptor and the Toll protein of insects. In mammals, TLRs function by recognizing viruses, bacteria, fungi, and parasites on the basis of their PAMPs, and then activating cells to produce cytokines including interferon (IFN) and inflammatory cytokines such as IL–1 and tumor necrosis factor that may either lead to local or systemic inflammation (reviewed in [1]). TLRs also activate the adaptive immune responses (B and T cells). As a result, they are critical to the initial host response to infection. TLR4 was originally described as the cell surface receptor that signaled the binding of lipopolysaccharide and was therefore responsible for sepsis syndrome caused by gram-positive organisms.

In this issue of the Journal, Bochud et al. [2] have noted an association between polymorphisms in TLR2 and recurrences of herpes simplex virus type 2 (HSV-2) infection. This type of study brings us closer to understanding how genetic predispositions define how one will respond to an infectious challenge.

If, in the future, we can use genetic polymorphisms to predict responses to pathogens, this would help in understanding and therefore potentially altering the course of an infectious disease. The concept that one could predict an individual’s response to an infectious agent on the basis of his/her genetic predisposition is the “holy grail” of molecular genetics. If this is correct, it opens the door to new diagnostic and therapeutic approaches. For example, one might selectively vaccinate those who are likely to develop overwhelming disease to try to shift their immunologic profile from a Th2 response pattern (characterized by high levels of antibodies and IL-10 production) to a Th1 response (characterized by cytolytic T cell responses and IFN-γ production). A particular TLR polymorphism might predict an inability to respond to a conventional dose of vaccine and mandate a different approach (perhaps the use of an adjuvant or another approach to prevention).

The interesting question is, “how does a polymorphism in a pattern recognition protein affect the pathogenesis of an infectious organism (table 1)?”

TLRs have been documented to have roles in antigen presentation, initial cytokine induction, virus replication, and the adaptive immune response. Several TLRs and their downstream adapter proteins have a major role of determining the outcome of infectious diseases. TLR2 plays an important role in the development of lethal encephalitis in HSV-1 infection [15]. In some cases, such as the reported TLR2 polymorphism and leprosy, there appears to be a straightforward association with disease manifestations: the variant allele that is associated with disseminated disease is associated with a lack of host response [6, 7]. It is easy to conceptualize that the type of cytokine response generated by the host might result in a different pattern of disease. In the case of leprosy, the most plausible explanation is that a lack of induction of secretion of an activating cytokine (such as IFN-γ) leads to disseminated disease, as opposed to a localized infection, when a robust cytokine response is induced. In this case activation activity of the TLR2 allele in vitro correlated with a lack of cytokine induction in vitro.

In other cases of TLR polymorphisms, the association of a TLR response with disease processes is less clear. For example, the role that the intracellular TLRs (TLR3, TLR7, TLR8, and TLR9) have in regulation of disease pathogenesis in response to bacteria is less well understood. TLR9 is
activated by bacterial DNA, but whether that is important physiologically is not clear. In the case of viruses, interactions with the intracellular receptors are critical to the outcome of infection. In addition to regulation of inflammatory and non-inflammatory cytokines, TLRs (particularly TLR3 and TLR4) also affect the production of IFN, which is essential to prevention of viral replication.

How can a TLR polymorphism lead to an increase in recurrences of HSV-2 infection? The process that leads to viral reactivation of a latent virus is complicated by the fact that an inflammatory process could itself lead to reactivation of virus. If a particular allele (through either structural differences or differences in cell surface expression) of TLR2 is associated with an increased number of recurrences, the differences could be related to either a decreased response (leading to increased viral replication) or an increased response leading to an increase in inflammation (and perhaps reactivation of latent virus). It is also possible that distinct polymorphisms for both increased and decreased risk of recurrence occur and could—in particular in haplotypes—offset each other (i.e., one polymorphism mitigating the effect of the other).

The disseminated “septic picture” seen uniquely in HSV-2 infection in neonates has been attributed to enhanced TLR2 responses seen in neonates [16]. Whether the polymorphisms reported in this study function in this manner or by some other mechanism is something that will require further study. Regardless of the outcome of that analysis, however, these observations bring us closer to understanding the genetics of host responses to infection. Eventually that understanding should lead us to tailoring our approach to the disease based on the individual patient’s genetic makeup.

References