Commentary

Viral interference with IL-1 and Toll signaling

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The cytoplasmic domain of both the IL-1 receptor (IL1R) and of molecules that function in host defense called Toll-like receptors (TLR) are homologous to one another and thus are called TIR (Toll/IL-1 receptor) domains (1). Two publications in recent issues of PNAS have sought for more Toll-like receptors in two different organisms. One paper, by Bowie *et al*. (2), describes the discovery of TLRs in the vaccinia virus, suggesting that the virulence of pox viruses depends on this measure to counter host defense. This is quite typical of pox viruses, which have over the years acquired several cytokine and cytokine-receptor genes that participate in modulating the antiviral host response. Another paper, by Tauszig *et al*. (3), describes more Toll-like genes in the fruit fly *Drosophila melanogaster,* where these genes were first described.

Initially, Toll was known to be involved in dorso-ventral axis formation in the fly embryo. However, it was discovered several years ago by the Jules Hoffmann group in Strasbourg, France, that these genes also participate in a fundamental form of host defense, which was until that time unknown (4). It is now clear, from several publications over the last 5 years, that the activation of the TIR domain leads to activation of NF-κB, which in turn activates a variety of cytokines, chemokines, and costimulatory molecules that are mounted on the cell surface. Furthermore, it is clear that the TIR domain is central to the functioning of an ancient form of host defense, without which the adaptive immune system cannot function. It is found in plants, invertebrates like *Drosophila melanogaster,* and in vertebrates like man and mouse. Only the latter two species, like most vertebrates with the noted exception of lampreys and hag fish, have the added ability to form antibody and T cell receptors. Thus, the existence of a TIR domain gene in the vaccinia viral genome is of great potential importance. In this paper, we will outline why we believe that these findings are of importance and some practical ideas about putting these sequences to work for mankind rather than against humans who contract pox viruses.

The first question that these data may be able to address is how much similarity is required by a TIR domain to be classified as such? The answer appears to be only some, and it occurs in patches in the C-terminal half of the viral homologue of the TIR domain. The pieces of sequence similarity or identity may represent the first clues as to the interaction of this TIR domain with other TIR domains or other molecules. That is because the sequence described by Bowie *et al*. (2) shows only limited similarity to a TIR domain, yet it is clearly shown to interfere with the activation of NF-κB, which depends on proper upstream signaling dependent on TIR domains. That is to say, expression of a few critical stretches of amino acids that are identical or similar to the TIR domains in Toll or the IL-1R is sufficient to interfere with IL-1R or Toll signaling. This is quite a remarkable result and will undoubtedly send other virologists running to their favorite virus to search for like degrees of similarity. It will certainly be interesting to be watching the scramble for other genomes to be explored.

The other things that can be learned by looking at these sequences are the apparently critical contact residues surrounded by filler that are basically needed to maintain spacing between the few amino acids that really are critical to build a TIR domain. These residues should rapidly become clear from the studies of other viral genomes, as well as from functional genomics. These sequences can be detected in the same way as those in vaccinia virus, or alternatively by direct-binding studies using bona fide TIR domains in a sensitive instrument such as a BIAcor. This procedure should rapidly define the minimal requirement for a TIR domain.

One practical application of these data could be to serve as a basis for designing new anti-inflammatory agents, first as peptido-mimetics and later by organic synthesis. If one had a drug to give to patients suffering from pox virus infection, and other illnesses that activate NF-κB, then think of all of the suffering that could be relieved. So one of the first implications of these papers is the design of new drugs to inhibit NF-κB activation. After all, if vaccinia can do it, we should be able to do it, and do it better than a virus.

As we mentioned earlier, this discovery should encourage other virologists to reexamine the genomes of their favorite organism. If vaccinia virus can pick up a potent antihost defense activity like a TIR domain, and with so little similarity, surely other examples can be found in the viral kingdom. This research could lead to a whole host of new medications that focus on the inhibition of TIR domains. It may be different with different viruses, so that we should not assume that having developed drugs that will cure vaccinia, a nonpathogen in humans, we should stop searching. In fact, we rather believe that vaccinia would be the last place to look for such an activity, and that more virulent viruses would be an even better place to search for similarities to TIR domains.

Finally, the data clearly indicate that viruses, like bacteria and fungi, encounter not only the adaptive immune system, which works by clonal selection of lymphocytes, but also the innate host defenses that originally were thought to be able to avoid detection by TLRs by being encoded by viral genomes. Whether these countermeasures evolved as a way of defeating the original system of host defense will remain an open question until such a virus is tested in mice that lack one or another of the TLRs. Alternatively, and more certainly, one could examine mice that lack the adaptor protein MyD88, which itself has a TIR domain, with which it interacts with both the IL-1R and the Toll-like receptors. These experiments, which can be anticipated to appear in short order, will tell us whether the innate host defenses can detect virus infection in the same way that they detect and resist bacterial and fungal infection.

Innate immunity is a complex system of host defense, of which the TLRs make up only a small fraction. In the end, we should learn a great deal about what makes a pathogen pathogenic by studying what it does to fight against host

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defense mechanisms. This will help us, in turn, to learn about the importance of host defense mechanisms by studying the genomes of pathogens. It's all there in the genes, and we just have to be smart enough to decipher these genomic puzzles. We have a lot of work ahead of us, but we can be sure that we are started on the correct path.

The paper by Bowie *et al*. (2), as well as the paper by Tauszig and coworkers (3), should help to emphasize the importance of the TLRs that now have been described as involved in host defense in humans, mice, invertebrates, and plants. That viruses have evolved countermeasures says that these are important to the success of even so mild a virus as vaccinia. This finding further emphasizes the importance of the innate immune system, and especially of the Toll-like receptors.

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