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"UNCOVERING NOVEL SIGNALING PATHWAYS ENGAGED DURING THE INNATE IMMUNE RESPONSE" Richard J. Ulevitch, Department of Immunology, The Scripps Research Institute, La Jolla CA 92037

The innate immune response is highly conserved throughout evolution. From studies in *Drosophila* we now appreciate that a family of transmembrane proteins comprised of an ectodomain made up of leucine-rich repeats (LRRs) and a cytoplasmic domain related to that found in members of the interleukin-1 receptor family (TIR domain). In *Drosophila* the *Toll* gene encodes a protein required for responses to Gram-positive bacteria and fungi. In contrast responses to Gram-negative bacteria are controlled by the *imd* gene. Activation of both pathways result in synthesis of anti-microbial peptides while only activation of the *imd* appears to be linked to cell death pathways. In mammalian cells innate immune responses are controlled by proteins comprising the ten-member Toll-like receptor family (TLRs). Like *Drosophila* Toll protein (dToll), the TLRs are comprised of similar structural domains; a ectodomain consisting of multiple LRRs and a cytoplasmic tail containing TIR sequences. One might predict redundant ligand recognition patterns as well as highly conserved signaling pathways for each of the TLRs. However this is not the case since there are now five distinct ligand-TLR pairs known. Moreover the common signaling pathways do not provide an explanation for the distinct downstream events occurring after engagement of a single TLR with a specific ligand. Here we will describe some unique features of the signaling pathways elucidated from our studies of specific TLR-ligand interactions.