

# Genetic analysis of innate immunity

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## Abstract

The principal receptors by which mammals detect microbial infection were identified by positionally cloning a spontaneous mutation (Lps) that abolished lipopolysaccharide sensing and left mice vulnerable to Gram-negative infection. These, the Toll-like receptors (TLRs) are required for mammals to recognize microbes and rapidly respond to them. Since most perception of microbes depends upon the TLRs, the adjuvant effect of microbes is also eliminated when TLR signaling is disrupted. But adaptive immune activation is not dependent upon TLRs *per se*, and alternative adjuvant pathways are being defined. The classical genetic approach has had much to offer since the TLRs were identified. By inducing new germline mutations with ENU, screening for innate immunodeficiency phenotypes, and positionally cloning the genes involved, we have found several new molecules that participate in TLR signaling, and have estimates the total number of essential signaling components. A broader look, utilizing a single well-defined pathogen as a screening tool, has revealed that there are about 300 genes encoding proteins with nonredundant function in host resistance to mouse cytomegalovirus (MCMV). Mutations in more than 30 of these genes have been produced, and positional cloning of these mutations will offer fresh entry points into the innate response at large. Since innate immunity is highly degenerate, many components of the MCMV resistome also offer protection against unrelated infectious (and possibly neoplastic) diseases. Insofar as innate resistance entails what we call the "inflammatory response," it is likely that at least some of the genes identified will prove to be responsible for sterile inflammation as well.