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INNATE IMMUNITY

TLR3: rising above redundancy

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Jean-Laurent Casanova and colleagues report in *Science* a Toll-like receptor 3 (TLR3) deficiency in two children with herpes simplex virus type 1 (HSV1) encephalitis (HSE), and identify autosomal dominant TLR3 deficiency as the second genetic aetiology of isolated HSE.

Despite the wealth of information that has been gained from experimental infections in mice deficient for individual TLRs, it has been unclear whether TLRs have a non-redundant role in natural human infections — in fact, no primary immunodeficiency that involves TLRs has been identified. Human TLRs and/or interleukin-1 receptors (IL-1Rs) have been implicated in host defence by the discovery of IL-1R-associated kinase 4 (IRAK4) deficiency in children with bacterial diseases, and another study from this group has shown that both these receptor types are vital for childhood immunity to pyogenic bacteria (see Further Reading). However, IRAK4-dependent TLRs (TLR7, TLR8 and TLR9) appear to have a redundant role in protective immunity to most infections, including HSE.

So why did the authors focus on TLR3? First, HSV1 is a double-stranded DNA (dsDNA) virus with dsRNA intermediates, and TLR3 recognizes dsRNA. Second, TLR3 is expressed in cells that are resident in the central nervous system (CNS), and HSV1 infection progresses from nasal and oral epithelial cells to the CNS in HSE. And last, a genetic aetiology for HSE has been reported in two children who lack a functional UNC93B protein. UNC93B is mainly found in the endoplasmic reticulum and, similar to IRAK4, is required for signalling through TLR7, TLR8 and TLR9, but also TLR3. Patients who are UNC93B deficient have impaired TLR3-dependent interferon (IFN) production. Therefore, the authors examined whether the TLR3-dependent induction of IFNs might be impaired in HSE.

Casanova and colleagues investigated two unrelated children with HSE, and found a previously undescribed heterozygous mutation in *TLR3* that was not found in healthy control individuals. The mutation leads to the replacement of a proline residue by a serine residue at position 554 (P554S). In dermal fibroblastic cell lines (which selectively express TLR3) derived from patients and controls, heterozygosity for the dominant negative P554S *TLR3* allele appeared to confer autosomal dominant hyporesponsiveness to the TLR3 agonist polyinosinic–polycytidylic acid (polyI:C), which mimics dsRNA. There was a causal relationship between heterozygosity for the P533S *TLR3* mutation and impaired TLR3 signalling, abnormally weak IFN production, enhanced viral replication and higher levels of fibroblast cell death upon viral infection.

The normal IFN response of blood dendritic cells and keratinocytes to polyI:C indicated that TLR3-independent pathways were involved, and correlated with the lack of clinical HSV1 dissemination, particularly in the blood, in patients with HSE. Blood cells from the patients also showed normal IFN responses to stimulation with several different viruses, which is consistent with the natural resistance of these patients to most viruses other than HSV1.

This study provides conclusive evidence that an individual TLR can have a non-redundant role in host defence in the setting of a natural infection.

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ORIGINAL RESEARCH PAPER Zhang, S.-Y. *et al.* TLR3 deficiency in patients with herpes simplex encephalitis. *Science* **317**, 1522–1527 (2007)
FURTHER READING Ku, C.-L. *et al.* Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. *J. Exp. Med.* **204**, 2407–2422 (2007)