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IMMUNOGENETICS

Lucky for some

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URLs
TIRAP
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=114609

Inheriting a particular variant of a key signalling molecule downstream of Toll-like receptors (TLRs) might help to protect you against several common infectious diseases, report the authors of a recent study in *Nature Genetics*.

The MyD88-adaptor-like protein (Mal, which is encoded by the gene *TIRAP*) mediates signalling downstream of TLR2 and TLR4. Given the importance of this signalling pathway in the generation of inflammatory responses against several microbial components, Khor *et al.* proposed that genetic variation in *TIRAP* might influence susceptibility to common infectious diseases. They analysed 33 single-nucleotide polymorphisms (SNPs) in *TIRAP* in multiple populations from the United Kingdom, Vietnam and several African countries. They found that one SNP — resulting in a serine-to-leucine substitution at position 180 (Ser180Leu) of Mal — occurred less frequently in individuals suffering from invasive pneumococcal disease, bacteraemia, malaria or tuberculosis than in control healthy individuals. Heterozygosity at *TIRAP* Ser180Leu was therefore associated with protection from these diseases.

The authors then asked whether this variation in *TIRAP* made a

difference to the activity of the protein. Whereas reconstitution of Mal-deficient cells with wild-type Mal (Ser180) restored efficient degradation of inhibitor of nuclear factor-κBα (IκBα) after stimulation with a TLR2 ligand, reconstitution with variant Mal (Leu180) did not. In addition, cells expressing Mal Leu180 were unable to induce interleukin-6 production after TLR stimulation, which indicates that the Mal variant is functionally defective. Moreover, cells transfected with both wild-type *TIRAP* and variant *TIRAP* also showed impaired TLR signal transduction, which indicates that the protective effect in heterozygous individuals might be due to attenuated TLR signalling.

On the basis of structural models of the Mal variant, the authors suggested that the presence of the leucine residue at position 180 might impair the ability of Mal to interact with TLR2. *In vitro* binding studies proved this to be the case.

So, being heterozygous for the Mal variant might confer protection from infectious disease by preventing the development of excessive inflammatory responses that could be detrimental to the host. By contrast, being homozygous for the mutant variant (Mal Leu180) might confer increased susceptibility to severe disease as a result of abolished TLR2 signalling. This is consistent with *TIRAP* Ser180Leu homozygosity being particularly rare in individuals in African countries, where the mutant allele might be subject to ongoing selective pressure from the high infectious-disease burden.

Lucy Bird

ORIGINAL RESEARCH PAPER Khor, C. C. *et al.* A Mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. *Nature Genet.* 25 February 2007 (doi:10.1038/ng1976)