IMMUNOGENETICS

Serving up variation to fight adversity

Two recent studies published in *Science Translational Medicine* and *PLoS Pathogens* provide striking examples of how genetic variation between human populations can affect inflammatory responses to pathogens.

Karlsson *et al.* studied human populations in Bangladesh, which is an area where cholera has an ancient foothold and is still highly prevalent today. The authors compared the genomes of individuals of Bengali ethnicity from Bangladesh (BEB) with the genomes of three other international ethnic groups. They identified 305 genetic regions that were positively selected for in the BEB population and that were enriched in genes associated with nuclear factor-κB (NF-κB) signalling and potassium ion transportation. In particular, they found that genes co-expressed with *IKBKG* (the gene encoding NF-κB essential modulator, which is a subunit of the IκB kinase complex that promotes NF-κB activation) were strongly enriched in the BEB population.

They next carried out an association study on BEB cohorts, comparing the genomes of patients with cholera with the genomes of individuals who had been exposed to cholera but who did not develop disease. Notably, they found that several of the genes identified by their selection study were also associated with susceptibility to cholera. Furthermore, they identified a new disease association in a selected region that contains genes related to inflammasome activation, including *PYCARD* (PYD and CARD-containing gene; which encodes the inflammasome adaptor protein ASC).

> “the inflammatory response … is ethnically heterogeneous”

Experiments in mice confirmed that cholera toxin induces interleukin-1α production in lipopolysaccharide-primed macrophages and that this is dependent on macrophage expression of ASC and caspase 1. Their findings suggest that cholera has exerted strong selective pressure on pro-inflammatory pathways. Interestingly, the authors also note that there is an overlap between the genes selected for in the BEB population and those associated with susceptibility to inflammatory bowel diseases.

The study by Coussens *et al.* compared two cohorts of patients with pulmonary tuberculosis that were based in the same city; one cohort was of African ancestry, the other was of European or Asian origin. The authors analysed inflammatory profiles in the cohorts and identified five parameters that significantly differed between the groups. Patients of African origin had lower serum levels of CC-chemokine ligand 2 (CCL2), CCL11 and vitamin D-binding protein, lower numbers of peripheral blood neutrophils and higher serum levels of CCL5.

The authors next examined whether this was due to variations in the infecting *Mycobacterium tuberculosis* strain. They found that individuals from a particular ethnic group showed a similar inflammatory profile, regardless of the particular *M. tuberculosis* isolate they were infected with. This suggested that host genetics account for the variation in the inflammatory profiles seen among the ethnic groups. Indeed, further genetic analyses showed that ethnic variation in the gene encoding vitamin D-binding protein was closely associated with the inflammatory profiles observed in the cohorts of patients with tuberculosis. The fact that the inflammatory response seen in patients with tuberculosis is ethnically heterogeneous could have important implications for diagnostic and treatment regimens.

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ORIGINAL RESEARCH PAPERS Karlsson, E. K. *et al.* Natural selection in a Bangladeshi population from the cholera-endemic Ganges River Delta. *Science Transl. Med.* **5**, 192ra86 (2013) | Coussens, A. K. *et al.* Ethnic variation in inflammatory profile in tuberculosis. *PLoS Pathog.* **9**, e1003468 (2013)