DDT Vol. 9, No. 6 March 2004

Pathogens maketh man

Jane Bradbury, BMN News

The infectious activity of pathogens over the centuries has left an indelible mark on the human genome, report evolutionary biologists. Now, protection that evolved against pathogens that blighted human populations hundreds of years ago appears to have evolved into protection against more recent arrivals, such as HIV.

Infection throughout history

Researchers at Duke University in Durham, North Carolina (http://www.duke.edu) have found that infection throughout history might have driven the selection of a single nucleotide polymorphism (SNP) in the promoter of the gene encoding the cytokine interleukin 4 (IL-4).

Gene variants like this that regulate the expression of genes particularly interest Duke Evolutionary Biologist Matthew Rockman. Many of them are present at varying frequencies in different human populations, he explains. 'As evolutionary biologists, we want to understand how these different frequencies arise.'

High IL-4 expression, which shifts T-cells towards the so-called Th2 phenotype and induces B cells to secrete IgE, is associated with allergies and some respiratory infections. Nevertheless, the -524T allele of IL-4, which increases IL-4 expression threefold compared with the -524C allele, is common in some human populations.

Genetic drift or natural selection?

Rockman set out to investigate whether the high frequency of the -524T allele in some populations had arisen through neutral changes such as genetic drift and migrations or through natural selection. His latest data, published in

Current Biology [1], indicate that the frequencies of the IL-4 polymorphism differ far more among human populations than would be expected on the basis of neutral drift, suggesting that natural selection is responsible.

Rockman's data do indeed support the idea that the -524T allele has been positively selected for, agrees geneticist Michael Dean, a Principal Investigator at the US National Cancer Institute in Frederick, USA (http://web.ncifcrf.gov/). 'This variant may have been beneficial to humans at some point, perhaps conferring disease resistance, even though it may be detrimental to some individuals.'

Which infectious diseases of the past might have selected the IL-4 polymorphism that is now more commonly associated with allergic immune responses is unclear and will be hard to determine, says Rockman. 'All we can say is that -524T, the allele that is common in Cameroon and China, is likely to be protective against extracellular pathogens, and -524C, which is common in India and Italy, should be better against intracellular pathogens.'

Exception to the rule: HIV-1

One exception to this rule is that the -524T allele is protective against the intracellular pathogen HIV-1, in part because IL-4 downregulates expression of the CCR5 receptor, via which HIV-1 gains entry to host cells. But, stresses Rockman, HIV-1 emerged too recently to have been involved in the selection of the -524T allele.

Similarly, HIV-1 is too much of a newcomer to have driven the selection of the CCR5–D32 mutation, a genetic variant of the CCR5 receptor that protects against HIV-1 infection. This allele, which is found at frequencies of about 10% in Caucasian populations, first appeared around 700 years ago, probably in the Viking population.

For some years, bubonic plague has been touted as the infectious disease that drove CCR5–D32 selection, but Montgomery Slatkin, Professor of Integrative Biology at University of California, Berkeley (http://www.berkeley.edu), doubts this explanation. 'Plague was only present briefly and episodically, and I do not believe that the mortality it caused was sufficient to select for the CCR5-D32 allele,' he said.

Instead, says Slatkin, smallpox could have driven CCR5–D32 allele selection. Smallpox has always been around, he says, and because it affects mainly children, it removes a greater reproductive potential than plague, which affects people of all ages.

Slatkin and colleagues published their latest work on this in the *Proceedings of the National Academy of Sciences*. 'Our analysis can not prove that smallpox drove selection of the CCR5-D32 allele but it certainly counts out the plague,' he said.

References

1 Rockman, M.V. *et al.* (2003) Positive selection on a human-specific transcription factor binding site regulating IL4 expression. *Curr. Biol.* 13, 2118–2123

2 Galvani, A.P. and Slatkin, M. (2003) Evaluating plague and smallpox as historical selective pressures for the CCR5-Delta 32 HIV-resistance allele. *Proc. Natl. Acad. Sci. U. S. A.* 100, 15276–15279

1359-6446/04/$ – see front matter PII: S1359-6446(04)03032-6