Herpes simplex virus and atopy in Finnish and Russian Karelian children

To the Editors:

Although the focus in the context of the hygiene hypothesis in explaining raised atopy prevalences has largely shifted from pathogens to commensals and saprophytes, the role of pathogens cannot be wholly ignored. Many pathogens are able to establish persistent or chronic infections, and have evolved strategies for immune evasion. A common immune subversion strategy used by such pathogens involves the increased production of the regulatory cytokines interleukin (IL)-10 and/or transforming growth factor-β by innate immune cells or *via* the generation of regulatory T (T-reg)-cells [1]. These cytokines, by inhibiting/downregulating the function of antigen-presenting cells and effector T-cells, appear, in turn, to be crucial for the development of tolerance against allergens.

We assessed whether seropositivities to three pathogens known to readily establish persistent/chronic infections *(Helicobacter pylori, Toxoplasma gondii*, herpes simplex virus (HSV)) and to hepatitis A virus (HAV; previously implicated in conferring protection against allergy) are associated with reduced risk of atopy. Schoolchildren aged 7–16 yrs were randomly recruited in Finnish (n=344; mean age 11.3 yrs) and Russian Karelia (n=425; mean age 11.5 yrs), two adjacent areas with contrasting lifestyles and high and low burden of atopic diseases, respectively. Atopy was defined as one or more positive ($\geqslant$0.35 kU·L^{-1}) immunoglobulin (Ig)E results to any of the 12 common inhalant and food allergens tested [2]. Specific IgG antibodies to the four pathogens were assessed using standard methods and cut-off points.

Overall, 49% of children in Finland were atopic, compared with 20% in Russia ($p<0.001$). Approximately 26% of the children in Russia showed antibodies to *T. gondii*, 76% to HSV, 66% to *H. pylori* and 12% to HAV. In Finland, seropositivity rates were considerably lower and ranged from 3% (*T. gondii)* and 4% (HAV) to 7% *(H. pylori*), with the exception of HSV, which showed a seropositivity rate of 15%. When seropositivities were stratified according to the atopy status of the children, a significantly higher rate of seropositivity to HSV was found among nonatopics in Finland but not in Russia. No other differences between atopics and nonatopics in either country were found (table 1). Multivariate regression analysis revealed that seropositivity to HSV was inversely and independently associated with atopy in Finland (odds ratio (95% confidence interval) 0.29 (0.15–0.59)) but not in Russia (0.86 (0.50–1.48)). Neither age nor other seropositivities among children in Finland or Russia appeared to be associated with atopy (table 1).

HSV is interesting from the perspective of tolerance and allergy. HSV infection leads to lifelong viral latency with the potential for subsequent reactivations. T-reg cells that produce IL-10 and suppress the function of CD4+ and CD8+ effector T-cells have been shown to be generated in HSV infection *in vivo* [3]. HSV has a glycoprotein-rich envelope that interacts with Toll-like receptor (TLR)2, and a double-stranded DNA genome rich in guanine and cytosine motifs interacting with TLR9 [4].

TABLE 1 Immunoglobulin G seropositivity to *Toxoplasma gondii*, herpes simplex virus (HSV), hepatitis A virus (HAV) and *Helicobacter pylori* among schoolchildren in Finland and Russia

	Atopic	Nonatopic	p-value#	OR	95% CI
Finland					
Subjects n	168	176			
T. gondii	2.4	4.0	0.411	0.77	0.21–2.82
HSV	7.5	21.5	<0.001	0.29	0.15–0.59
HAV	3.1	4.1	0.65	0.75	0.22–2.49
H. pylori	6.6	6.8	0.94	0.83	0.34–2.00
Age				1.01	0.93–1.11
Russia					
Subjects n	84	341			
T. gondii	30.9	25.0	0.244	1.58	0.93–2.67
HSV	71.4	76.5	0.327	0.86	0.50–1.48
HAV	13.2	12.1	0.780	1.22	0.59–2.50
H. pylori	57.7	67.7	0.070	0.66	0.40–1.08
Age				0.93	0.85–1.02

Data are presented as %, unless otherwise stated. Data are stratified according to atopy status and associations between seropositivity and atopy derived from multiple logistic regression analysis. OR: odds ratio; CI: confidence interval. #: calculated using Chi-squared tests.

Ligation of both TLR2 and 9 on human cells has been shown to be associated with the development of T-reg cells and/or tolerance [5, 6]. We found that HSV infection conferred protection against atopy among Finnish children only. Besides the fact that atopy is infrequent in Russian Karelia, the overall exposure to microorganisms is overwhelming and the impact of saprophytes and other pathogens may well override the possible effects of HSV on the Russian side.

In summary, in an area with a relatively low microbial burden such as Finnish Karelia, herpes simplex virus appears to be able to exert immunomodulatory potential, which may have implications for the occurrence of atopy. This finding confirms the result shown previously in two other Western populations [7, 8].

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SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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Variation in the tumour necrosis factor gene is not associated with susceptibility to COPD

To the Editors:

In a recent issue of the *European Respiratory Journal*, TANAKA *et al.* [1] studied polymorphisms in the tumour necrosis factor (TNF) and lymphotoxin A genes with respect to their effect on lung function of smokers, and failed to find any association with chronic obstructive pulmonary disease (COPD) phenotypes. TANAKA *et al.* [1] acknowledge that their work is not a true case–control study, but that it would be better described as an investigation of genetic contribution to disease severity. There have been several studies of variation in TNF with respect to susceptibility to COPD, although many of these have used relatively small sample sizes and are therefore underpowered, and so are likely to lead to results that cannot be replicated.

As part of a European Union collaborative project, we have studied polymorphisms within the TNF gene in a large collection of well-characterised Caucasian COPD patients (n=1,018) and control subjects (n=911). COPD cases and

TABLE 1 Frequency of single nucleotide polymorphisms (SNPs) genotyped in the tumour necrosis factor gene#

	COPD patients	Controls
rs1799964¶ (T-1031C)	0.207	0.193
rs1800629¶ (G-308A)	0.179	0.178
rs361525¶ (G-238A)	0.055	0.049
rs1800610 (G489A)	0.096	0.096
rs3093662 (A851G)	0.084	0.077
rs1800628 (G3512A)	0.127	0.119

COPD: chronic obstructive pulmonary disease. #: numbering with respect to the transcription start site is shown in parentheses; ¶: SNPs studied by TANAKA *et al.* [1].