HLA antigens and cervical carcinoma

SIR — Wank and Thomssen[1] claimed the association of HLA-DQw3 and HLA-DR5, the latter possibly as a result of linkage disequilibrium, with increased risk of squamous carcinoma of the cervix. They also noted a significant decrease in the frequency of HLA-DRw6. We have tissue-typed 65 patients (mean age 52.7 years, range 23–87) with histologically proven squamous cell carcinoma of the cervix (21, 27, 15 and 2 patients presenting with stage I, II, III and IV disease, respectively) and compared the HLA antigen frequencies with a local control group comprising 857 organ donors from the northwest of England; 347 females and 510 males with similar HLA antigen frequencies when divided by sex. The cervical cancer patients were referred for radiotherapy at the Christie Hospital from the same geographical area as the control group.

Our data, tabulated for HLA-DR and HLA-DQ, show no statistically significant associations of any HLA-A, -B, -Cw, DR or -DQw serologically defined antigen with the disease. In particular there is no increased frequency of HLA-DQw3 or decreased frequency of HLA-DRw6 in our patients, although the frequency of these antigens in control populations in both studies was similar. The frequency of DR5 in the United Kingdom population is about half that found in Germany but again there is no difference between the incidence of this antigen in our patient and control groups. Furthermore, neither DR4 nor DR5, both of which are established to be in close linkage with DQw3, are increased in frequency in our patients. Comparisons for DR and DQ of probable homozygotes also show no difference in patient and control groups.

On the basis of our results, it may be premature to conclude that certain HLA haplotypes carry increased risk for development of squamous carcinoma of the cervix. Possible explanations of the differences between these similar sized studies may lie in an unintentional selection of either the patient or the control groups. Alternatively, different viral factors may be involved in the development of cervical cancers in the United Kingdom compared to southern Germany. It is also possible that there is microheterogeneity of DQ molecules in the two populations which might influence susceptibility. Molecular typing rather than serology may ultimately resolve whether DQw3 is truly a susceptibility gene for cervical cancer.

It remains a possibility that certain HLA antigens influence the development of squamous cell carcinoma of the cervix. Many immune responses are controlled by the genes of the major histocompatibility complex (MHC) and loss of MHC class I expression has been demonstrated in a significant proportion of cervical squamous carcinomas[2]. Further, our recent studies (S.S.G. *et al.*, manuscript submitted) demonstrate that most of these tumours, in contrast to normal cervical squamous epithelium, express HLA class II antigens. There may thus be several MHC factors contributing to the overall immune response to these tumours and to the viral agents that have been implicated in their aetiology.

HLA CLASS II PHENOTYPE FREQUENCIES

HLA-	IWC[4] (UK)	LC	Patients	χ^2	Significance
DR	*N* = 166	*N* = 857	*N* = 64		
DR1	26.9	19.3	15.6	0.85	NS
DR2	31.6	28.4	35.9		
DR3	24.8	28.8	23.4		
DR4	35.8	35.2	40.6		
DR5	10.5	12.7	12.5	0.021	NS
DRw6	14.9	23.6	15.6	1.69	NS
DR7	24.8	26.3	31.3		
DRw8	7.0	3.5	0		
DR9	1.2	1.9	1.6		
DRw10	0	1.4	1.6		
Single antigen	8.4	18.9	21.9		
DQ	*N* = 174	*N* = 65	*N* = 65		
DQw1	56.4	69.2	59.4		
DQw2	41.0	32.3	42.2		
DQw3	43.1	66.2	53.1	1.57	NS
Single antigen	33.1	32.3	45.3	3.36	NS

IWC(UK), International Workshop caucasian UK controls; LC, local caucasian controls; patients, people with squamous cell carcinoma of the cervix. Serological typing for 15 HLA-A, 22 HLA-B, 7 HLA-Cw, 11 HLA-DR and 4 HLA-DDQ antigens was performed by routine methods[3] using a local panel of typing antisera obtained from our own screening programme, supplemented by sera obtained by mutual exchange with UK and international laboratories. All sera were thoroughly characterized by their reactions with local cell panels which had been typed using IHW antisera. Statistical analysis was by Fischer's exact test. No significant difference was found between patients and control groups. χ^2 values are given only for those HLA antigens that have previously been reported[1] as significantly altered in the patient group, or those which we found to have differences. The frequencies of DR antigens for the 65 DQ-typed local controls showed no significant differences from those of the patient group.

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SIR — Our recent report[1] of a significant association between squamous cell carcinoma of the cervix and the HLA antigen DQw3, as defined serologically, suggests that genes of the MHC may influence the effectiveness of an immune response against this tumour, which is thought to be virally induced[2,3]. Now, using sequence-specific oligonucleotides to define the specific DQ alleles[4] associated with this susceptibility, we not only confirm our previous study but also find a preferential increase in the frequencies of the DQB1*0301 (40 of 50 patients) and *0303 alleles (9 of 50) in 50 DQw3-positive patients. Furthermore, in seven patients lacking a DQ3-related allele, five share a DQB1*0602 allele. Even more striking is the virtual absence of the DQB1*0302 allele in the DQw3-positive patient group (1 of 50) although it accounted for 36% of the DQw3 alleles in controls ($P < 0.0002$) (manuscript in preparation).

In the absence of monoclonal antibodies and alloantisera specific for HLA-DQw8 or HLA-DQw9, the serological distinction of these antigens is based on a series of reactions whose interpretation is often supported by information on the DR specificities, owing to the strong linkage disequilibrium of the genes encoding DR and DQ (ref. 5).

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