Letters to the Editor

Major histocompatibility genes and Type 1 (insulin-dependent) diabetes mellitus

Dear Sir,

By sequencing genes encoding the HLA-DQ alleles of persons with Type 1 (insulin-dependent) diabetes mellitus Todd et al. [1] and Horn et al. [2] have demonstrated that amino acid position 57 in the DQ beta chain has a critical role in susceptibility to Type 1 diabetes. Aspartate (Asp) at position 57 is protective, whereas substitution of Asp by alanine (Ala), valine (Val) or serine (Ser) is permissive.

The serologically- and RFLP-defined alleles which show association with Type 1 diabetes are consistent with this finding. For example, the DQw3.2 (DQw8) molecule contains Ser at position 57 while DQw3.1 (DQw7) which occurs infrequently in Type 1 diabetes contains Asp at this position. The DQw2 allele on the DR3 haplotype and the DQw1 allele on the DR1 haplotype are also Asp negative. Todd et al. [1] find that 90% of Caucasians with Type 1 diabetes are Asp negative at position 57 on both DQ haplotypes, while 10% are Asp heterozygotes. Hence, they conclude that Asp homozygosity at position 57 confers almost complete resistance to the development of Type 1 diabetes. This interpretation implies that the structure of the DQ molecule determined by the residue at position 57 in the beta chain specifies the response (? autoimmune) that leads to B-cell destruction. These findings, while focussing attention on the importance of single residue changes do not, however, fully explain the effect of HLA molecules in conferring susceptibility to Type 1 diabetes. We have shown [3] that there is an interactive effect of DR1 and DR4 in Type 1 diabetes which is qualitatively different from the well-known DR3/DR4 interaction. Some 35% of DR4 haplotypes which occur with DR1 contain DQw3.1 (DQw7) whereas 95% of DR4 haplotypes which occur with DR3 are DQw3.2 (DQw8). Sequencing data demonstrate that many of the DR4 haplotypes occurring in association with DR1 have Asp at position 57 on the DQ molecule (H. Erlich, personal communication). The finding of Nepom et al. [4], of hybrid molecules consisting of the DQw2 alpha chain and the DQw3 beta chain in DR3, DQw2/DR4, DQw3 individuals, provides a possible molecular explanation for the observed interactive effect in DR3/4 individuals. Both serological and sequencing data indicate that the molecular basis of the DR1/4 interactive effect is different from that in DR3/4 patients. Indeed, there is no evidence to date that the DQ locus on the DR4 haplotype in the DR1/4 patients plays any role in conferring disease susceptibility. This interpretation does not of course exclude the possibility that the Asp negative status at position 57 of the DQw1 molecule on the DR1 haplotype has a role in whatever interactive events are taking place in this sub-group of patients.

We have also shown [3] that the B44-DR4-DQw8 haplotype is decreased in DR3/4 patients but not DR1/4 patients, which indicates

that this haplotype is not a risk factor when DR3 is on the homologous chromosome regardless of the presence of DQw8. Thus, a single residue change at position 57 in DQ β does not account for susceptibility in all Type 1 diabetic patients. Attention should also be directed to the HLA alleles on the homologous chromosome and their interactive roles.

The evidence is that there are HLA subgroups whose susceptibilities to Type 1 diabetes have different molecular bases. When other genetic loci such as Gm are considered further sub-grouping occurs [5]. This genetic heterogeneity in Type 1 diabetes probably denotes a range of environmentally-induced mechanisms leading to B-cell destruction.

Your sincerely, B.D. Tait and L.C. Harrison

References

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