EDITORIALS

MHC-ENCODED TAP GENES IN RHEUMATIC DISEASES

It is now 6 yr since it was recognized that cell lines depleted of genes in the MHC class II region that mapped between the HLA DQB2 and HLA DPA1 genes failed in HLA class I antigen presentation to cytotoxic T cells [1, 2]. Subsequent studies identified genes coding for the transporters associated with antigen presentation (TAP1 and 2). They belong to the family of ATP-binding membrane transporters and associate together to form heterodimers that load peptides into HLA class I molecules [3]. Initially found in rodents, their equivalents were soon identified in humans [4]. We now have a clearer idea of their precise biological function. Self or foreign proteins are degraded in the cytoplasm into peptides, then transported by TAP molecules into the endoplasmic reticulum in an ATP-dependent process [5], where they encounter class I molecules. Once loaded with peptide, the HLA class I molecules move through the Golgi apparatus to the cell membrane, where they can present the peptide to class I restricted CD8 (cytotoxic) T cells. Thus, the cytotoxic arm of the immune system is able to identify and destroy cells which are synthesizing viral or tumour-associated proteins to which the individual T cells are not tolerant.

TAP proteins are characterized by a conserved hydrophilic cytoplasmic ATP-binding domain, which is thought to couple energy to the hydrophobic domain within the membrane, forming part of a transport channel. There are four TAP1 alleles arising from two single amino acid substitutions: one within the membrane-spanning segment and one in the cytoplasmic tail. For TAP2, there are eight alleles arising from four single amino acid substitutions: one within the transmembrane segment and three in the cytoplasmic tail [6]. TAP genes are polymorphic in both rat and human, although the extent of amino acid substitution is much greater in the former [7]. Great excitement was generated when it was realized that TAP polymorphisms in the rat gave rise to an altered spectrum of peptides bound to class I molecules [8]. This finding raised the possibility that polymorphic variants of TAP might be involved in generating variability of cytotoxic or regulatory immune responses relevant to the development of autoimmune disease.

Within a short period of time, many groups began to examine possible associations between human TAP alleles and autoimmune diseases. The rationale for studying class I-associated diseases, such as ankylosing spondylitis and Reiter's syndrome (RS), was the obvious possibility that certain TAP variants might be more efficient in presenting antigens to cytotoxic T cells, with clinical disease resulting from cross-reactivity with self-antigens or bystander damage. Alternatively, some TAP variants might be less efficient, with immune-mediated injury occurring as a result of failure of elimination of a pathogen.

HLA class II-associated diseases, such as insulin-dependent diabetes (IDDM), coeliac disease and rheumatoid arthritis (RA), were also studied, because the location of the TAP genes within the HLA class II region offered an opportunity to examine the physical limits of the associations of these diseases with DQB1, DQA1/DQB1 and DRB1, respectively. In addition, it was possible that the expression of these class II-associated diseases might be altered by the effects of 'immunoregulatory' class I restricted T cells.

The first studies of TAP in RA were reported from our own group and that of Wordsworth (see Table I) [9, 10]. Both showed a significant excess of TAP2D in RA patients, but this was no longer seen once comparison with HLA DR4-matched controls had taken place. Hence, the apparent association was

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of patients</th>
<th>TAP allele association</th>
<th>Association independent of HLA type?</th>
<th>Method</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>60</td>
<td>2B reduced, 2D raised</td>
<td>No</td>
<td>ARMS-PCS</td>
<td>[10]</td>
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<tr>
<td>RA</td>
<td>185</td>
<td>2D raised</td>
<td>No</td>
<td>ARMS-PCR</td>
<td>[9]</td>
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<td>68</td>
<td>2C/D raised</td>
<td>Yes</td>
<td>PCR-SSO</td>
<td>[11]</td>
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<tr>
<td>RA</td>
<td>82</td>
<td>1D reduced, 2C/D raised</td>
<td>No</td>
<td>PCR-ASO</td>
<td>[6]</td>
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<tr>
<td>AS</td>
<td>285</td>
<td>1B and 2C/D raised</td>
<td>Yes, for 1B</td>
<td>PCR-RFLP</td>
<td>[13]</td>
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<tr>
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<td>115</td>
<td>None</td>
<td>Not applicable</td>
<td>SSCP</td>
<td>[12]</td>
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<td>Reiter's</td>
<td>34</td>
<td>1C and 2A</td>
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<td>PCR-RFLP</td>
<td>[13]</td>
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<td>JCA</td>
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<td>Yes</td>
<td>PCR-RFLP</td>
<td>[13]</td>
</tr>
<tr>
<td>JCA</td>
<td>58</td>
<td>1C absent, 2B raised</td>
<td>Weakly, for EOPA only</td>
<td>PCR-SSO</td>
<td>[14]</td>
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<tr>
<td>Behget's</td>
<td>1C only</td>
<td>Yes</td>
<td>ARMS-PCS</td>
<td>[15]</td>
<td></td>
</tr>
</tbody>
</table>

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RA = rheumatoid arthritis; AS = ankylosing spondylitis; JCA = juvenile chronic arthritis; PCR = polymerase chain reaction; ASO = allele-specific oligonucleotide; ARMS = amplification refractory mutation system; SSO = sequence-specific oligonucleotide; RFLP = restriction fragment length polymorphism; SSCP = sequence-specific conformational polymorphism; EOPA = early-onset pauci-articular juvenile arthritis.
due to linkage disequilibrium with DR4. In a paper published recently in this journal, Vandevyver and colleagues examined TAP polymorphisms in Belgian RA patients [6]. They compared RA patients stratified according to disease severity with random and HLA DR-matched normal controls. The paper corroborated the earlier studies showing the same excess in TAP2D frequency, which did not survive comparison with DR4-matched controls. There was also a significant decrease in the TAP1D allele frequency in patients.

Of all the groups who have examined TAP in RA, only Singal et al. [11] found a small but statistically significant rise in TAP2C/D frequency between Canadian control (11.4%) and RA (35.5%) patients that withstood comparison with DR-matched controls. However, the number of DR-matched controls was small and these findings buck the trend. Hence, it now appears to be well established that TAP alleles have no major independent role in predisposition to RA.

What of other inflammatory rheumatic diseases? Ankylosing spondylitis (AS) has a well-established association with the class I molecule HLA B27, but the fact that only a minority of subjects possessing this molecule develop the disease indicates a role for other genetic and/or environmental factors. To date, two groups have examined TAP in AS, as shown in Table I. There was no association between any TAP allele and AS independent of HLA B27 status in either study, although the more recent one found a significant association between TAP1B and extra-sacral disease. The latter was defined as peripheral joint arthritis or uveitis. These studies suggest that TAP alleles are not important in AS susceptibility, but that they may have a minor effect on disease phenotype. However, as with all genetic association studies, this latter report is subject to confirmation.

In the related condition of RS, one recent study of a rather small number of patients found minor increases in TAP1C and 2A frequencies independent of B27 [12]. The authors suggested a role for TAP genes in RS susceptibility, but this awaits confirmation in larger studies.

Two groups have examined TAP in juvenile chronic arthritis (JCA). Ploski et al. [13] found an association between JCA as a whole and TAP1B which was much weaker than the known DR8 association. Donn et al. [14] found a different (TAP2B), but equally weak association with a disease subtype, early-onset pauci-articular JCA. These studies suggest little independent role for TAP alleles in JCA susceptibility, but underline the heterogeneity of the disease.

Lastly, there has been one study relating to Behçet’s disease [15]. Although this did show an absence of the TAP1C allele in patients, the fact that this allele is rare in normal Caucasoids (1–10%) makes interpretation difficult given the small number of patients studied. The association with TAP2B, shown in Table I, was secondary to linkage disequilibrium with HLA-DQB1*0501.

Taken together, these studies show clearly that TAP variants are probably of no relevance to rheumatic diseases, whether they be class I or class II associated. Similarly disappointing results have been found in IDDM [16], coeliac disease [17] and several other immune-mediated diseases. One explanation for these findings has come from the same kind of basic science that encouraged clinicians to examine TAP in human diseases in the first place. Obst et al. [18] recently showed that in the human, unlike the rat, TAP polymorphisms have no effect on peptide selection.

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REFERENCES


12. Barron KS, Reveille JD, Carrington M, Mann DL, Robinson MA. Susceptibility to Reiter’s syndrome is
THE PROVISION OF RHEUMATOLOGICAL INFORMATION

It is now accepted that patient education is an important part of the management of patients with chronic rheumatic diseases [1]. This task would be relatively simple if the scientific and therapeutic issues likely to be discussed by patients and their doctors were fully elucidated. Unfortunately, this is rarely the case in rheumatology and it is easy for patients to mistake dogmatism for wisdom. This leaves the intellectually scrupulous rheumatologist in an invidious position; any expression of doubt or uncertainty may lead the patient to seek advice from another doctor or unorthodox practitioner whose opinion may prove more forthright, but also more harmful. The current debate on the treatment of early rheumatoid arthritis with corticosteroids illustrates the dilemma and serves as a good model for the more general issues at stake. If rheumatologists are so divided on this issue, what are our patients to conclude? The attitude of patients and doctors to corticosteroids is understandably ambivalent. The anti-inflammatory power of these agents is so dramatic that the term 'steroid sparing agent' has given them a gold standard status in the rheumatological lingua franca. In contrast, their dose-related adverse effects are universally feared. Nevertheless, most doctors have learned to balance the pros and cons of steroid therapy in the long-term management of serious diseases such as polymyalgia rheumatica and systemic lupus erythematosus, and in the short-term care of allergic disorders. It would be surprising, therefore, and even a little remiss of the rheumatological community if the place of steroid treatment in the management of rheumatoid arthritis were not properly re-evaluated. This need is strengthened by the change in attitude to the treatment of rheumatoid arthritis whereby potent anti-rheumatic drugs are used early in its treatment and the term 'second line drug' has become virtually anachronistic in the minds of many influential rheumatologists [2].

The recently published study by Kirwan and his colleagues [3], and its reception, well illustrate the issues involved in properly informing patients. The authors report a trial of prednisolone in early rheumatoid arthritis which follows accepted precepts for trials of this kind. The study was randomized, double-blind, placebo controlled and of reasonable duration for clinical evaluation. Predictably, prednisolone was more clinically effective than placebo at some time points in the study. Less predictably, the acute-phase response was not significantly affected. However, the main purpose of the trial was to evaluate the influence of steroid treatment on joint erosion judged by standard radiological techniques. The authors claimed that steroids conferred a significant protective advantage on the treated group. The Larsen score increased by a mean of only 0.72 units in the placebo-treated group was taken as evidence of more severe joint damage.

Since the paper addresses many unresolved and important issues, it is not surprising that it has proved controversial in informal seminars and editorials alike [4]. One issue is the relative merits of alternative anti-rheumatic agents, given either alone or in combination in the early stage of the disease. Furthermore, the introduction of more selective forms of immunological manipulation has increased the therapeutic options. The factors determining this decision are well known, namely proven efficacy, clinically relevant benefit, tolerance, compliance, convenience of administration and monitoring, and costs [5, 6]. More imponderably, the characteristics of...