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Role of Genetic Factors in Drug-Related Autoimmunity

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Although there is evidence to suggest that genetic factors play a major role in the pathogenesis of many of the rheumatic diseases, far less is known of their role in the induction and expression of human autoimmunity resulting from long-term exposure to drugs, chemicals and environmental agents.

Pharmacogenetic factors represent an important source of interindividual variation in response to drugs; most research to date has focused on genetic polymorphism of drug metabolism via N-acetylation, S-methylation or cytochrome P-450-catalyzed oxidation.

In drug-related autoimmunity, there is limited evidence that the host's genetic background plays a major role beyond the expression of autoantibodies.

More recent prospective studies have concentrated on the association of MHC-genes in the expression of autoimmunity and the susceptibility of patients to develop drug-related clinical syndromes.

Key Words: Genetic factors Drugs Autoimmunity

Introduction

The roles of environmental factors and genetics on the induction and expression of autoimmunity is of great clinical interest. Establishment of an unequivocal genetic basis would allow identification of persons at risk for developing autoimmunity and lead to innovative therapeutic strategies. However, the clinical utility of genetic markers may be limited by the relative requirement of environmental factors for the induction of disease.

It is well accepted that the susceptibility to many autoimmune diseases is influenced by the MHC genes[1–3]. Support for this hypothesis includes: (1) the cosegregation of HLA alleles and disease within families, (2) the increased frequency of certain HLA alleles/haplotypes in groups of unrelated patients, and (3) inbred animal models of autoimmunity. Conversely, family and twin studies of patients with SLE and other autoimmune diseases have suggested that environmental factors may be responsible for disease expression[2–3].

Cytokine gene polymorphisms have recently attracted considerable attention as possible candidate genes for many polygenetic conditions such as chronic inflammatory autoimmune diseases[4–6]. An allelic polymorphism within the TNF-α promoter region has been associated with HLA-A1, B8 and DR3 haplotypes[4]; other studies reported that an HLA class II molecule controls a signal transduction mechanism that is responsible for expression of interleukin-1β and TNF-α[5,6].

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Worldwide studies of rheumatoid arthritis (RA) have reported that the strongest associations are at the DRβ1 loci; however, none of these associations has been absolute and recent data suggest that other factors such as the transporter-associated peptide (TAP1 and TAP2) genes may be equally important in the expression of RA[7]. Class II promoter elements, including trans-acting factors may also be important in the regulation of expression in autoimmune diseases[8–10].

A plethora of drugs, environmental and biologic agents have been implicated in the pathogenesis of autoimmunity and lupus-like syndromes[11–15]. For some of these the evidence has been based solely on case reports of serologic changes following brief exposure. Since similar serological and clinical findings occur in the rheumatic diseases, it may be difficult to definitely attribute these to drug-related lupus (DRL)[11,12].

The major drugs that elicit autoantibodies are procainamide (PA), hydralazine, isoniazid, methyldopa and chlorpromazine[11,12]. PA, an antiarrhythmic agent, is the drug most commonly associated with DRL, with lupus-like clinical features occurring in up to 30% of autoantibody-positive patients[11,12,16,17]. However, a direct role of MHC genes in the induction and/or expression of DRL has not been well defined[11,17].

Pharmacogenetic parameters have also been associated with the development of toxicity and autoimmunity in patients receiving long-term drug therapy, some of which are genetically controlled: these include polymorphisms of N-acetylation, S-methylation, cytochrome P-450 and the N-oxidative pathways of metabolism. Other less well delineated reactions are often called idiosyncratic: these

include selective *in vivo* biotransformation and conformational changes in nucleoprotein, apoptosis and direct cytotoxicity by reactive metabolites of drugs[11,17,18].

HLA associations

Most of the MHC associations with SLE have included the class II DRβ1 alleles[2,3,19] and the class III C4A and C4B null alleles of complement[20,21]. Studies have reported that extended haplotypes including the DR2 and DR3 alleles are associated with an increased frequency in SLE in the Caucasian population of Western Europe, while DR2 is significantly increased in Orientals and DR3 in black Americans[20,22]. However, the degree of association varies considerably from one ethnic group to another[3,20,22,23]. Some class II alleles may be in linkage disequilibrium with other alleles making it difficult to determine if it is the 'reported' gene itself or some other linked gene that is responsible for the disease association[19].

Data reported by Stephens *et al.*[24] led them to suggest that the DR4 and DQw7 haplotype may represent a disease severity marker for RA. Other evidence suggests that the DQ gene products may influence autoantibody expression; for example, the DQw2 allele has been associated with anti-Ro and La antibodies[25]. Increased frequencies of C4A and C4B allotypes and null alleles have been reported in drug-related autoimmunity[17,26], but they are not a prerequisite for the development of autoimmunity[17].

Although the inciting agent is known in drug-related autoimmunity, there is considerably less evidence that host genetic factors play a major role in determining susceptibility and expression of clinical features. There have been limited studies of HLA associations with drug-related autoimmunity. Early work by Batchelor *et al.*[27] in 1980, revealed the frequency of DR4 in patients who developed hydralazine-related lupus to be 79% compared with 25% in the asymptomatic hydralazine-treated controls. In the patient population that developed clinical symptoms, 25 of 26 were slow acetylators. There was no significant difference in the frequency of DR4 between the asymptomatic slow-acetylator patients and the control subjects suggesting a lack of association between acetylator phenotype and the DR4 antigen. In contrast, 4 years later Brand and coworkers[28], in a study of 18 Australian patients with hydralazine-related lupus, failed to show any increased frequency of HLA-DR4 in their patient population compared with a normal Melbourne population. In 1987, Russell *et al.*[29] reported a frequency of HLA-DR4 of 70% in their group of 20 patients with hydralazine-related lupus compared with a frequency of 33% for the general population. Of these patients, six had been included in the study reported by Batchelor[27] in 1980.

A further study by Batchelor's group[30] examined the possible role of polymorphisms of the HLA class III gene in 21 patients with hydralazine-related lupus. The genes which code for C2, C4A and C4B are located on chromosome 6 between HLA-B and HLA DR regions and their alleles exhibit linkage disequilibrium with both the HLA-B and DR alleles. Sixteen of the 21 cases (76%) were found to have one or more null alleles compared with 35 (43%) of 82 normal controls: this difference was significant. Fourteen (67%) of the patients had the HLA-DR4 antigen which was significantly higher than that of the controls. The HLA-DR4 antigen is known to be in linkage disequilibrium with the C4B null allele which leads one to postulate that it may be the C4 null allele in linkage disequilibrium with the DR4 that is more important in determining susceptibility to the development of hydralazine-induced lupus than the HLA-DR4 antigen itself. If there were no linkage disequilibrium between HLA-DR4 and C4 null alleles among the Australian population, this may explain the apparent discrepancies between the results of the two studies.

Studies looking for an association between immunogenes and the development of other drug-related lupus-like syndromes has been very limited. Whiteside *et al.*[31] reported that the HLA-DR6Y antigen was present in 18 of their 34 (53%) PA-related lupus patients compared with 25% of patients with PA-related antinuclear antibodies and 17% of controls; this difference was significant. However, no significant increase in the frequency of either HLA-DR4 or DR3 antigens was found. Totoritis *et al.*[32] failed to identify a significantly increased incidence of HLA class II antigens in six of their patients with PA-related lupus. In 1982, Canoso *et al.*[33] reported an increased frequency of HLA-BW44 in those patients who developed autoimmunity while receiving chlorpromazine (46%) compared with 19% of the normal population.

Of interest are the reports of positive associations between HLA-DR3 antigen and the development of toxicity in rheumatoid arthritis patients receiving either gold[34] or D-penicillamine[35]. In a small study of six patients with rheumatoid arthritis who developed a lupus-like syndrome while receiving D-penicillamine, Chalmers *et al.*[36] reported an increased frequency of HLA-A11 (present in three of these patients) and HLA-B15 (present in five of these patients) compared with a control population of rheumatoid arthritis patients. D-penicillamine-related toxicity has been associated with the HLA-DR3 antigen[35]; HLA-DR3, DR5, B8 haplotypes have been reported to occur more frequently in patients developing features of scleroderma following exposure to vinyl chloride[37]. The frequencies of MHC class I, II and III antigens and immunoglobulin allotypes (Gm factors) were determined by Grosse-Wilde[38] in 56 patients who had developed a lupus-like syndrome following treatment with venocuran or venopyronun dragees. They reported an increased frequency of HLA-DR4 (51.1%), HLA-DRw53 (75%) and HLA-DQw3 (75%) in their pseudolupus patients compared with healthy controls who had a frequency of 27% for DR4, 50% for DRw53 and 51%

for DQw3 alleles. The recent observation of the association of HLA-DP.B1 glutamate in 32 of 33 beryllium-exposed workers provides a real stimulus to study various occupational associations[39].

Immunogenetic studies by Oursler *et al.*[40], of nine patients with eosinophilia-myalgia syndrome (EMS) revealed the presence of HLA-DR4 in four and HLA-DR3 in three patients. Kauffman *et al.*[41] reported that 55% of their patients with L-tryptophan EMS had HLA-DR4 allele expression compared with 37% of their controls; however, this difference was not significant. Varga *et al.*[42] noted an increase, which was not significant, in HLA-B7 phenotype in their patients with EMS (50%) compared with the controls (19%). Based on these data, it is likely that further studies including larger numbers of patients will be needed to establish the role that genetic factors play in determining susceptibility to EMS.

A positive association of DQβ1 DQw7 (split of DQw3) with autoantibodies to histone subfractions (H2A-H2B), Z-DNA and poly A has been reported in asymptomatic patients receiving PA[17]. Subsequent studies have shown that, although high titers of autoantibodies are produced in these patients on PA, no hapten-specific antibodies to PA or its metabolites were detected[43]. More recent studies of these patients have revealed that all those serologically typed as DQw7-positive were either DQβ1*0301/*0302. Only 26% had a positive haplotype association of DR4 with DQw7 and the incidence of DR4 was not significantly different from that of the normal Cincinnati population (L.E. Adams *et al.*, unpublished data).

Mean levels of IL-1α and TNFα produced by *in vitro* stimulated leukocytes from the patients on PA did not differ significantly from those levels produced by cells from the controls. However, there was a significant increase in the spontaneous synthesis of both cytokines by leukocytes from 83% of those patients who were positive for DQβ1*0301/*0302, suggesting an intrinsic upregulation of the macrophages in these patients. These unique findings support the speculation that variations within the TNF locus may be associated with MHC-related autoimmunity. A genetic polymorphism of the TNFα gene has been reported in SLE patients that is in linkage disequilibrium with HLA-DR2, DQw1 haplotypes, and increased levels of TNFα have been found in patients with diabetes, Graves's disease or celiac disease who have HLA-DR3 and DR4 haplotypes[4,44]. Given these findings it is interesting to speculate that TNF class III genetic polymorphisms may contribute to development of PA-related autoimmunity. The role of the increased spontaneous synthesis of IL-1 *in vitro* is unclear; however, it is well documented that IL-1 activates the cytokine network and has various effects on T and B cells[45], suggesting that it may act as an immunomodulator.

Although statistically significant HLA class II and III gene associations in patients expressing autoantibodies following exposure to certain drugs, chemicals and other environmental agents have been reported, no specific genetic determinant has yet been unequivocally shown to be the direct cause for the induction of clinical symptoms. However, it is likely that genetic factors contribute to the predisposition of an individual to develop autoimmunity upon exposure to a triggering agent(s).

Acetylation polymorphism

Acetylation is a major route of metabolism for most drugs and chemicals. Acetylation polymorphism in animals and in humans has been investigated[46–49]. Slow acetylators are homozygous recessive, while fast acetylators are either heterozygous or homozygous dominant[46]. Numerous reports have implicated slow acetylator phenotype as a determinant of susceptibility for drug-associated side-effects in humans. Drugs most frequently implicated include hydralazine[47–49], dapsone[50] and PA[46,48,49]. Studies suggest that the frequency of slow versus fast acetylator phenotype may vary due to ethnicity of the study population and the assay methods[51,52]. The N-acetyltransferase (NAT) studies suggest that the genotype, rather than simply the phenotype, may be important[53,54]. NAT isoforms can be phenotypically classified according to their substrate specificity[53,54]. The monomorphic (NAT-1) preferentially acetylates substrates such as p-aminobenzoic acid, whereas the polymorphic (NAT-2) acetylates substrates such as sulfamethazine[53]. NAT-1 is expressed in a variety of tissues, including leukocytes[55]. In contrast, NAT-2 is principally expressed in the liver. Grant *et al.* demonstrated that slow acetylation is associated with a decrease in the quantity of both NAT-1 and NAT-2 in the liver[53].

The clinical consequence of acetylator status is that slow acetylators usually develop drug-related autoimmunity at lower doses and earlier in the treatment regimen than rapid acetylators[46,47,56]. However, while acetylation of the hydrazine group is the predominant metabolic pathway for hydralazine and isoniazid[47,49], the oxidative pathway may also be important for PA[11,17,56–58].

Oxidation polymorphism

Oxidation by cytochrome P-450 isozymes is the most common pathway by which drugs are metabolized in the first pass through the liver. A multiplicity of P-450 isozymes with different substrate specificities and different physical, chemical and immunological properties have been identified[59–61]. Cytochrome P-450 represents >95% of the known enzymes that introduce a functional hydroxyl group and is important in the metabolism of a wide range of drugs and environmental agents such asβ-blockers, mephenytoin, diazepam and alcohol[53,60,61]. The P-450-mediated reactions often lead to the formation of metabolites, which may be

cytotoxic (e.g. PA-hydroxylamine; PAHA)[56,57,62,63]. Although PAHA has not been identified in the circulation of humans or animals, nitroprocainamide (NPA), an end product of oxidative metabolism, has been isolated in the urine of humans and laboratory animals dosed with PA[17,62,63], suggesting that this pathway is important in the metabolism of PA. Preliminary studies with PAHA suggest it may induce a conformational change in DNA following *in vitro* exposure (L.E. Adams *et al.*, unpublished data). Recent data have also shown that hydralazine induces Z-DNA conformation in a polynucleotide and elicits anti-Z-DNA antibodies in patients following long-term therapy[64].

The debrisoquine polymorphism studies have shown that most Caucasian patients are 'extensive metabolizers'; up to 10% are homozygous for the autosomal recessive allele and these patients exhibit debrisoquine toxicity[32,61]. Baer *et al.*[65] reported a significant increase in the frequency of 'poor oxidative' metabolizers, determined by a single dose of debrisoquine, among their 42 patients with SLE (21%) compared with 8% in a group of healthy volunteers. However, Seideman[66] failed to detect any difference in the frequency of 'poor hydroxylators', also using debrisoquine, in their group of 27 SLE patients. The possible role of debrisoquine oxidation polymorphisms in the development of environmentally or drug-related lupus symptoms has yet to be determined. Oxidation metabolism of many of the β-blockers and some of the antiarrhythmic drugs exhibit a genetic polymorphism which is similar to debrisoquine[52]. Some of the β-blockers have been implicated in the development of lupus-like symptoms and autoantibody production[23] and one can therefore speculate that this genetically determined metabolic pathway is important in the development of autoimmunity.

It is premature to suggest that polymorphisms within these enzyme systems play an unequivocal role in determining susceptibility of individuals to developing toxic reactions and/or autoimmunity in response drugs and other environmental agents. However, such associations may help explain the interindividual differences in response to these agents, and future studies may add support to the importance of genetic factors in the induction and expression of autoimmunity.

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