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HUMAN MHC CLASS III AND IV GENES AND DISEASE ASSOCIATIONS

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1. ABSTRACT

The major histocompatibility complex (MHC) was initially defined as the genetic locus encoding the Class I and Class II highly polymorphic cell surface antigens that are now known to present antigen to matched sets of T cell receptors. Genes for several diverse complement components, specifically Bf, C2, and C4 were found between the Class I and II genes, in a region later dubbed Class III. More recently, several genes have been described that are encoded in the telomeric end of the Class III region and that appear to be involved in both global and specific inflammatory responses. Due to this commonality of function this gene-rich region was dubbed Class IV, and includes the TNF family, AIF1, and HSP70. The genes of the Class III and Class IV regions are sufficiently divergent in sequence and structure so that clustering is not explicable in terms of gene duplication or divergence. We present some of the newer pertinent information and puzzling features of the genes embraced in the Class IV region and discuss possible roles in specific autoimmune diseases linked to this region.

2. INTRODUCTION

The major histocompatibility complex (MHC)(1) was initially defined as the genetic locus encoding the Class I and Class II highly polymorphic cell surface antigens that are now known to present antigen to matched sets of T cell receptors. It soon became evident that genes for several complement components, specifically Bf, C2, and C4 were encoded in DNA located between the Class I and Class II region. This middle segment of DNA was therefore termed the Class III region. Subsequently several other classes of genes that are involved specifically in immune system functions have been found to reside in the MHC. At present these genes represent at least 10 groups(2) that are sufficiently divergent in sequence and structure so that clustering is not explicable in terms of gene duplication and divergence.

The clustering of immune system related genes seems beyond what would be expected by chance and no explanation for this clustering has emerged in terms of biochemistry or molecular biology. Instead it has been

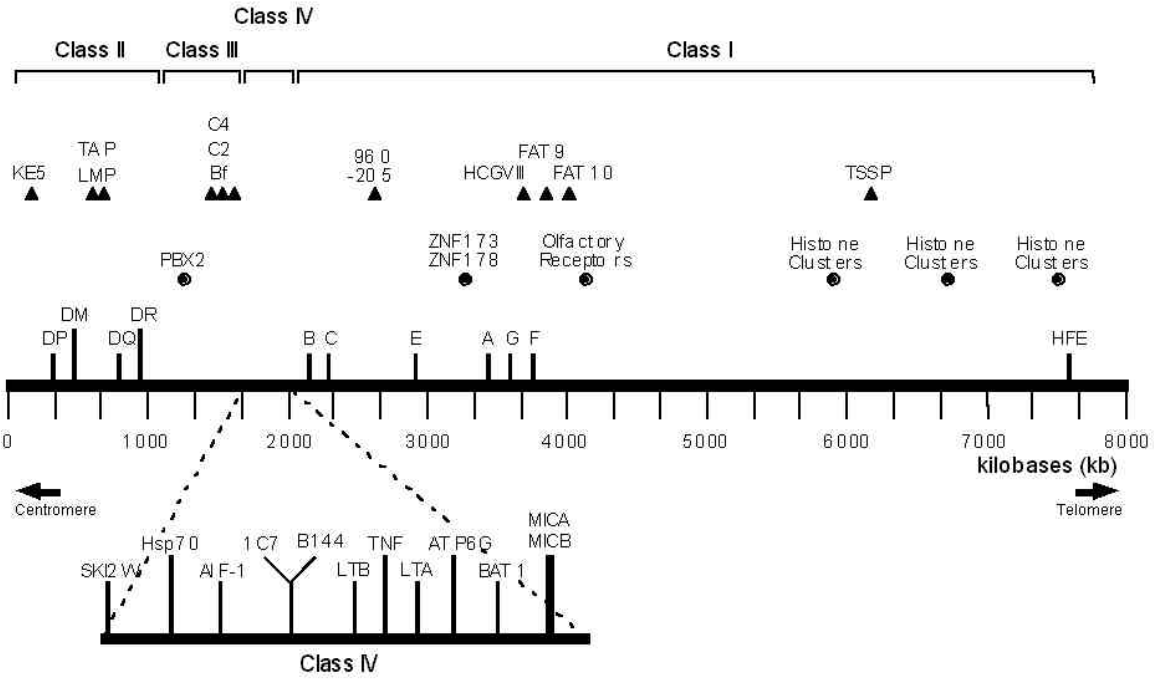

Figure 1. Map of the MHC showing the MHC Class I, II, III, and IV regions (modified from [3]). Physical map and organization of the human MHC and selected genes. Expressed HLA Class I and Class II genes (rectangles) are positioned on the horizontal median. Genes with putative immune function (triangles) and other genes (circles) are elevated above the horizontal median. An enlargement of the Class IV is shown beneath the median.

proposed that the clustering was favored during evolution as a result of coordinate selection for particular combinations of alleles, and that this selection would be stronger because of the rapid diversification of the Class I and Class II antigens themselves (See Table 1).(3)

There are also suggestions of clustering of groups of functionally related but structurally diverse genes within particular portions of the MHC. In particular, tapesin (TAP(4)), gamma interferon inducible subunits of the proteasome, and peptide transporter (LMP) are all located at the centromeric proximal portion of the MHC, and all function in preparing and loading peptides onto Class I MHC genes for antigen presentation (See Figure 1). Also in the portion of the MHC just proximal to the conventional Class I region there are at least six different types of genes that are implicated in various aspects of acute response to inflammatory stimuli. For this reason it has been suggested that these should be recognized as being distinct from the complement gene region, and referred to as the Class IV region of the MHC. In the present brief review, we present some of the newer pertinent information and puzzling features of the genes embraced in this Class IV region.(3)

3. TNF FAMILY CLUSTER

A cluster of genes for three related cytokines/cytokine receptors, tumor necrosis factor (TNF, formerly known as TNF-alpha or cachectin), lymphotoxin alpha (LTA), and lymphotoxin beta (LTB), lies in the Class IV region shortly before the most centromeric Class I related genes. TNF has been very extensively studied(5) and plays an important role in inflammation, bacterial(6) and viral infection,(7) tumor cachexia and the immune response. It is produced by a variety of cells including prominently monocytes, macrophages, and some T cell subsets.

LTA (also called TNF beta) has actions that are very similar to those of TNF on a cellular basis but its pattern of expression is considerably more limited. Remarkably, deletion of the LTA gene leads to a specific absence of lymph nodes, Peyer's patches, and splenic germinal centers in mice(8, 9) whereas mice lacking TNF develop lymph nodes and Peyer's patches but lack splenic primary B cell follicles.(10) Deletion of the p55 TNF receptor results in normal lymph node development and architecture, normal migration of lymphocytes into the lamina propria and epithelium of the small intestine, but no organized Peyer's patches and absence of germinal centers.(11) Based on these observations it is speculated that the effect of LTA on the development of lymphoid organs may be mediated by distinct receptors, some functioning in an organ specific context.

LTB (also called TNF C) is a membrane bound molecule that forms a heterotrimer with LTA.(12) This LTA-LTB complex can then induce activation of NF kappa B in certain cell lines by binding with the LTB receptor, a member of the TNF receptor family.(13) (14) NF kappa B is a pleiotropic transcription factor capable of activating the expression of a great variety of genes critical for the

Table 1. Genes of Class III and IV Regions and Putative Functions

TNF Family Cluster	
• TNF	Cytokine activity
• LTA	Cytokine activity
• LTB	Cytokine activity
B144/LST1	Morphogenesis of dendritic cells
1C7	NK cell activating antigen
G1/AIF1	Marker of inflammation
SKI2W	Confers resistance to killer toxin RNA viruses
BAT 1	Helicase motifs characteristic of RNA helicases
HSP70	Protection against excessive inflammation
MIC /PERB11	
• MIC-A	Activation of NK cells
• MIC-B	Activation of NK cells
ATP6G	May delay apoptosis in activated neutrophils

Immunoin flammatory response.(14) The LTA-LTB complex is also weakly cytotoxic to some tumor cells but does not appear to induce apoptosis.

4. B144/LST1

Twelve years ago Steinmetz, Olds and colleagues(15) reported the presence of a gene, B144, in the central region of the murine MHC that encoded a small transcript present in B cells and macrophages. In 1989 the human homologue of this gene was identified,(16) which was subsequently referred to as LST1.(17) An expressed sequence tag (EST) corresponding to the rat B144 gene has recently appeared in GenBank (Accession number AA894045).

Although the mRNA for human B144 is quite small and encodes less than 100 amino acids, the gene encodes nine non-overlapping exons. The splicing pattern of the mRNA is remarkably complex(3, 18) (Ragunathan, Reddy, Weissman unpublished results). There are five alternative first exons (exons 1-5) containing only 5' untranslated sequences. At least one composite first exon may be generated when exon 1 is spliced into exon 5. Cultured cell lines such as Jurkat or U937 may use all of these exons in alternative forms of the mRNA. mRNA species are formed that retain both, either, or neither of coding exons 7 and 8. In addition there are multiple alternative splice sites at one or another end of certain exons such as the occurrence of four alternative splice sites at the beginning of exon 9. One of the 5' splice sites used to remove intron five begins with the highly atypical dinucleotide GA. In all, there is a potential for almost 200 alternative splice forms of the mRNA and many of them may be found in the same cell type in culture. Although the splicing pattern of the mouse B144 gene is much less complex, there are at least three alternative splice forms and again one uses a very atypical splice site.

In spite of the complex pattern of mRNA splicing seen in B144 and the differences in position of alternative splice sites between man and mouse, the most abundant form of the murine mRNA encodes a peptide that is highly homologous to that encoded by a major human form. In both cases the encoded peptide has a very short amino terminal hydrophilic sequence followed by a hydrophobic presumptive transmembrane sequence that is very rich in leucines and glycines. Similar sequences in other proteins have been found to self-associate strongly and specifically. Downstream of this hydrophobic region are a pair of conserved cysteines and two highly conserved hydrophilic sequence stretches of unknown function.

There is very little published with regard to the specific function(s) of the B144/LST1 protein. B144 is expressed in T cell, monocytic, and macrophage cell lines, and is also substantially expressed in both murine and human dendritic cells in culture. In the cultured cells B144 levels rise as the cells mature. *In-vivo*, B144 protein has been examined by immunohistochemistry in spleen and thymus. It is prominent in scattered cells at the medullo-cortical junction and in the medulla of murine thymus. In human and murine spleen it is strongly visible in scattered cells at the edge of follicles in the white pulp, although a background of immunostaining is seen in a wider range of cells. The most darkly staining cells in tissues are at least consistent with dendritic cells.

B144 has a fairly dramatic effect on transiently transfected cells (Ragunathan and Weissman, unpublished). It causes a variety of cell types to form elongated filopodia and/or actin containing microspikes. These effects involve rearrangement of actin in the cell and are blocked by dominant negative forms of the ras-related protein CDC42. Although several other proteins such as syndecan2(19) can produce some of the same effects in transfected cells, the morphologic effects of B144 are particularly striking. Given this and its pattern of cellular expression it is plausible that this gene may be specifically involved, among other effects, in morphogenesis of dendritic cells. Dendritic cells are the professional antigen presenting cells of the body, and are one of the few cell types equipped to activate naïve T cells. *In-vivo*, they take up antigen from peripheral tissues and migrate to secondary lymphatic organs where they may stimulate antigen-specific T cells to respond. If this hypothesis is correct then control of dendritic cell morphogenesis represents yet another facet of antigen presentation affected by genes of the MHC.

5. 1C7

The 1C7 gene was originally detected as part of a cDNA selection experiment performed with a YAC covering a central part of the MHC.(20) The gene is located immediately adjacent to the B144 gene. RNA for B144 and 1C7 are transcribed in convergent directions such that there is a slight overlap between the 3' ends of the two mRNAs. Recently the murine and rat homologues of the 1C7 gene have been identified, and show substantial conservation of amino acid sequences as compared to the human gene. Partial sequences for the rat 1C7 transcripts are available in the public databases. However, the mouse gene sequence predicts a premature termination codon, suggesting that

murine 1C7 may not be functional. Curiously, human 1C7 also shows multiple splice forms with 9 forms of the human mRNA reported so far.(21) The major forms encode proteins containing a leader sequence, a probable trans-membrane segment, an external sequence including an immunoglobulin-like domain, and at least three alternative forms of the putative intracellular segment of the protein. One alternative splice modifies the structure of the immunoglobulin-like domain, changing it from a sequence more closely resembling those of the V regions of Ig molecules to one that is more similar to IgC2 regions. Of the three alternative putative intracellular domains, one encodes multiple proline repeats suggestive of SH3 binding domains.

The mRNA for 1C7 is found in Jurkat T cells and U937 monocytic cells. It is prominent in human (but not mouse) spleen, and strongly expressed in NK cells. In mouse, the mRNA is present in liver where it localizes to a subset of non-parenchymal cells by *in-situ* hybridization. The 1C7 protein is prominent in human liver extracts. Although nothing specific is published as to 1C7 function, it is listed in GenBank as an NK cell activating antigen (Accession number AJ223153).

6. G1/AIF1

AIF-1 (allograft inflammatory factor-1) is a Ca^{2+} binding protein predominantly expressed by activated monocytes, originally identified in rat cardiac allografts with chronic rejection.(22) The human cDNA homologue is 86% identical to the rat (90% identical to the amino acid sequence) and was identified by reverse transcriptase-PCR of endomyocardial biopsy specimens from human heart transplants and in macrophage cell lines.(23)

The specific role of AIF-1 in inflammation is less clear. In human heart allografts it is expressed by a subset of CD68+ macrophages in interstitial and perivascular spaces.(23) Analysis of isolated neutrophil and macrophage cell populations shows that expression is up-regulated by T cell-derived cytokine IFN-gamma, which can be blocked by a diet deficient in essential fatty acids or by administration of soluble CTLA-4 protein.(23) The latter works by blocking lymphocyte activation. AIF-1 is co-expressed in concert with a host of known inflammatory markers including LFA-1, IL-4, IFN-gamma, and iNOS in a heterotropic murine heart transplant model with vascular thickening induced by anti-CD4/CD8 therapy.

More recent immunocytochemistry experiments with monoclonal antibody against AIF-1 suggest an inflammatory role in the central nervous system in certain experimentally induced autoimmune models. In an experimental rat model of autoimmune encephalitis, neuritis, and uveitis, widespread activation of AIF-1-positive microglial cells is observed in the parenchyma, which is suppressible by dexamethasone.(24, 25) Microglial cells are strategically placed regulatory elements of CNS surveillance, implicating AIF-1 in the autoimmune process.

The existence of the G1 gene was initially noted as a part of a screen of MHC cosmids for embedded genes. The G1 and AIF1 transcripts appear to be derived by alternative splicing from partially overlapping genomic templates. A third human interferon gamma-responsive transcript, IRT-1, has been noted that shares some internal sequences with both G1 and AIF1, but on the basis of the predicted open reading frame it shares only limited amino acid sequences with G1. Yet another form of transcript templated in the genomic DNA containing G1/AIF1 may be present in the rat. A more complete description of these various splice forms of RNA is presented by Neville and Campbell.(26)

All three forms of human transcript share amino acid sequences homologous to the E/F hand calcium binding motif, although the IRT1 transcript has inserted amino acids in the center of this motif. Homologous rat transcripts are reported to have an amino terminal hydrophobic domain raising the possibility that it might represent a secreted protein. However the precise function of any of these transcripts remains to be determined.

7. SKI2W

In yeast cells, Ski2 (superkiller 2) protein confers resistance to killer toxin RNA viruses by blocking translocation of non-polyadenylated or non-capped viral mRNAs targeted for degradation.(27) The human homologue, SKI2W, shares the structural motifs of an RNA helicase, which accounts for its putative anti-viral activity. Genomic sequence shows it is encoded by 28 exons in the Class IV region.(28) It is widely expressed in multiple tissues. Immunocytochemistry and co-sedimentation experiments show that SKI2W localizes to nucleoli and the cytoplasm where it is closely associated with the 40s ribosomal subunit.(29)

8. BAT 1

BAT1 was originally identified as one of a series of anonymous cDNAs hybridizing to a cosmid containing DNA from the central MHC, near HLA-B(16) (hence B-Associated Transcript). The transcript is expressed widely and encodes a protein containing helicase motifs characteristic of RNA helicases.(30) There is no evidence that this transcript is differentially expressed during the inflammatory reaction, and it may well be a co-incidence that an RNA helicase of unknown function is encoded adjacent to a group of genes with such complex and unusual splicing patterns.

9. HSP70

Heat shock proteins (HSPs) are a family of molecular chaperones induced by environmental stresses such as oxidative injury, and contribute to protection from and adaptation to cellular stress.(31) The mechanisms by which such protection occurs include prevention of reactive oxygen species-induced DNA strand breaks and lipid peroxidation as well as protection from breeches of mitochondrial structure and function. HSP70 may also

exert protective effects in the immune system by contributing to the processing and presentation of bacterial and tumoral antigens.(32) Furthermore, HSP70 may regulate NFKB expression in response to heat shock. (33)

The putative role of HSPs in inflammation is even more intriguing. Following bacterial infection with Listeria monocytogenes, TGF-beta and IL-10 are produced by HSP70 reactive CD4+ T cells. In turn, TGF-beta and IL-10 regulate TH1-cell-mediated excessive inflammation after the battle against the bacteria has been won. Thus, HSPs play important roles in protecting against excessive inflammation not only via cytoprotection but also induction of immunoregulatory T cells.(34)

HSP70 expression is regulated along several pathways. Induction of HSP70 appears to be mediated, in part, by the prostaglandin pathway, with an inverse relationship between COX-2 expression and HSP70 expression.(35) In the presence of aspirin or another cyclo-oxygenase inhibitor, indomethacin, heat shock transcription factor is maintained in the activated DNA-binding state for a period twice as long as control, which results in enhanced and prolonged HSP70 mRNA transcription. The modulation of the heat shock response by aspirin and indomethacin is associated with the ability of these drugs to potentiate the effect of hyperthermia and prolong thermotolerance.(36) NO induces HSP70 expression as well. In a cultured rat hepatocyte model of liver injury and apoptosis induced by TNF-alpha, NO induces HSP70 expression and prevents apoptosis; an effect that can be blocked by HSP70 anti-serum.(37) In contrast, the pro-inflammatory cytokine, IL-1beta, depresses HSP70 expression in glomerular mesangial cells, and IL-1-pretreated cells are more susceptible to apoptotic death triggered by oxidative stress.(38)

HSP70 has a cytoprotective role in a variety of human diseases mediated by ischemia, inflammation, and infection.(39) HSP70 plays a role in liver(40-42)and renal(43) ischemia. It also plays a role in the inflammation of asthma,(44) rheumatoid pseudocysts,(45) atopic keratoconjunctivitis,(46) and experimental osteoarthritis.(47) Finally, HSP70 has a role in infections due to Shigella flexnari(48)and septic shock.(49, 50) The precise role in each of these clinical situations vary. In a study of bronchial lavage aspirates from asthmatics and normal controls, HSP70 and HLA-DR up-regulation was present in professional and non-professional antigen presenting cells (APCs). This implies a role for HSP70 in antigen processing and/or presentation with APC activation, which is essential for the initiation and modulation of the asthmatic immune response in chronic asthma. Inhaled steroids (fluticasone proprionate) down-regulated HSP70 expression in the aspirates.(44) In the setting of septic shock, endotoxin inhibits HSP70 expression in peripheral blood mononuclear cells, which may contribute to the cellular dysfunction of immunocompetent cells concerning antigen presentation, phagocytosis, and antibody production associated with decreased resistance.(49)

10. MIC GENES

The MIC /PERB11genes(51, 52) include two genes, MIC-A and MIC-B located respectively 60 and 160 kilobases centromeric to HLA-B, and transcribed in a telomere to centromere direction. The genes were discovered as part of the effort to locate additional genes near HLA-B. In addition to these two members of the MIC family three other pseudogenes are located in the distal Class I region of the MHC. The MIC-A and B proteins share about 84% amino acid identity and are distantly related to conventional Class I genes, with an average of 27% amino acid identity. Nevertheless the general organization of the proteins and genes seem clearly related to that of the Class I gene family. Sequences homologous to MIC-A occur in a variety of mammals. However the genes do not play a vital function in humans, as subjects have been reported who are homozygous for a deletion inactivating both genes, and yet apparently healthy.(53)

The MIC proteins appear to be expressed on cell surfaces without beta-2 microglobulin, and at least MIC-A is preferentially expressed on epithelial cells of the intestine as well as in a range of epithelial malignancies. The expression of the genes is not controlled by gamma-interferon but they are up-regulated by heat stress, suggesting a role in general stress response. The coding regions of MIC-A and B are impressively polymorphic, with over 30 alleles of MIC-A recognized by sequencing.(53-55) The pattern of polymorphisms differs from that in classical Class I genes, not being concentrated in the peptide binding groove.(56) This is consistent with the proposal that these proteins may not bind peptides.

Several recent very interesting observations have been made with respect to the possible functions of the MIC genes. They can act as activating genes for NK cells, γδ-T and CD8+ αβ-T cells that carry the NKG2D receptor. They are recognized in cytotoxicity assays by intestinal intra-epithelial γδ-T cells expressing a variety of Vδ1chains, and by γδ-T cells infiltrating MIC-A and MIC-B positive tumors.(57, 58)

11. OTHER GENES

Vacuolar ATPase is a multi-subunit protein complex that transports H^+ ions**.** It functions in general to mediate acidification of cellular vacuoles, and consequently in receptor recycling, lysosome formation, and cellular pH control. Recently Campbell and co-workers have identified sequences centromeric to the BAT1 gene that encode exons of a gene, ATP6G, homologous to the G subunit of the vacuolar H+ ATPase of a number of species.(26) The mRNA for this gene had two alternative splice forms, with the shorter form removing the presumptive translation initiation codon of the longer form and therefore removing an amino terminal region of high homology to other G subunits. The longer splice form was selectively expressed in some B and T cell lines as compared with myelomonocytic lines. Vacuolar ATPase subunit G is up-regulated in neutrophils exposed to non-pathogenic bacteria (Yeramilli and Weissman, unpublished). The ATPase is also up-regulated in neutrophils by GM-CSF or phorbol myristic acid. Up-regulation of the ATPase is one of the mechanisms that may delay apoptosis in activated neutrophils. However a specific role for the ATP6G in

Table 2. Disease Associations

Immunological Diseases
Systemic lupus erythematosus
Ankylosing Spondylitis
Psoriasis vulgaris
C2 deficiency
TNF and Infectious Diseases
Non-Immunologic Diseases
Congenital adrenal hyperplasia

inflammation remains to be established by more specific means.

A gene encoded by sequences upstream of ATP6G has been described as NF Kappa B-like on the basis of its encoded ankyrin repeats.(59) However the gene is broadly expressed and does not have obvious motifs related to DNA binding or transcription regulation. Again, more specific experiments are needed before this gene can be assigned any role in the inflammatory process.

12. DISEASE ASSOCIATIONS

Diseases or traits are said to be MHC associated if one or more alleles are significantly increased or decreased when a patient group or subgroup is compared with a relevant control group. An association suggests that there are one or more genes within the MHC region that contribute to genetic susceptibility. Remarkably, there are several diseases associated with the MHC including ankylosing spondylitis (probably an autoimmune disorder), hemochromatosis (a metabolic disorder of iron homeostasis), and C2 deficiency (a complement disorder). The diversity of these diseases is as impressive as their number with no single mechanism explaining the wide range of disease associations (See Table 2). This statistical association is presumed to be due to polymorphisms of the Class I and II gene products or perhaps to intervening non-HLA genes, as in the case of 21-hydroxylase deficiency. Conventional wisdom has suggested that allelic polymorphisms of Class I and II gene products effect the binding efficiency of certain autoantigens, which can result in a peripheral T cell-mediated immune response and autoimmune sequelae. However, recent results in an animal model of autoimmune diabetes, the nonobese diabetic mouse, suggest a new hypothesis to explain the role of the MHC in autoimmunity.(60) This hypothesis proposes that the genetic association between MHC and autoimmune disease results from altered thymic selection in which high-affinity self-reactive (and potentially autoreactive) T cells escape selection in the thymus as a result of the poor self peptide-binding properties of the disease-associated MHC molecules.(61) In essence, some forms of MHC-associated autoimmune diseases are a result of a developmental error.

Regardless of the pathophysiology, most of the disease associations are with Class I and II gene products. However, allelic associations in this region generally span large haplotypes so that precise localization of disease genes has proven challenging. Given the expanse of associated haplotypes over several million bases it is possible for causative genes to be located in the Class III or Class IV regions as well.

12.1. Immunological Diseases

12.1.1. SLE: A Model of Autoimmune Disease

The underlying cause for the MHC association with different autoimmune diseases remains obscure.(62) Systemic lupus erythematosus (SLE) is a chronic, remitting, relapsing, inflammatory, and often febrile multi-system disorder of connective tissue. It is acute or insidious in onset and is principally characterized by involvement of the skin, joints, kidneys, and serosal membranes. Of unknown etiology, SLE is thought to represent a failure of the regulatory mechanisms of the immune system. Gaffney *et al*.(63) described the results of a genome-wide screen on 105 SLE sib-pair families, and found the strongest evidence for linkage with a marker in the MHC. Haplotype analyses have shown an association with an HLA-B8.1 ancestral haplotype in Caucasians, which contains a single C4 gene in the Class III region. Fielder *et al*.(64) found an unexpectedly high frequency of null (silent) alleles at the C4A, C4B and C2 loci in SLE patients.

On a cellular level, Abraham *et al*.(65) showed increased TNF-[alpha] activity in culture supernatant of some homozygous HLA-B8 lymphoblastoid cell lines, compared with that of cells homozygous for other MHC ancestral haplotypes. Similarly, others have found increased TNF production in mitogen-stimulated monocytes.(66, 67) Jacob and McDevitt(68) suggested that elevated TNF production may help to explain why this haplotype is associated with multiple autoimmune diseases. Other haplotypes that influence SLE probably act in different ways.

In addition, there are associations between HLA and the types of autoantibodies found in SLE. For example, HLA-B8, HLA-DR2, and HLA-DR3 have been reported to be associated with antidouble-stranded DNA antibodies.(69, 70) These and similar associations are consistent with high titers of autoantibodies in SLE patients, including antidouble-stranded DNA, anti-SSA, and anti-SSB. These findings do not imply a peptide-specific role for Class I or II HLA alleles. Hajeer *et al*.(71) found increased frequencies of TNF a2, b3 and d2 alleles in patients who had anti-SSA and/or anti-SSB autoantibodies, but not those negative for both. And it is unlikely that presentation of specific peptides by HLA-B8 or HLA-DR3 is the primary cause of SLE. The 8.1 haplotype is associated with many autoimmune diseases and may function as a general influence on immunoregulation or tolerance, including polyclonal B-cell activation, rather than in a purely antigen-specific manner. The same haplotype is also associated with the rate of progression of AIDS after HIV infection,(72, 73) the response to hepatitis B vaccination,(74) and influences the incidence of IgA deficiency.(75) It may be that the 8.1 haplotype is basically a high responder but a poorly regulated haplotype, presumably because it contains a set or haplotype of relevant alleles at multiple sites or loci within the MHC region.

12.1.2. Ankylosing Spondylitis

Ankylosing Spondylitis (AS) is an arthritic disease characterized by enthesitis (inflammation involving the insertion point of ligaments into bone) and the absence of rheumatoid factor.(76) It primarily involves the large joints of the spine and sacroiliac joint but the process spreads to involve synovial joints as well. Eventually, about 50% of cases will have significant hip arthritis, and involvement of the synovial zygo-apophyseal joints is universal. The association between AS and HLA-B27 in the Class I region is remarkable in several respects. First, HLA-B27 is clearly a powerful marker in that its absence protects from the development of AS unless there are other factors such as psoriasis vulgaris present. Secondly, it is the broad serologically defined specificity of B27 rather than any particular partial subtype or exonic sequence that seems to be associated.(77-79) Third, transgenic rat models of AS that have multiple copies (55 and 150) of B*2705 develop arthritis, but bacteria and gut inflammation play a prominent role along with genetic background in this model.(80) Several interesting studies have compared the sequence subtypes 2701 to 2711 in terms of susceptibility. Although there is evidence that at least most subtypes are associated, there are indications that some (2706, 2707 and 2709) may be less so or even protective, possibly by virtue of an Asp or His at position 116.(81) However, a further study urges caution because, whereas 2706 may be protective in Thais, it is found in Chinese AS.(82) These data, together with the disappointing peptide data,(79) have reawakened interest in the possibility of a linked gene with a critical allele associated with, and marked by, B27.(83) MIC-A (PERB11.1) has been suggested,(78) but all components of a B27 haplotype, including MIC-A, should be considered.

12.1.3. Psoriasis Vulgaris

Psoriasis vulgaris (PV) is a multifactorial disease that affects approximately 2% of the population.(84) Psoriatic lesions are characterized by a clinical triad consisting of skin induration, scaling, and erythema. The histologic correlates of these clinical findings include inflammation, abnormal keratinocyte proliferation/terminal differentiation, and dermal angiogenesis. The inflammatory infiltrate, particularly pronounced at the dermal-epidermal junction, consists largely of activated T cells and antigen-presenting cells and precedes the development of epidermal hyperproliferation. Increased levels of inflammatory cytokines are detectable in lesional psoriatic epidermis, which may result in the potentiation of T cell activation(85) as well as hyperproliferation and accelerated differentiation of keratinocytes.(86) These and other data derived from T cell-based therapeutics suggested to Abrams *et al*.(87) that activated T cells play an important role in triggering and perpetuating the disease.

It has been known for some time that PV is associated with the HLA-B57.1 ancestral haplotype.(88) Associations with HLA-B57, -Cw6 and -DR7 had been demonstrated before it was appreciated that these are all component alleles of perhaps the oldest and most widespread of current haplotypes.(89) A recent study from Thailand identified a common association with the HLA-B57.1 haplotype in that population.(90) Dawkins *et al*.(91) found that an allele of MIC-A (PERB11.1), tentatively designated PERB11.1*06, is associated to about the same extent in PV as other components of 57.1. When the results are expressed as relative risks, PERB11*06, HLA-Cw6 and C4A6 are all similar. MIC-A appears to be a transmembrane receptor with a similar structure to Class I but with a different groove and a different distribution of polymorphic residues(92) (See discussion of MIC genes above). MIC-A is expressed on mucosal and epithelial surfaces(93) and it has been suggested that it may have a role in superficial defense(94) (See discussion above). The gene product is associated with migratory cells in the dermis but concentrated in the basal cells of the epidermis - including hair follicles and sweat glands - before progressing to the surface.(91) The fact that MIC-A appears to be expressed in relevant locations and the presence of a polymorphism within the extracellular exons suggests that it may be implicated in the pathophysiology of PV. Interestingly, expansion of a transmembrane triplet repeat in MIC-A (6 repetitions) has been associated with Behçet's disease, although the association with HLA-B*501 might account for the MIC-A association.(95, 96)

12.1.4. C2 Deficiency

C2 deficiency is the most frequent complement deficiency state and occurs in about 1 in 10,000 Caucasians.(97) About half of C2 deficient persons have autoimmune disease, most commonly SLE, Henoch-Schonlein purpura, or polymyositis. Serum from patients with C2 deficiency lack functionally and immunologically detectable C2 protein. Clinically, C2 deficient patients are not unduly vulnerable to infections. There is some heterogeneity with cases of C2 hyposynthesis (Type I), and others showing a secretory block (Type II). About 90% of C2 deficiency is associated with the HLA-A25, B18 haplotype (Type I), caused by a 28 base pair deletion in the single exon of the C2 gene.(98) The rarer Type II form is linked to 2 other MHC haplotypes with 2 different missense mutations.(99)

12.1.5. TNF and Infectious Diseases

A number of association studies have been performed on polymorphisms in and around TNF (Reviewed in Hill(100); Knight and Kwiatkowski(101)). Perhaps the most striking association is with an increased prevalence of a homozygous base change at position -308 of the TNF promoter in children with cerebral malaria from The Gambia.(102) Cerebral malaria is associated with markedly elevated serum levels of TNF. Wilson *et al*.(103) reported that the -308 promoter variant is a stronger transcriptional activator than the common allele in reporter gene assays using human B cell lines. This -308 variant has also been associated with mucocutaneous leishmaniasis(104) and lepromatous leprosy,(105) both diseases with high TNF levels. These genetic associations support the view that the high levels of TNF observed in these diseases are causally involved in pathogenesis rather than just a marker of an ongoing pathological process. The same TNF promoter variant has also been associated with scarring trachoma,(106) persistent hepatitis B virus infection, mortality from meningococcal meningitis,(107)

as well as with asthma.(108) A high heritability for whole blood TNF production probably mainly related to non-MHC genes was found in a Dutch twin study, and children with first-degree relatives who had low TNF and high IL-10 production were more likely to die of meningococcal disease.(109) In a small study of HIV, an allele of a microsatellite close to the TNF gene was associated with slow disease progression.(110) In several but not all of these studies, HLA Class I and II alleles were also typed, allowing an independent effect of the TNF region to be assessed.

12.2. Non-Immunologic Diseases

12.2.1. Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH), due to mutations of the 21-hydoxylase gene (CYP21) in the Class III region, is the most common cause of the clinical syndrome, and was also the first HLA-linked disease ultimately found to be caused by a non-HLA gene.(111) CAH is an autosomal recessive disease that results from a deficiency of one of the enzymes of cortisol biosynthesis. In about 95% of cases, 21-hydroxylase is impaired in the zona fasciculata of the adrenal cortex so that 17-hydroxyprogesterone is not converted to 11-deoxycortisol. Due to this defect in cortisol synthesis, ACTH levels increase resulting in overproduction and accumulation of cortisol precursors proximal to the block. This causes excessive production of androgen that results in virilization.

Different clinical forms of CAH are associated with characteristic HLA haplotypes. Holler(112) found that the salt-wasting form was associated with the HLABw47 haplotype, the simple virilizing form was associated with the HLA-Bw51 haplotype, and the non-classic form was associated with the HLA-B14 haplotype. Mutational analysis has shown that a missense mutation, Val281Leu in CYP21, is consistently associated with the non-classical form on the B14 haplotype.(113) A large deletion of part or all of the CYP21 gene is associated with the Bw47 haplotype, but is also observed in other HLA haplotypes as well.(114)

13. DISCUSSION

The genes briefly described above, except for BAT1, are all differentially regulated during some aspect of acute inflammation or stress. However, neither the types of cells in which they are expressed at high levels nor the stimuli directly inducing them are the same. For example, several are induced by gamma-interferon but the MIC genes are induced by heat shock,(115) and specifically described not to be gamma-interferon inducible. Heat shock proteins are broadly expressed, MIC genes are expressed in intestinal epithelium, and 1C7 is expressed at relatively high levels in NK cells and B144 in maturing dendritic cells. The divergence in molecular regulation of these various genes itself suggests that any force favoring clustering of the genes would operate because of their functional rather than specific molecular interrelationships. Unlike the situation with Class I and II antigen presentation, the molecular roles for many members of the Class IV region are either unknown, or only in the process of being worked out. Detailed suggestions about possible functional interrelationships therefore remain quite speculative, although in a very broad sense these genes might influence cellular aspects of inflammation or tissue damage that culminate in antigen presentation.

A number of autoimmune diseases may be influenced by allelic variations in the Class IV region and adjacent proximal Class I region. However this region covers a relatively small amount of DNA and recombination within the region is infrequent. In addition, allelic variation in different genes in the cluster may have either synergistic or antagonistic effects on the same physiologic or pathologic process, making disease association with specific nucleotide changes particularly difficult. Nevertheless, regulation of TNF genes has been implicated as a modulating factor in experimental lupus and in malaria response in humans, HLA-B itself seems to be a primary MHC determinant for susceptibility to ankylosing spondyloarthropathies, and MIC gene polymorphisms may be associated with specific diseases. Detailed molecular study of the less-well understood immune system genes of this region would be highly desirable as a complement to difficult genetic mapping studies of disease associations, in addition to their importance for basic immunology.

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