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MHC-I-opathy: A Unified Concept for the Etiology of Several Major Histocompatibility Complex–Associated Conditions Including Psoriasis and Psoriatic Arthritis

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ABSTRACT. At the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting, Drs. Dennis McGonagle and Wilson Liao discussed "MHC-I-opathies," a class of immune-mediated diseases genetically associated with major histocompatibility complex class I (MHC-I) and class I peptide processing. MHC-I-opathies demonstrate epistatic interactions, genetic associations, and immunopathology that are distinct from classic B cell and autoantibody-driven autoimmune diseases. Investigations into the pathomechanisms of MHC-I-opathies have revealed a blend of tissue-specific innate immunity and CD8 T cell responses. Several functional pathomechanisms by which MHC-I molecules increase psoriasis (PsO) susceptibility were presented by McGonagle and Liao, and there were multiple associations within the HLA-C locus. Antigen presentation to T cells, HLA regulation of natural killer cells and CD8 T cells through killer immunoglobulin-like receptors, and HLA regulation of dendritic cells through leukocyte immunoglobulin-like receptors were discussed. Interestingly, MHC-I associations are not only linked to excessive inflammation in MHC-I-opathies but also to the spontaneous suppression of infection (eg, HIV-1 elite controllers). This striking prominence of MHC-I in PsO and antiviral immunity provides insight into why autoimmune alleles are maintained in the human genome and how protective antiviral pathways may be linked to aberrant activation of MHC-I-opathies. Outside of spinal inflammation in HLA-B27–positive axial psoriatic arthritis (PsA), the basis for MHC-I genetics in PsA remains less clear and is at least partly linked to greater PsA heterogeneity. Understanding the contribution of MHC-I in PsO and PsA may have important implications for therapy development.

Key Indexing Terms: GRAPPA, immune diseases, MHC class I, psoriasis, psoriatic arthritis

Key concepts in MHC-I-opathies

At the outset of the MHC-I-opathies discussion at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting, Dr. Dennis McGonagle reviewed the background and key features of MHC-I-opathies. The seronegative spondyloarthropathy concept was formulated in 1974 by Moll and colleagues, who recognized a group of inflammatory conditions not linked to autoantibodies but to oligoarthritis, spinal inflammation, intestinal inflammation, infection, and various cutaneous rashes.[1] In the ensuing years, these entities, including psoriasis (PsO), Behçet disease (BD), uveitis, and axial spondyloarthritis (axSpA) were demonstrated to have major histocompatibility complex class I (MHC-I) associations, and an epistatic interaction with endoplasmic reticulum aminopeptidase 1 *(ERAP1)* involved in peptide trimming.[2] Outside the MHC, all these diseases also showed multiple single-nucleotide polymorphisms (SNPs) in the interleukin (IL)-23/17 axis, most notably IL-23R.[3-7] Such IL-23/17 immunogenetics neatly tie in with the clinical phenotypes characterized often by neutrophilic inflammation in the eye (hypopyon in HLA-B*27–related uveitis), skin (Monroe abscess in HLA-C*06:02–associated psoriasis [PsO] and pustules in HLA-B*51–associated BD), and gut inflammation in inflammatory bowel disease where MHC-I associations are weaker.

The SpA family of diseases was formally classified as being intermediates between classical autoimmune diseases and innate immune or autoinflammatory disorders.[8] Being distinct from the classical autoimmune disease where B cells and autoantibodies figure prominently, these intermediate diseases or "MHC-I-opathies" are centrally related to CD8 T cell immunopathology.[8] Since this original classification, several studies have since demonstrated the presence of tissue resident CD8 memory T cells in the skin in PsO[9-11] and in the synovial fluid.[12] Collectively, this shows how tissue-specific CD8 resident T cells might be linked to site-specific inflammation distinct from primary autoimmunity, where events played out in lymphoid organs with autoantibody generation are central to disease etiology. McGonagle's work has shown that the normal enthesis,

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a key target in the skeleton for the SpA spectrum of diseases, has both CD4 and CD8 tissue resident memory T cells.[13] Further support for the importance of the MHC-I-opathy concept comes from increased CD8 T cell-inducible production of IL-17A in psoriatic but not rheumatoid synovial fluid. Moreover, single-cell sequencing demonstrated T cell clones in the synovial fluid, with initial studies showing enrichment in CD4 T cell or Th17 cell–IL-17 production, rather than CD8 T cell–IL-17 production.[14,15]

In diseases included within the MHC-I-opathy concept, individuals carrying disease-specific MHC-I alleles exhibit earlier onset, more severe, more extensive, and more recurrent disease compared to noncarriers, possibly pointing toward earlier induction of adaptive immunity leading to severe inflammation.[2,16-21] In patients with axSpA who are HLA-B*27 negative, the HLA-B*40:01 allele emerges as the second most common HLA-B variant, whereas in uveitis, the HLA-A2 allele is frequently expressed. Both alleles are associated with the *ERAP1* SNP *rs30187*.[21,22] Additionally, individuals carrying both HLA-B27 and specific *ERAP* haplotypes have been shown to be at a significantly higher risk for a more severe disease phenotype, including bamboo spine, compared to those who do not carry these genetic factors.[23] This suggests that many class I antigens may lead to the SpA or uveitis phenotype. Given this diversity in peptides, antigen-specific therapy may not be possible, but therapies that control T cell biology are more likely to be successful.

This concept has been examined by the McGonagle group in axial PsA, where patients are often HLA-B*27 negative. Axial PsA is often asymmetrical, possibly suggesting a local innate immune tissue-specific dysregulation, which occurs in older subjects, rather than the disease in younger subjects, which is more linked to the MHC-I-opathy concept.[24] Another interesting aspect of the MHC-I-opathy concept is what McGonagle and collaborators term "differential immunopathology," whereby, for example, nail disease is not linked to HLA-C*06, intestinal inflammation is not linked to HLA-B*27, and neurological or intestinal involvement in BD is not linked to HLA-B*51.[2] We believe that this reflects different antigenic composition and distinct microbiota interactions in various target tissues throughout the body, possibly due to regional variations in immune surveillance, epithelial barrier function, and microbial colonization patterns, which could shape tissue-specific immune responses.

A recent refinement of the MHC-I-opathy concept recognizes that these diseases may be driven not only by excessive IL-23/17 pathway activation but also by classical type 1 immunity with tumor necrosis factor (TNF) activation. Takayasu arteritis (TA) exemplifies this distinction, as it occurs at an early age and is characterized by granulomatous rather than neutrophilic inflammation, often responding to TNF blockers. Beyond its phenotypic overlapping with SpA and PsO,[25] TA's inclusion within the MHC-I-opathy framework is supported by its strong association with HLA-B*52, the role of IL-12B SNPs in disease susceptibility and severity, the dominance of CD8+ T lymphocytes, and the contribution of biomechanical factors to sustained inflammation. Recognizing these immunological and genetic differences, the McGonagle group stratified MHC-I-opathies into type 1 and type 17 subgroups, a distinction that may have significant therapeutic implications.[26]

MHC-I–driven mechanisms that promote PsO

Dr. Wilson Liao described 3 critical mechanisms through which MHC-I promotes PsO: (1) antigen presentation, (2) MHC-I activation of natural killer (NK) and CD8 T cells, and (3) MHC-I activation of dendritic cells. Several genome-wide association studies (GWAS) investigating PsO have consistently found a strong signal within the MHC region on chromosome 6. Whereas the HLA-C*06:02 allele is most strongly associated with PsO, multivariate conditional analysis has revealed at least 11 other MHC-I alleles are independently associated with PsO. After adjusting for the effects of HLA-C*06:02, other PsO-associated alleles include A*02:01, B*38:01, B*39:01, A*01:01, B*15:18, B*27:05, B*55:01, B*57:01, B*58:01, C*03:04, and B*50:01. MHC-I genetics are less well understood in PsA, but key observations have been that HLA-C*06:02 is linked to PsO but not PsA, HLA-B*27 is linked to axial disease, and other class I antigens including HLA-B*39, HLA-B*08, HLA-B37, HLA-C*07, and HLA-C*02 are linked to peripheral arthritis.[27,28]

How the HIV-1 control phenotype provides a clue to MHC in PsO

GWAS studies have helped to identify striking similarities between the genetics of PsO and an HIV host phenotype called HIV-1 controllers. Patients with HIV-1 control have been infected by HIV-1, but they have immune systems that can spontaneously keep viral load low to undetectable without antiretroviral therapy. Liao cited a GWAS in PsO that identified *rs2395029* as a top SNP in the MHC region, which is notably the same SNP identified in a GWAS of patients with HIV-1 control.[29-31]

There are 4 similarities between the genetics of PsO and HIV-1 control. First, stepwise regression modeling to identify independent effects in PsO revealed that after adjusting for HLA-C*06:02, the HLA-B*57 and HLA-B*27 alleles (major HIV-1 control alleles) were risk factors for PsO (*B*57*: $P = 5.8 \times 10^{-4}$, odds ratio [OR] 1.52; *B*27*: $P = 1.2 \times 10^{-5}$, OR 1.75). HLA-B*35, an unfavorable allele associated with HIV-1 progression, has a protective effect for PsO ($P = 3.2 \times 10^{-6}$, OR 0.65). Additionally, analysis of PsO-specific HLA amino acids within the peptide-binding groove found sites at HLA-C 97 and 156 and at positions identical to those of HIV-1 control (HLA-B 67, 70, 97).[32] Together, this suggests that specific antigens may trigger both diseases.

The second genetic similarity is increased HLA-C cell surface expression associated with both PsO and the HIV-1 control phenotype. This amplified expression beneficially reduces HIV-1 viral load, likely through greater antigen presentation, and correlates with an allelic deletion polymorphism within the 3′ untranslated region (UTR).[33] PsO is also associated with the same 3′ UTR deletion polymorphism and a subsequent increase in HLA-C expression.[33]

Third, close evaluation of MHC-I regulation of NK cells revealed that a specific epistatic interaction between *KIR3DS1* activating receptor and HLA-B delays the progression to AIDS, an effect that is not present with *KIR3DS1* or HLA-B alone.[34] This same epistatic interaction between the *KIR3DS1* receptor on NK or CD8+ T cells and the HLA-B Bw4-80I ligand leads to a 4-fold increase in the odds of developing PsO ($P = 1.54 \times 10^{-7}$, OR 3.92). Similarly to HIV-1 control, this effect is not seen with either the receptor or ligand alone.[33]

Finally, MHC-I regulation of dendritic cell receptors shares similarities between HIV-1 control and PsO. Interaction between inhibitory *LILRB2* and HLA-B leads to a downregulation of the inhibitory receptor and a consequential upregulation of T cell activation in HIV-1.[35] *LILRB2* is expressed on skin dendritic cells and is decreased in PsO. Through assessing multivariate stepwise models that included all class I and II HLA alleles, Liao and colleagues found that this specific interaction between *LILRB2* and HLA-B had an effect independent of HLA-C*06:02 and other alleles ($P = 2 \times 10^{-9}$). In functional analysis, small interfering RNA knockdown of *LILRB2* in dendritic cells increased antigen presentation.[36]

Conclusion

The continued investigation of pathogenic mechanisms across MHC-I-opathies is paving the way for improved understanding and development of targeted therapies for individuals with these conditions. McGonagle and a European Alliance of Associations for Rheumatology (EULAR) study group are currently leading a multidisciplinary collaboration to investigate gaps in current knowledge of MHC-I-opathy pathophysiology. These efforts include initiatives such as the creation of a standardized annotation of disease symptoms, as well as the integration of GWAS data of MHC-I-opathy–related diseases to facilitate fine genetic mapping. Additionally, previous research has revealed the potential role of pathogens and microbial agents and immune response in these diseases, as demonstrated in both SpA and PsO.[37,38] This discovery, along with recent technological advancements that have improved immunopeptidome analysis of disease-affected tissue, may further elucidate CD8 T cell–mediated mechanisms in MHC-I-opathies.[37]

These findings in SpA and PsO also represent a fascinating theoretical framework for why autoimmune diseases persist throughout evolution as the immune system encounters various pathogens and retroviruses. An important research question remains: Why are autoimmune alleles maintained in the human gene pool? Liao explained that the answer may lie in positive selection where specific alleles are protective against pathogens and viruses, as with the case of HIV-1 control. If aberrantly activated, these alleles may lead to autoimmune diseases like PsO. MHC-I-opathies including PsO may have antigenic triggers that could involve viral or virus-like peptides (eg, human endogenous retroviruses), and the clinical disease processes are the aberrant activation of antiviral pathways.

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ETHICS AND PATIENT CONSENT

Institutional review board approval and patient consent were not required.

PEER REVIEW

As part of the supplement series GRAPPA 2024, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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