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REVIEW ARTICLE

The Etiopathogenesis and Genetic Factors in Idiopathic Inflammatory Myopathies: A Review Article

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Abstract:

Introduction:

Idiopathic inflammatory myopathies (IIM) are a group of heterogeneous systemic autoimmune diseases characterized by muscle inflammation from unknown causes resulting in chronic weakness. Recent studies have shown the role of the cellular immune response affecting muscle fibers in polymyositis (PM), inclusion body myositis, and to a lesser extent, dermatomyositis (DM), wherein humoral immunity is more involved. The value of genetic factors of the class II major histocompatibility complex (MHC II) has also been highlighted. In studies of murine models, the presence of HLA-DR3 favors a higher risk of developing inflammatory muscle disease, including PM and juvenile DM. In recent years, few studies have provided timely information regarding this, thus the researchers initially proposed a review of existing literature to broaden the context regarding what was described and to visualize proposals that may enhance the understanding of this group of inflammatory pathologies.

Methods:

The design, implementation, analysis, and reporting of this study were followed according to the search with MeSH terms (Autoimmune myopathy, Inflammatory myopathies, Idiopathic inflammatory myopathies AND Major histocompatibility complex and genetics). We analyzed 12 articles for this review article.

Conclusion:

In the etiopathogenesis of IIM, both humoral and cellular immunity are observed, considering the presence of a trigger that causes the immune response. As for the immunogenetics, this review highlights what has been reported in Chinese and Mexican populations, where HLADRB1*09:01 is related to the presence of DM, and is observed as the first variant identified in various populations. This increases interest in this allele in the particular case to study DM and strengthens research that proposes the study of IIM independently for each nosological entity.

Keywords: Autoimmune myopathy, Dermatomyositis, Inflammatory myopathies, Idiopathic inflammatory myopathies, Major histocompatibility complex, Myositis, Myositis idiopathic.

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1. INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of heterogeneous systemic autoimmune diseases characterized by muscle inflammation from unknown causes resulting in chronic weakness. Different causes and pathogenic mechanisms are responsible for inflammation and muscle damage; infectious agents, vaccines, neoplasms, drugs, and

some immunological abnormalities, both cellular and humoral, have been considered in etiopathogenesis. Recent studies have highlighted the role of the cellular immune response in the affection of muscle fibers in polymyositis, inclusion body myositis, and to a lesser degree, dermatomyositis, wherein there is greater humoral immunity involvement [1 - 4].

Two observations have supported the hypothesis that IIM are autoimmune disorders. The first is the association with other autoimmune diseases, including Hashimoto's thyroiditis, Graves' disease, myasthenia gravis, type I diabetes mellitus,

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primary biliary cholangitis, and connective tissue diseases [5 - 8]. The second is the high prevalence of circulating autoantibodies [9 - 14]. Histopathological findings in the striated muscle of patients with inflammatory myopathies have discovered the involvement of several pathologic mechanisms. These include microangiopathies and muscle ischemia, as well as inflammatory infiltration of the endomysium, mostly by B lymphocytes but also by CD4+ T cells and macrophages. This emphasizes the involvement of the humoral immune response in dermatomyositis (DM) [15 - 18].

It also highlights the importance of genetic factors located in the immune histocompatibility class II antigen [19, 20]. This has been demonstrated in studies of murine models, where the presence of HLA-DR3 favors an increased risk of developing inflammatory muscle disease, including polymyositis (PM) and juvenile DM. Similarly, the presence of anti-Jo-1 antibodies and HLA-DR52 appears to be correlated; there is also a reported association between HLA-DR1, DR6, and DQ1 and inclusion body myositis [21 - 25]. These elements together provide valuable data on immunogenetic, cellular, and humoral lines in the development of inflammatory myositis that allow for a better understanding of the genesis of IIM [26 - 28]. However, more studies are required to expand these concepts and validate the results, in addition to identifying possible population variants. In recent years, few studies have provided timely information regarding this. Therefore, this study initially proposed a review of the published literature to broaden the context of what has been described and to visualize proposals that allow for a better understanding of this group of inflammatory pathologies.

Idiopathic inflammatory myopathies are classified according to the EULAR/ACR (European League Against Rheumatism)/(American College of Rheumatology) in Dermatomyositis (DM), Amyopathic Dermatomyositis (ADM), Polymyositis (PM) and Inclusion Body Myositis (IBM) [29]. Recently, IIM was related to clinical manifestations and specific antibodies according to phenotypic, biological and immunological criteria that describe subgroups and established risk factors for mortality [30 - 32].

The genetic relationship of IIM is variable and depends on the age group; in the European population, it was identified that the heritability ranges from 22-24% for first-degree relatives and siblings, the family risk of Systemic Lupus Erythematosus and Rheumatoid Arthritis is higher in patients with Dermatomyositis or Polymyositis. The genes involved in the innate and adaptive immune response beyond the HLA region are STATA 4 (signal transducer and activator of transcription 4), TRAF6 (TNF receptor associated factor 6) and PTPN22 (Protein Tyrosine Phosphatase Non- Receiver Type 22). PTPN22 and STAT4 affect T-cell signaling, while TRAF6 affects B-cell and nuclear factor kappa- β (NF- κ B) signaling [33 - 35].

Other pathogenic mechanisms include the NLRP3/caspase-1/IL-1 β axis because it induces the class I Major Histocompatibility Complex in PM, and *in vitro*, its inhibition reduces the expression of IL-1 β and MHC-I, and the use of IL-1 β neutralizing monoclonal antibody decreases muscle enzymes and C-reactive protein, and for this reason, it

proposed a therapeutic target in PM [36 - 38]. On the other hand, complement involvement has been demonstrated in studies in patients with Juvenile Dermatomyositis (JDM). C4A deficiency is a genetic risk factor for patients with HLA*DR [39], and patients with anti-Jo antibodies or anti-Pm/ScL have lower plasma concentrations of complement [40].

In Dermatomyositis, some associated antibodies are posited to establish: anti-Mi-2, anti-TIF-1, anti-NXP2, anti-SAE y anti-MDA-5 [41]. Currently, phenotypes of Dermatomyositis associated with the anti-MDA-5 antibody are described as a systemic syndrome different from other patients with myositis, 3 subgroups with manifestations from mild to severe and variable prognosis [42 - 44]. The genetic component is related to nucleotide polymorphisms (SNP) in the Major Histocompatibility Complex (MHC) and with others outside the HLA, without differences according to gender or age [45].

The association of antibodies in the Caucasian population suggests that HLA DRB1*0301 is associated with anti-Jo-1 y anti-PL-12 antibodies, and in the African-American population, the antibody anti-Mi-2 is associated with HLA DRB1*0302 [46, 47].

HLA-DRB1 is associated with the specific anti-MDA-5 antibody in patients with DM in the population of Japan. The signal transducer and activator of the transcription 4 (STAT4) gene is related to some autoimmune diseases such as Systemic Lupus Erythematosus. STAT 4 is a transcription factor to trigger Th1 and Th17 responses, considering a risk factor for the development of IIM [48]. There is evidence of the genetic association with environmental factors such as smoking with HLA-DRB1*03 and anti-histidyl tRNA synthetase, on the other hand, HLA-DRB1*11:01 and statins for the development of anti-histidyl tRNA synthetase antibodies [49].

Myositis specific autoantibodies (MSAs) associated with genetic factors are: HLA-DRB1*12:02 associated with anti-MDA5, HLA-DRB1*14:03 with anti-SRP, HLA-DRB1*07:01 with anti-Mi-2, HLA-DRB1* 13:01 with anti-TIF1 γ [18], and HLA-DRB1*11:01 with anti-Hydroxy methyl glutaryl coenzyme A reductase antibody [50].

In inclusion body myositis (IBM), genetic factors may influence susceptibility to disease. The strongest association is with amino acids 26 and 11 of the HLA-DRB1 molecule [51 - 53]. In muscle biopsies, inflammatory and degenerative alterations are found; there is inflammation of the endomysium and positive regulation of the class I MHC. Degenerative aspects include the formation of tubulofilamentous vacuoles seen in electron microscopy, mitochondrial changes and deposition of myotoxic proteins such as amyloid p62 and DNA-binding protein TAR-43 (TDP-43) [54].

2. METHODS

2.1. Search Method

The design, implementation, analysis, and reporting of this study were followed according to the search with MeSH terms. We analyzed observational studies that were published from February 10, 2014 to December 08, 2020, using the following terms in titles, abstracts, and keywords: myositis, idiopathic

myositis, inflammatory myopathies, idiopathic inflammatory myopathies, dermatomyositis, autoimmune myopathy, genetics and HLA. The literature search was not subject to language restrictions. The retrieved literature was reviewed for the following criteria: Patients over 18 years of age, diagnosis of IIM according to Bohan and Peter’s criteria, observational genetic characterization studies evaluating the association of HLA and MII (DM and PM subtypes) were considered, the study of cases and controls and years of publication since February 2014 to December 2020.

3. RESULTS

We identified twelve articles that were thus selected for full-text analysis. Table 1 shows the studies that were included in the review. All the material was published during the search period.

4. DISCUSSION

Among the findings described in several publications, microangiopathy and muscle ischemia, together with inflammatory infiltrates composed mainly of B lymphocytes [62 - 64], and smaller proportions of CD4+ T cells and macrophages in the endomysium suggest that the participation of the humoral immune response is crucial in DM. Moreover,

the activation of the complement membrane attack complex C5b-9 is an early element of utmost importance that triggers the release of pro-inflammatory cytokines and chemokines by endothelial cells. [65 - 67] These facilitate the migration of activated lymphocytes to the perimysial and endomysial spaces, resulting in necrosis of endothelial cells and a decrease in the number of endomysial capillaries, as well as ischemia and destruction of muscle fibers like those found in microinfarcts [68 - 70]. Another important finding is the response observed in capillaries “unaffected by the inflammatory process” that usually show dilation of their inner diameter in reactivity to the ischemic picture [71 - 77].

Polymyositis and inclusion body myopathy (IBM), T-lymphocyte-mediated cytotoxicity and necroptosis are the predominant pathogenic mechanisms. [78, 79] Initially, CD8+ T lymphocytes and macrophages surround, invade, and destroy healthy non-necrotic muscle fibers, and cytokines are produced apoptosis that induce overexpression of MHC class I (MHC-I) molecules [80 - 82]. The CD8/MHC-I complex is a characteristic of these two diseases, and its detection has become necessary to confirm the histological diagnosis. [83 - 86] Cytotoxic CD8+ T lymphocytes contain perforin and granzyme granules targeted against the surface of muscle fibers and are capable of inducing muscle cell necrosis [56].

Table 1. Articles included for review.

Author, Year	Type	Population	Outcome	Remarks
Gao X, <i>et al.</i> (2014) [55]	Cases and controls	Chinese	HLA susceptibility DM and PM	HLA and DM association
Miller F, <i>et al.</i> (2015) [52]	Cases and controls	Caucasians	HLA and phenotype correlation	HLA 8.1 defines the genetic risk of the MII phenotype
Rothwell S, <i>et al.</i> (2016) [56]	Cases and controls	Caucasians	Association of HLA susceptibility to MII	No differences were found in the overall analysis, but differences were found in the analysis by subgroups
Zhang CE, <i>et al.</i> (2016) [57]	Cases and controls	Chinese	HLA susceptibility DM	HLA SNP associated with DM
Lin JM, <i>et al.</i> (2017) [23]	Cases and controls	Chinese	HLA and pathogenesis of DM	HLA associated with DM
Chen Z, <i>et al.</i> (2017) [58]	Cases and controls	Chinese	HLA and susceptibility to anti-MDA5 in DM	HLA, Anti-MDA5, ILD and DM association
Houtman M, <i>et al.</i> (2018) [2]	Cases and controls	Swedes	T cell, HLA and association of PM/DM	PM and DM are two clinical phenotypes that differ in T-cell phenotypes related to gene expression
Peng QL, <i>et al.</i> (2018) [13]	Cases and controls	Caucasians	HLA Susceptibility to MII	HLA association with AS.

Other pathogenic mechanisms, such as the interferon signature, have been analyzed [87 - 89]. The expression of IFN α and β inducible genes was high in DM, moderate in antisynthetase syndrome (AS), and low in IBM. In contrast, the expression of IFN γ inducible genes was high in IBM; these differences propose potential therapeutic targets [90]. Class I and II MHC upregulation is an early finding in the skeletal muscle in PM; IFN- γ transcript expression has been shown up-regulated in PM muscle compared to other IIM and involved in the induction of MHC class II molecules. [91 - 93].

Human leukocyte antigen (HLA) genetic variability is crucial in the pathogenesis of DM and PM; this may be attributed in part to the influence of HLA molecules on T-cell receptor development, peripheral tolerance, and immune response to environmental agents. It has been established that

geographic location and ethnicity may affect susceptibility to autoimmune disease; HLA-DRB1*03:01 and HLA-DQA1*05:01 alleles have been described as risk factors for myositis in Western populations [71, 72], while DRB1*08:03 may increase PM susceptibility among the Japanese population. [2, 6, 15, 62] DRB1*01:01, DRB1*04:10, and DRB1*15:02 were high in the Japanese patients with IBM [19, 94]. In other populations in northern China, positive associations between HLA-DRB1*04, HLA-DRB1*07, and HLA-DRB1*12 and the development of DM have been reported, while HLA-DQB1*04:01 [26, 27] is a risk factor for both DM and PM in this same population. Studies also show that HLA class II alleles may influence DM and PM susceptibility of adults in the Han Chinese population [2], particularly HLA-DRB1*09:01 and HLA-DRB1*12:01 [14, 16

- 18].

Furthermore, three studies involving the Mexican population have been published on the association of IIM and HLA. In 1996, Arnett F found no association between HLA alleles and susceptibility to present IIM [6]. Subsequently, Ejaz A. Shamim *et al.* described the association of different HLA-DRB1 and DQA1 with anti-Mi-2 antibodies [73]. In 2018, Lugo G. *et al.* also reported positive and negative associations between HLA polymorphisms and DM subtypes and found that HLA-A*01:01, HLA-A*03:01, HLA-B*07:02, HLA-DRB1*01:02, and HLADRB1*09:01 are significantly associated with susceptibility to this disease, the latter being similar to that reported in the Chinese population [8, 12]. Meanwhile, DRB1*16:01 and DQB1* 03:02 alleles are considered protective factors in the Mexican population [12].

CONCLUSION

In the etiopathogenesis of IIM, the participation of different mechanisms is observed, involving humoral and cellular immunity, following an underlying trigger that would set off the immune response. The immunogenetic participation highlights the presence of HLA DRB1*09:01 in Chinese and Mexican populations, wherein it is related to the presence of DM in both studies, and is observed as the first variant identified in different populations. Therefore, interest in this allele in the case of this myopathy is increased. The independent study of the different diseases encompassed by IIM is also strengthened since no results identifying similar alleles associated with the presentation of IIM as a whole in different populations have been identified, unlike the evidence documented regarding DM.

AUTHORS' CONTRIBUTIONS

Dr. Gustavo Esteban Lugo Zamudio, Rosa Elda Barbosa Cobos, and Lucía Verónica Maya Piña contributed to the coordination of the project, analysis of the information and structure of the manuscript.

Dr. María Mercedes López Mayorga, Ivonne Arenas Silva and Diana Sarai Arellano Álvarez contributed to the search for scientific information and review of case information.

Magister Scientiae Dolores Delgado Ochoa contributed to histocompatibility tests.

LIST OF ABBREVIATIONS

ACR	= American College of Rheumatology
ADM	= Amyopathic Dermatomyositis
AS	= Antisynthetase Syndrome
DM	= Dermatomyositis
EULAR	= European League Against Rheumatism
HLA	= Human Leukocyte Antigen
IIM	= Idiopathic Inflammatory Myopathies
IBM	= Inclusion Body Myopathy
JDM	= Juvenile Dermatomyositis
MCH	= Major Histocompatibility Complex
MSAs	= Myositis Specific Autoantibodies

PM = Polymyositis

PTPN22 = Protein Tyrosine Phosphatase Non- Receiver Type 22

STAT4 = Signal Transducer and Activator of Transcription 4

TRAF6 = TNF Receptor Associated Factor 6

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

We confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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