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Review

Antiphospholipid syndrome's genetic and epigenetic aspects

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ABSTRACT

Studies on last genetic and epigenetic predisposition to APS are summarized. It is well known that genetic predisposition is in HLA system (DR4 and DRw53) and that lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) are both associated with the same HLA antigens. Other genes, outside the MHC, give their contribution to the development of this autoimmune syndrome, such as IRF5, STAT4 and those related to inherited thrombophilia - factor V Leiden and G20210A prothrombin polymorphisms. Finally, post-transcriptional modifications of anti-beta2GPI antibodies could be implicated too. The most important discovery of last years is that altered microRNAs' expression is linked to autoimmunity, thrombosis, early atherosclerosis, and oxidative stress in APS.

1. Introduction

The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL) in serum together with clinical manifestations such as thrombosis (both arterial and venous), fetal losses, hemolytic anemia, and thrombocytopenia. The etiology of this syndrome is still unknown and it could be ipotizable that should arise in a predisposed subject after antigenic stimuli. Proofs of the genetic predisposition of APS lie on the observation of familiar clustering of cases, greater prevalence of aPL in the serum of subjects sharing the same descent of patients, animal models (mice), and association with various alleles both in and outside the major histocompatibility complex (MHC, HLA in men).

A review on the genetic and epigenetic aspects of APS was published by us in 2016 [1]. Since then, some new interesting data have been reported in literature, and prompted us to provide an updating on the most recent studies dealing with this topic.

2. HLA, antiphospholipid syndrome and antiphospholipid antibodies

Many autoimmune diseases are associated with genes in the MHC region. In some autoimmune disorders, such as systemic lupus erythematosus (SLE), MHC antigens seem to be associated with specific autoantibodies, including anticardiolipin (aCL) and anti-beta2GPI (antiβ2GPI), rather than with the disease itself [2]. It appears that MHC genes may influence not only the expression of autoimmune diseases, but also the production of autoantibodies that can be found in these diseases.

Many researchers in the field of immunogenetics have investigated possible associations between APS or the various antibodies directed against negatively charged phospholipids and MHC genes or their products.

However, there is increasing evidence that aPL represent an heterogeneous group of antibodies, which includes lupus anticoagulant (LA), aCL, antiβ2GPI, antibodies to prothrombin, annexin V, phosphatidylethanolamine, phosphatidylserine and other oxidized phospholipids. Thus, it appears evident that the spectrum of HLA associations with APS might become clearer if more specific autoantibody subgroups are studied.

The question of whether a genetic predisposition to develop APS and to produce aPL exists can be examined both in animal models and in humans. The presence of aPL has been reported in some, but not all, SLE-prone mice [3–5] and this means that genetic background of mice can influence the production of aPL and this production can be modulated by hormones. For example, using microsatellite markers in the NZW × (NZW × BXSB)F1 backcross male progeny, Ida et al. mapped BXSB alleles contributing to the generation of aCL, platelet-binding antibodies, thrombocytopenia and myocardial infarction [6]. They found that the generation of each disease character was controlled by two major independently segregating dominant alleles, and that a combination of the two alleles appeared to produce full expression of each character, as a complementary gene action. This finding suggests that no single factor, such as aCL, can explain the pathogenesis of APS.

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Rather, a combination of susceptibility alleles characterises unique features in male (NZW × BXSB)F1 mice, that are prone to develop APS.

Recently, Papalardo et Al. studied the influence of MHC class II alleles on the production of aPL in a mouse model of APS [7]. They immunized three groups of mice, MHC class II–deficient (MHCII2/2) mice, MHCII2/2 mice transgenic for human HLA–DQ6 (DQ6), DQ8, or DR4 alleles, and the corresponding wild-type (WT) mouse strains; half were immunized with human β2GPI, and the other half were immunized with control ovalbumin (OVA) protein. Thrombus formation in vivo, tissue factor activity in carotid and peritoneal macrophages, and serum levels of tumor necrosis factor (TNF), aCL antibodies, and anti-OVA antibodies were determined. Immunization with β2GPI induced significant production of aCL and anti-β2GPI in WT mice compared with control mice immunized with OVA but diminished aCL and antiβ2GPI production in MHCII2/2 mice. This is the first study showing that MHC class II alleles influence not only quantitative aPL production but also the pathogenic capacity of induced aPL.

In humans, the contribution of immunogenetics to the development of aPL and APS has been addressed mainly by family studies and by population studies looking at the HLA region. The APS may exist both as a primary condition as well as in the setting of another autoimmune disease (mainly SLE), and this implies possible differences in the association with HLA. Some aPL can be found in autoimmune diseases, but others appear during the course of infectious diseases, neoplasias, or are drug related; they can also be present as an isolated phenomenon in healthy individuals. Therefore, what we call “antiphospholipid antibodies” may comprise a group of antibodies whose unique common feature is their reactivity against phopsholipids, but with different specificity and different HLA associations.

Recently, Islam MA et al. conducted an interesting systematic search of English articles (up to 4th September 2017) using Web of Science, PubMed, Scopus, ScienceDirect and Google Scholar databases. [8]. Eligible studies were selected based on the inclusion criteria. They found that 16 genes contribute significantly in patients with thrombotic primary APS when compared with controls. (Table 1). These genes are expressed in 32 different organs and may pose higher risk of developing thrombosis anywhere in the body of primary APS patients.

2.1. Family studies

Familial occurrence of aPL with or without clinical evidence of APS has been documented since 1980 [9–11]. Family studies suggest a genetic predisposition to APS, either when it presents as a primary condition or when it is seen in the context of SLE. It appears that this genetic predisposition is in part accounted for by the HLA system, the most consistent associations being those with DR4 and DRw53. Furthermore, it appears that LA and aCL are both associated with the same HLA antigens, even if these two methods of detecting aPL do not overlap completely.

Various studies examined HLA by serological methods. Dagenais et al. described an English Canadian family in which aCL were associated with a spectrum of clinical manifestations, from asymptomatic carriers to the typical thrombotic disease in association with SLE and autoimmune thyroid disease [12]. They found the paternal haplotype A30; Cw3; B60; DR4; DRw53; DQw3 to be associated with aCL. The occurrence of LA in families carrying haplotypes that contained either DR4 or DR7 also has been reported by others [13,14]. May et al. have described a family, including identical twins and their mother, in which all members had SLE and presented with different manifestations of APS [15]. The mother and the twins shared the HLA haplotype that included DR4, DRw53 and DQw7, whereas C4A or C4B deficiencies could not be implicated in the autoimmune process.

A recent study revealed an association between a mutation of the F2 gene, which codes for coagulation factor II, thrombin, and the risk of thrombophilia in a Han Chinese family, of which four members had a history of deep venous thromboembolism. [16]. To identify the abnormality underlying the increased thrombophilic risk, whole-exome sequencing technology was used to analyze two affected individuals. An exonic missense F2 mutation, T165M (NM_000506:c.C494T:p.T165M;rs5896), was identified from a total of 2222 and 2203 genetic variations observed in the two affected individuals, respectively, which were subsequently filtered and confirmed using Sanger sequencing.

This deleterious mutation in heterozygous form was not identified in normal controls.

2.2. Population studies on primary antiphospholipid syndrome

HLA associations in population studies on primary APS and in population studies in diseases other than primary APS have been previously reported and discussed [1] and are summarized in Table 2.

2.3. Population studies on antiphospholipid antibodies in diseases other than primary APS

Most of these studies deal with SLE and aCL, probably because aCL are more easily detectable than LA. They are summarized in Table 3.

We performed a very large study on about 600 patients with SLE, all of European origin, analysing the association of aCL and anti-beta2GPI with HLA class II alleles [27]. Data showed that aCL are positively associated with HLA-DRB1*04, -DRB1*07, -DQA1*0201, -DQA1*0301, -DQB1*0302, -DRB3*0301, and that anti-beta2GPI have a positive association with DQB1*0302. DQA1*0501 and DRB3*0202 showed a negative association with aCL. For the first time it was demonstrated that aCL and anti-beta2GPI are associated with HLA-DRB1*0402 and -DRB1*0403, among the alleles of the DRB1*04 series. Indeed, DRB1*0402 carried the highest relative risk for the presence of both aCL (RR = 8.1) and anti-beta2GPI (RR = 4.6), and it was noteworthy that 75% of patients carrying the DRB1*0402 allele were aCL-positive. We could not find any association with alleles at DRB4 locus (DRw53), and found that aCL are associated with DR4 in SLE patients both from Spain and Italy, two Latin countries. Thus, it can be argued that both DR4 and DR7 are independently associated with aCL, and that aCL in patients with SLE are associated with alleles at DRB1 locus but not with

Table 1
Genetic risk factors in thrombotic primary antiphospholipid syndrome: a systematic review with bioinformatic analyses [8].

PF4V1 (platelet factor 4 variant 1)
SELP (selectin P)
TLR2 (toll like receptor 2)
TLR4 (toll like receptor 4)
SERPINE 1 (serpin family member 1)
APOH (apolipoprotein H)
ITGA 2 (integrin subunit alpha-2)
GP1BA (Platelet glycoprotein I b alpha chain)
F2R (coagulation factor II, thrombin receptor)
F2RL1 (F2R like trypsin receptor 1)
TFPI (tissue factor pathway inhibitor)
F3 (coagulation factor III, tissue factor)
VEGFA (vascular endothelial growth factor A)
FLT1(fms related tyrosinekinase 1)
TNF-ALPHA

Table 2
HLA associations with APS, data from population studies on primary antiphospholipid syndrome.

HLA-DQw7 (DQB1*0301 allele)
DQB1*0604/5/6/7/9-DQA1*0102-DRB1*1302
TNFA-238*A-DQB1*0303-DRB1*0701
HLA-DR5
HLA-DRB1*03
HLA-DMA*0102

Table 3
Association between HLA alleles and anticardiolipin antibodies in various diseases.

	HLA	Frequency[a]	Ethnic origin	Ref.
SLE	C4Q0	92	African-American	Wilson, 1988 [17]
CBFP[b]	C4Q0	71	Swedish	Stephansson, 1993 [18]
SLE	C4A	No association	American	Petri, 1993 [19]
SLE	DR7	61	Northern Italian	Savi, 1988 [20]
SLE	DR4	87	English	McHugh, 1989 [21]
Possible PAPS[c]	DR4,DRw53	56,83	Australian	McNeil, 1990 [22]
SLE	DR4,DR7,DRw53	81	Caucasian	Hartung, 1992 [23]
SLE	DRB1*0901	41	Japanese	Hashimoto, 1998 [24]
SLE	DR,DQ	No association	Caucasian and African American	Gulko, 1993 [25]
SLE	DR	No association	Central Italian	Sebastiani, 1991 [2]
SLE	DPB1*1401,0301	45	Central Italian	Galeazzi, 1992 [26]
SLE	DRB1*0402/3,DRB1*07, DQA1*0201,DQA1*0301, DQB1*0302	75/56,36 36,47, 45	Caucasian	Galeazzi, 2000 [27]
SLE	DPB1*1501, *2301	50,63	Caucasian	Sebastiani, 2003 [28]
PSS[d]	DR	No association	American	Asherson, 1992 [29]
JCA[e]	A,B,C,DR	No association	Canadian	Malleson, 1992 [30]

[a] Frequency of HLA allele in aCL-positive patients (%).
[b] Chronic biologically false positive reactors (some affected by SLE).
[c] Patients with aCL and occlusion of coronary artery bypass grafts.
[d] Primary Sjogren's syndrome.
[e] Juvenile chronic arthritis.

those at DRw53 locus. According to these results, it seems that DRB1*0402 and DRB1*0403 are slightly more important than DR7 and that the association with DRw53 is only apparent because patients typing positive for DRw53 possess haplotypes that also contain either DR4 or DR7.

Subsequently, we showed that aCL and some clinical manifestations share the same HLA association. This was the case of the association of IgA aCL and Raynaud's phenomenon with DRB1*07 and DQA1*0301, of haemolytic anemia and IgM aCL with DQA1*0301 and of thrombocytopenia and IgG aCL with DRB3*0301. Therefore it could be considered that the association of HLA alleles with particular clinical manifestations of APS, found in our study, might be a consequence of the association of these alleles with aCL and/or anti-beta2GPI. In addition, we analysed whether HLA-DPB1 alleles contribute to the genetic predisposition to develop APS and aPL (aCL and anti-beta2GPI) in the same European cohort of patients with SLE [28]. HLA-DPB1 alleles association of anticardiolipin and anti-Beta2GPI antibodies in a large series of European patients with SLE. Lupus 2003; 12:560-3. An interesting association between anti-PT and the HLA- DQB1*0301;DQA1*03;DRB1*04 haplotype was found. It had already been shown that anti-beta2GPI antibodies are associated with these same alleles in patients with SLE. It is widely accepted that antibodies to PT and beta2GPI are two major autoantibodies responsible for LA activity, anti-PT responsible for PT-dependent LA and anti-beta2GPI antibodies for beta2GPI-dependent LA. For this reason, the observation that anti-PT and anti-beta2GPI antibodies share a common genetic background is of interest. In addition, it was found that anti-AnnV are positively associated with HLA-DRB1*08 and negatively associated with -DQA1*0102; anti-PS were positively associated with -DQB1*0301. These associations need confirmation in other studies, because they have never been reported and appear to be weak association. However, they reinforce the hypothesis that aPL production is under genetic control [31]. Arnett and coll. Analysed the association of anti-beta2GPI with HLA class II alleles in three ethnic groups, Mexican Americans (41 patients), white Americans (122 patients) and black Americans (99 patients) [32]. Authors examined rather a heterogeneous group of patients affected by primary APS, SLE and other connective tissue diseases. They found that HLA-DR4 haplotypes, especially those carrying HLA-DQ8 (DQB1*0302), are strongly associated with anti-

Table 4
Association of HLA alleles with anti-beta$_2$GPI and antiphosphatidylserine/prothrombin antibodies in SLE and PAPS.

Disease	aPL	HLA	Frequency[a]	Ethnic origin	Ref.
PAPS	anti-beta $_2$GPI	DRB1*1302- DQA1*0102-DQB1*0604/5/6/7/9	14	British Caucasoid	Caliz, 2001 [33]
SLE	anti-beta $_2$GPI	DRB1*0402/3, DQB1*0302	67/56,50	European	Galeazzi, 2000 [27]
PAPS + SLE[b]	anti-beta $_2$GPI	DQB1*0302	32	white American	Arnet, 1999 [32]
PAPS + SLE[b]	anti-beta $_2$GPI	DR4-DQB1*0302	64-64	Mexican American	Arnet, 1999 [32]
PAPS + SLE[b]	anti-beta $_2$GPI	DRB1*1302-DQB1*0604/5	36-36	black American	Arnet, 1999 [32]
PAPS	aPTS/PT[c]	DRB1*04-DQA1*0301/2-DQB1*0301/4	31-31-35	British Caucasoid	Bertolaccini, 2000 [34]
SLE	anti-beta $_2$GPI	DPB1*0301,*1901	28,67	Caucasian	Sebastiani, 2003 [28]
SLE	aPT[d]	DQB1*0301-DQA1*03-DRB1*04	19-31-29	Caucasian	Sebastiani, 2008 [31]

[a] Frequency of HLA allele/haplotype in aPL-positive patients (%).
[b] Forty-eight patients affected by PAPS, 196 patients affected by SLE, 18 patients affected by other connective tissue diseases (of whom 4 with APS).
[c] Antiphosphatidylserine/prothrombin antibodies.
[d] Antiprothrombin antibodies.

Table 5
a. The role of non MHC genes in APS susceptibility. b. APS association of thrombofilic hereditary factors.

Gene	APS association	Ref.
IRF 5	Weak	Fredi, 2010 [36]
STAT 4	Strong	Yin, 2009 [37]
12q24.12	Strong	Ochoa, 2013 [38]
PTPN22	Strong	Bottini, 2006 [39]
PTPN22	Weak	Castro-Marrero, 2001 [40]
Valine/leucine247 polymorphism of β2-glycoprotein	Strong	Hirose, 1999 [41], Lee, 2001 [42]

Factor/gene	APS association	Ref.
Factor V Leiden, G20210A prothrombin polymorphism	None	Berman, 2013 [43]
G20210A prothrombin polymorphism	single case report	Pretorius, 2014 [44]
Heterozygous F2 G20210A prothrombin polymorphism	strong	Ames, 2001 [45]
MTHFR C677T	Weak	Ames, 2001 [45]
Plasma homocystein	Strong	Ames, 2001 [45]
PROCR H1 haplotype	Strong (protective effect)	Plasin Rodriguez, 2018 [46]

beta2GPI in whites and Mexican Americans, and less so in blacks, who normally have low frequencies of these alleles. In addition, they found that the HLA-DRB1*1302;DQB1*0604/0605 haplotype was associated with anti-beta2GPI primarily in blacks.

Summarizing, the majority of the reports on SLE seem to indicate that aPL are associated with DR4, DR7, the closely linked antigen DRw53, and DQB1*0302 (Tables 3 and 4). The association of aCL with C4A or C4B alleles is less evident, and it may be of some importance only in American Blacks. In addition, it appears that the disease itself may influence the aCL-HLA associations, since no association can be found in diseases other than SLE.

A question is emerging from most recent studies: is PAPS a different entity from SLE-associated APS? There is an increased body of evidence of genetic differences between these two entities. Differences between PAPS and secondary APS have been shown in mitochondria biogenesis and function, in oxidative stress, IFN signature and various genes mediating atherosclerotic/inflammatory signaling in secondary APS patients) [35]. Future studies on the genetic factors associated with SLE and PAPS may allow a better characterisation of these entities and identify if there are specific genetic features in PAPS which predispose to evolution into SLE.

3. The role of non MHC genes in APS susceptibility

Additional genes, outside MHC, give contribution to the development of APS: they have been previously reported and discussed [1] and are summarized in Table 5.

Yomna K et al. recently genotyped 60 APS Egyptian patients and 41 controls for protein Z-79 G/A gene polymorphism using the PCR [47]. It's known that Protein Z (PZ)-dependent inhibitor (ZPI), tissue factor pathway inhibitor (TFPI) and antithrombin play the main role in regulating the function of factor X. However, ZPI is relatively inactive in the absence of its cofactor, PZ. Deficiency of ZPI or PZ has been associated with venous thrombosis and peripheral arterial disease. Protein Z deficiency is also said to contribute to pregnancy morbidities and an impairment in the ZPI/PZ inhibitor system has been reported in APS patients. The polymorphism was then analysed in relation to thrombosis and pregnancy morbidities in APS patients. They observed a higher prevalence of the A allele in the controls when compared to the APS patients ($P < .001$). G79A polymorphism, as well as its minor A allele, were not associated with an increased risk of thrombosis or pregnancy morbidities in APS. So, protein Z-79 G/A gene polymorphism may be of a protective value against thrombosis in APS.

Another marker of protection seem to be Complement Factor B (BF) that is involved in the activation of the complement system [48]. It serves as a B cell growth factor, stimulates mononuclear cell cytotoxicity, induces macrophage distribution and solubilizes immune complexes. A high serum level of BF split products has been correlated with increased disease activity in SLE. Experimental studies in lupus animals knock out for BF with SLE central nervous system involvement showed that the lack of this protein is associated with reduction in local deposition of immune complexes. This deficiency is also connected with less nephritis and vasculitis, and higher serum levels of C3, highlighting the importance of this component in the pathophysiology of SLE and as a future therapeutic target. There is a link between phenotype BF SS07 and allotype BF*S07 with IgM-aCL in SLE patients; BF*F allotype could be considered a marker of protection against the development of antiphospholipid antibodies in these patients.

4. Thrombofilic hereditary factors

Berman et al. studied the prevalence and the clinical significance of inherited thrombophilia - factor V Leiden and G20210A prothrombin polymorphism in patients with APS [49]. One hundred patients with APS (77 with primary APS and 23 with APS secondary to SLE), one hundred patients with a first episode of lower extremity deep venous thrombosis (DVT), and 200 healthy individuals as a control group were analysed. Patients and controls were tested for factor V Leiden and prothrombin G20210A gene polymorphism. Factor V Leiden variant was found in 1% of APS patients, in 3% of healthy individuals, and 16% of patients with first DVT. Prothrombin gene polymorphism was found in 6% of APS patients, in 2.5% of healthy subjects, and 13% of patients with DVT. Factor V Leiden was present in 1.3% (1/77) PAPS patients, and prothrombin gene polymorphism in 6.5% (5/77). No patient with SLE-APS had factor V Leiden, and prothrombin gene variant was present in only one patient (4.3%). Patients with prothrombin polymorphism had higher prevalence of venous thrombosis, even if the difference didn't reach statistical significance (80% vs. 47.9%, $p = .35$). There were no differences in the prevalence of recurrent thrombosis before or after APS diagnosis in patients with or without prothrombin gene polymorphism. Authors concluded that Factor V Leiden and G20210A prothrombin variant seem to play no role in either the development of APS or in the type of involved vessel, with no increased risk of re-thrombosis during follow-up.

Pretorius et al. also reported on a case of a prothrombin mutation G20210A coexisting with APS and iron overload in a 37-year-old woman who suffered from transient ischemic attacks and amaurosis fugax [50]. Authors present an ultrastructural depiction of erythrocytes, platelets, and the fibrin network, to explain the clinical manifestations of the thrombotic state seen in this patient. There was a

polymorphism in the 3′-UTR (untranslated region) of the prothrombin due to a G to A transition at nucleotide 20,210. This abnormality is associated with elevated plasma prothrombin (factor II) levels, resulting in hypercoagulability and 2–8 fold increased possibility of carriers to develop venous thrombosis.

Ames et al. evaluated the prevalence of F2 G20210A prothrombin polymorphism and methylenetetrahydrofolate reductase (MTHFR) C677T in 40 patients with primary APS and in 27 persistent carriers of antiphospholipid antibodies without underlying diseases [51]. Non APS thrombotic patients and healthy subjects served as control groups. Homocysteine was measured in all patients with antiphospholipid antibodies and in 51 subjects from the healthy control group. Heterozygous F2 G20210A was more frequent in the thrombotic group without APS (18%) than in the control (4%), aPL (11%) or APS (12%) groups, whereas homozygous MHTFR C6677T was equally distributed. After genotype sub-grouping, plasma homocysteine was higher in APS patients with homozygous MHTFR C677T compared with non-homozygous APS patients and with homozygous MTHFR C677T controls. In the APS group, mean age at first event was lower in homozygous MTHFR C677T patients than in non-homozygous patients. In the same group, homozygous MTHFR C677T patients had an increased average number of events per person than non-homozygous patients. It was also shown that heterozygous F2 G20210A contributed little to the thrombotic tendency of primary APS, whereas plasma homocysteine in aPL subjects may influence age at first event and number of events. Hyperhomocysteinemia is common in APS patients and may contribute to major severe thrombosis.

Plasin Rodriguez et al. studied the EPCR gene called PROCR, a gene coding for endothelial PC receptor, in one hundred and seventy-five patients (62 with PAPS, 30 with SLE- associated APS, 40 with SLE without antiphospholipid antibodies and 43 with SLE and antiphospholipid antibodies) and 66 healthy controls. [46]. PROCR H1 haplotype was less frequently found in APS patients with arterial thrombosis, suggesting a protective effect of PROCR H1 against arterial thrombosis in APS patients.

All these associations are showed in Table 5.

5. Post-transcription modifications of anti-beta2GPI antibodies

The hypothesis of two hits in APS pathogenesis is well known. Production of anti-beta 2GPI is the initial hit that increases the risk of thrombosis; infectious agents are the second hit provoking the typical manifestations of APS by activating toll-like receptors or complement [52]. This hypothesis doesn't explain why some people with aPL are healthy. It probably depends on the structural differences in the epitope specificity or the glycosylation of the antibodies that causes modifications of their effectors functions. It was demonstrated that there is a hyposialylation in the glycans terminate portion of anti-beta2GPI IgG determining a pro-inflammatory action.

It is known from Literature that the majority of circulating beta2GPI exists in a form containing unpaired cysteins (free thiols) which constitutes the reduced form of beta2GPI [53]. The oxidation of beta2GPI may increase the immunogenicity of the molecule through a TH1 immunological mechanism because it is able to induce maturation of dendritic cells.

It's also known that an imbalance in the activating/inhibitory receptors expressed on the surface of dentritic cells has been linked to increased susceptibility to develop autoimmune diseases underscoring their immunogenicity potential. There are recent data relative to the role of dentritic cells in systemic autoimmune pathogenesis and their use as a therapy to restore tolerance. [54]. We Know that microRNAs are small noncoding RNAs of approximately 19–25 nucleotides. Six microRNAs, involved in atherothrombosis development, were quantified in purified leukocytes from 23 APS and 64 SLE patients, and 56 healthy donors. Levels of microRNAs in neutrophils were lower in APS and SLE than in healthy donors. Gene and protein expression of microRNA biogenesis-related molecules were also reduced. Accordingly, >75% of identified microRNAs by microRNA profiling were underexpressed. In monocytes, miR124a and -125a were low, while miR-146a and miR-155 appeared elevated. Altered microRNAs' expression was linked to autoimmunity, thrombosis, early atherosclerosis, and oxidative stress in both pathologies. In vitro treatment of neutrophils, monocytes, and ECs with IgG-aPL or IgG-anti-dsDNA antibodies deregulated microRNAs expression, and decreased microRNA-related proteins. Monocyte transfections with pre-miR-124a and/or -125a caused reduction in atherothrombosis-related target molecules. In conclusion, microRNA biogenesis, significantly altered in neutrophils of APS and SLE patients, is associated to their atherothrombotic status, further modulated by specific autoantibodies [55]. These emerging epigenetic studies provide new insights into APS and autoimmune diseases. The identification of specific epigenetic dysregulation may inspire more discoveries of other uncharacterized mechanisms. Disorders of epigenetic processes, which involve DNA methylation, histone modification, non-coding RNA and nucleosome remodeling, may influence chromosomal stability and gene expression, resulting in complicated syndromes [56].

6. Conclusions

Genetic factors are important in the development of APS. Some HLA alleles carry the risk to produce aPL, and this is independent of the clinical context. In fact, we find the same associations between HLA and aPL in primary APS and in APS secondary to SLE. The association of HLA-DR4, -DR7, -DRw53, and –DQB1*0302 with aCL that has been demonstrated in primary APS, can also be found in SLE, a disease with a completely different pattern of HLA allele association (DR2, DR3, DRw52). In addition, the various aPL (aCL, LA, antibeta$_2$GPI, antiphosphatidylserine/prothrombin antibodies) show similar HLA association, again independent of the clinical context (PAPS or SLE), and across various ethnic groups. The various studies performed indicate that the HLA allele most frequently associated with APS are HLA-DRB1*04 (DR4), DRB1*07 (DR7), DRB1*1302 (DR6), DRw53, DQA1*0102, DQA1*0201,DQA1*0301, DQB1*0302 (DQ8), DQB1*0604/5/6/7/9.

Other genes, outside the MHC, give their contribution to the development of this autoimmune syndrome. Furthermore, additional genetic risk factors for thrombosis have been described in patients with APS [57–59].

Studies on primary APS indicate that it is genetically distinct from SLE. The genetic predisposition to APS can be at least in part explained with an influence of certain HLA alleles. However, these alleles could only be apparent because of their linkage disequilibrium with an as yet unidentified primarily involved HLA-locus, or they could act in co-operation with other genes, even residing outside the MHC. For this reason, the search for a more strongly associated polymorphism is actively pursued whenever new loci are identified in the HLA region. Given that APS is characterized mainly by the presence of thromboembolic events, it seems that several genetic factors are involved in its pathophysiology. The role of epigenetic mechanisms in the interaction between environment and genetic factors should also be better elucidated in APS [60,61] and in other autoimmune diseases [62–64].

Declaration of Competing Interests

None.

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