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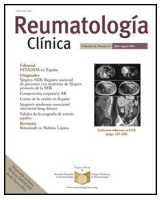

Review Article

Genetic component of autoimmune rheumatological diseases☆

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ABSTRACT

The purpose of this review is to present the main aspects of the genetic component of autoimmune rheumatic diseases, including the characteristics of the multifactorial or polygenic inheritance model, and its monogenic forms, as well as the main associated genes in both cases. The epigenetic changes involved, and the influence of the environment and sex that confer greater risk to women suffering from any of these diseases. Finally, to make known the advances that the study of omic sciences has allowed, opening the way to a new molecular classification of these diseases, aimed at personalized medicine. A review of the literature of the last 5 years, of English-language publications, in the PubMed database was performed and 28 review articles, and 19 original articles were included. Knowledge of the genetic factors involved in the aetiology of autoimmune rheumatic diseases, thanks to the availability of molecular studies, allows a better understanding of their pathophysiology and the possibility of diagnosis and treatment based on molecular markers in the future.

Componente genético de las enfermedades reumatológicas autoinmunes

Palabras clave:
Enfermedades autoinmunes
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RESUMEN

El propósito de esta revisión es presentar los principales aspectos del componente genético de las enfermedades reumatológicas autoinmunes, incluyendo las características del modelo de herencia multifactorial o poligénico y sus formas monogénicas, así como los principales genes asociados en ambos casos. De igual manera, los cambios epigenéticos implicados, además de la influencia del ambiente y el sexo para conferir mayor riesgo a las mujeres de padecer alguna de estas enfermedades. Finalmente, se comenta acerca de los avances logrados por el estudio de las ciencias ómicas, abriendo camino a una nueva clasificación molecular de estas enfermedades, y así dirigirlo a una medicina personalizada. Se revisó la literatura de los últimos 5 años de publicaciones en lengua inglesa mediante la base de

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datos PubMed, se incluyeron 28 artículos de revisión y 19 artículos originales. Se discutió el papel de los factores genéticosque participan en la etiología de las enfermedades reumatológicas autoinmunes, gracias a la disponibilidad de estudios moleculares, lo que permite mayor comprensión de la fisiopatología y la posibilidad de realizar en un futuro cercano un diagnóstico y tratamiento basado en marcadores moleculares.

Introduction

Most autoimmune rheumatic diseases are considered multifactorial or polygenic inherited, as genetic, and environmental factors are involved in their aetiology. Current advances in the study of the human genome have made it possible to identify the genome variants associated with these diseases, to create a new taxonomy to reclassify them according to their molecular characteristics and thus predict clinical manifestations to prevent and reduce their high morbidity and mortality rates[1]. The aim of this review is to present an overview of the genetic components of the main autoimmune rheumatic diseases.

Methods

We reviewed publications in indexed, English-language journals from the PubMed database, covering a period from 2015 to 2019. The keywords used for the search were autoimmune diseases, genetics, epigenetics and sex, and the review was conducted in the digital library of the Benemérita Universidad Autónoma de Puebla. Anti-plagiarism rules within the ethical foundations were considered in drafting this paper.

Seventy articles were reviewed, of which we selected 47 as presenting the most relevant data in relation to the topic; 28 were reviews, and 19 were original.

Development

Multifactorial inheritance of autoimmune diseases

Most autoimmune diseases are diseases of polygenic or multifactorial inheritance, since their aetiology involves alterations in multiple genes, with some exceptions where monogenic cases have been described. Alterations in these genes make individuals susceptible, who then develop the disease after exposure to certain environmental factors[2].

We use the term heritability to refer to the contribution of genetic factors in relation to environmental factors in a multifactorial disease, rheumatological autoimmune disease in particular. For example, a heritability of 43.9% has been determined in systemic lupus erythematosus (SLE) and of 43.5% in rheumatoid arthritis (RA), which means that approximately half the phenotypic variance is explained by genetic factors in both diseases[3,4]. Concordance between twins is another important aspect to consider. Concordance between monozygotic twins of 24% and in dizygotic twins of 2% has been reported in SLE, which confirms the importance of the genetic component, since the more genes shared, the greater the probability that two related individuals will present the same disease[5]. A family study of patients with rheumatic autoimmune diseases shows that there is familial aggregation and coaggregation when there are several cases of the same autoimmune disease in the same family, or when several family members are affected, but the autoimmune disease is different in each. In individuals with a first-degree relative with RA, a relative risk (RR) of 5.28 and 95% confidence interval (95% CI) of 4.60–6.07, a RR of 2.91 and 95% CI of 2.49–3.42 for SLE and a RR of 3.13 and 95% CI of 2.50–3.93 for primary Sjögren's syndrome (SS) have been reported[4]. However, the same individual may have more than one autoimmune disease, which is explained by the fact that the different diseases in this group share up to 69% of their risk *loci*[1].

The risk of developing an autoimmune disease also increases depending on the degree of kinship and the sex of the affected family member. The risk is reported to be higher among first-degree relatives and decreases as the degree of kinship increases, the risk will also increase if the index case is of the less frequently affected sex. Because in most autoimmune rheumatic disease females are the most frequently affected sex, if the index case is male, the risk will be higher. In the case of RA, the risk of RA in a first-degree relative of an affected individual is increased 5-fold compared to the risk of an individual in the general population, and if the affected relative with RA is female the RR is 5.21 and the 95% CI 4.47–6.08, whereas if male the RR increases to 6.12 and the 95% CI 4.90–7.65[4].

Susceptibility genes

HLA genes

The major histocompatibility complex (MHC), located at 6p21.3 region, is a group of highly polymorphic genes. A single nucleotide polymorphism (SNP) is a change in nucleotide sequence that is found in more than 1% of the population and is therefore considered a normal variant[4]. This means that the MHC genes have multiple possible different alleles, which gives each individual identity, as they possess a unique combination of these alleles. The human version of these genes is known as human leukocyte antigen (HLA) and comprises 3 main regions, class I HLA region is made up of the *HLA-A*, *HLA-B* and *HLA-C* genes; the class II HLA region contains the *HLA-DP*, *HLA-DQ* and *HLA-DR* genes; and the class III HLA region contains the complement genes *C2*, *C4A*, *C4B* (classical pathway) and *FB* (alternative pathway), as well as the genes for tumour necrosis factor (TNF), and lymphotoxin *LTA* and *LTB*, inter alia, all of which are important in the inflammatory response characteristic of innate immunity[6].

Genes of the class I HLA region are expressed on all nucleated cells and their function is to recognise and present antigens that come from within cells to the cytotoxic T $CD8^+$ T cells via a T cell receptor and its co-receptor CD8, triggering the death of the infected cell expressing the antigen. In turn, class II HLA region genes are expressed on the surface of professional antigen-presenting cells to display epitopes that come from the extracellular milieu to $CD4^+$ T cells, which requires interaction with a T cell receptor and the CD4 co-receptor, thus triggering cytokine release, macrophage, and B-lymphocyte activation, the latter having the capacity to produce antibodies[7].

Variants in MHC genes form the main component of heritability in autoimmune diseases. There are risk alleles mainly at the level of the class II HLA genes. Table 1 shows the main risk alleles for various autoimmune diseases.

Other non-HLA genes

The availability of molecular studies such as genome wide association studies (GWAS), which allow analysis of up to one million SNPs in disease affected and unaffected individuals to compare the

Table 1
MHC variants associated with autoimmune diseases.

	HLA-I			HLA-II				HLA-III
	HLA-A	HLA-B	HLA-C	HLA-DPB1	HLA-DQA1	HLA-DQB1	HLA-DRB1	
RA		*08:01 *40:02		*02:01 *02:02 *04:01 *04:02 *05:01 *16:01 *19:01 *23:01	*03:01	*03:02	*01:01 *01:02 *04:01 *04:02 *04:03 *04:04 *04:05 *04:07 *04:08 *09:01 *10:01 *14:02 *16:01	
SLE					*01:02	*02:01 *03:03 *04:02 *06:02 *08:01	*03:01 *03:04 *07:01 *08:01 *08:02 *08:03 *09:01 *15:01 *15:02 *16:02	*TNXB, SKIV2L, NOTCH4*
SSc				*03:01 *13:01	*05:01	*02:01 *03:01 *06:02	*08:04, *11:04 *15:02 *16:02	
SS	*01:01	*08:01	*07:01	*01:01	*01:01 *01:03 *03:01 *05:01	*02:01 *04:01 *06:01	*03:01 *04:05 *05:01 *08:03 *15:01 *80:32	
AS	*02:01	*27:02 *27:05					*01:03	
MS	*02:01	*37					*15:01	*MICB-LST1*
DM				*17				

AS: ankylosing spondylitis; DM: dermatomyositis; MS: multiple sclerosis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; SSc: systemic sclerosis.
Source: taken from Barturen et al.[1] and Matzaraki et al.[7].

allele frequency in both groups and thus identify risk alleles, has made it possible to identify both HLA and non-HLA genes associated with different autoimmune diseases. Most of these genes are related to inflammatory response, B and T cell function, phagocytosis, apoptosis, and gamma interferon production[8].

To date, GWAS have been performed for the most common autoimmune rheumatic diseases, reporting approximately 300 risk loci*. RA and SLE have the highest number of associated loci, probably because a greater number of GWAS have been performed in these diseases[1]. We describe below some genes that have shown variants or risk alleles for the presence of different autoimmune diseases.

Interferon regulatory factor 5 (IRF5): located in region 7q32.1, it has been associated with SLE and RA; it encodes for a transcription factor called interferon regulatory factor 5, whose function is to control the expression of proinflammatory cytokines. Expression of the gene is increased in individuals with the risk variants. It is strongly associated with SLE in Latin American populations[9].

Interferon regulatory factor 7 (IRF7): encoded in region 11p15.5, it is associated with SLE and systemic sclerosis (SS) and encodes a transcription factor for type I interferon (IFN-I)[10].

Protein tyrosine phosphatase, non-receptor-type 22 (PTPN22): encoded in region 1p13. 2, it is associated with SLE, RA and SSc; it encodes an intracellular lymphoid-specific protein tyrosine phosphatase, which controls signal transduction in T and B cells. Risk alleles generate higher interferon alpha (IFN-α) and lower TNF levels, and have been associated with the production of double-stranded anti-DNA antibodies[11].

Signal transducer and activator of transcription (STAT4): encoded in region 2q32.2–q32.3, it is associated with SLE, RA, SSc, multiple sclerosis (MS) and SS. It encodes a signal transducer protein and transcription factor that can be activated by interleukins 12 and 23. It also stimulates IFN- γ production and is critical in the IFN-I signalling pathway; risk variants increase the response to IFN-α signalling[12].

B-cell scaffold protein with ankyrin repeats 1 (BANK1): encoded in region 4q24, it is associated with SLE, encodes a B-cell scaffold protein with ankyrin repeats 1, reduces IFN-I production by B-cells. Risk variants alter this suppression, increasing the function of this cell type[13].

B lymphocytekinase (BLK): encoded in region 8p23.1 region, it is associated with RA, SLE, SSc and SS. It encodes a protein tyrosine kinase, which is expressed in B lymphocytes, its function is signal transduction specific to its lineage[14].

Fc gamma receptor (FCGR): encoded in region 1q23.3, it makes up a family of receptors that bind to the Fc portion of immunoglobulin G (IgG), classified into high-affinity (FCGR1A, FCGR1B and FCGR1C) and low-affinity (*FCGR2A, FCGR2B, FCGR2C, FCGR3A* and *FCGR3B*) receptors. FCGR2B is the only low-affinity receptor with inhibitory function, as the rest activate the receptor SNPs in the FCGR2B gene. They have been reported as a risk factor for SLE and RA, as well as useful for predicting response to monoclonal antibody therapy such as rituximab[15]. The *FCGR2C, FCGR3A,* and *FCGR3B* gene sequences have copy number variations (CNV), which confer susceptibility to both deletions and duplications, and deletions in *FCGR3B* have been reported to increase the risk of RA and SLE[16].

Neutrophil cytosolic factor (NCF): it encodes for a component of the NADPH oxidase complex. Variants in the *NCF2* (1q25.3) and *NCF1* (7q11.23) genes decrease their function by decreasing reactive oxygen species (ROS), which regulate macrophage activity to prevent inflammation, and have therefore been associated with RA, SLE, and MS[9,17].

The increase in levels of IFN-I and genes associated with its expression is a pathophysiological mechanism common to several autoimmune rheumatic diseases that has been termed the interferon signal and is observed in diseases associated with the presence of antinuclear antibodies, such as SLE, SS, SSc, dermatomyositis (DM), and mixed connective tissue disease (MCTD)[18].

Epigenetic factors

The genes described above have shown variants at the nucleotide sequence level, increasing, or decreasing the function of the genes. However, the expression of a gene can be modified by changes that do not affect the nucleotide sequence, but occur on a base or histones of chromatin, and by the action of non-coding RNAs such as micro RNAs (miRNAs) and long non-coding RNAs. These changes are known as epigenetic and can be both reversible and heritable; epigenetic modifications have been implicated in enhanced immune response, generated through environmental factors, contributing to the pathophysiology of autoimmune rheumatic diseases[19].

DNA methylation is the addition of a methyl group on the nitrogenous base cytosine through DNA methyltransferase (DNMT) enzymes. These cytosines are located before a guanine in the same DNA chain, there are regions of more than 300 base pairs that have a high density of these sequences, which is why they are called CpG

islands, located in the promoter region of genes. However, cytosines that are not part of a CpG dinucleotide can also be methylated. There are several DNMTs, such as DNMT2, DNMT3A, DNMT3B, and DNMT3L, responsible for *de novo* methylation, while DNMT1 maintains pre-existing methylation[20].

Histones can undergo various changes, including acetylation, methylation, ubiquitination, phosphorylation, and sumoylation. In the process of acetylation, histone acetyltransferases transfer an acetyl group to the amino acid lysine, thus activating the expression of the gene in question, while histone deacetylases remove the acetyl group and result in inactivation of the gene. Histones, on the other hand, can be methylated or demethylated, reactions catalysed by histone methyltransferases and histone demethylases, respectively. The amino acids of histones that accept these marks are the lysine and arginine of histones H3 and H4, with different effects on gene expression, for example, when 3 methyl groups are added to histone 3 lysine 4 (H3K4me3), gene expression is increased by increasing its transcription; conversely, if 2 methyl groups are added to lysine 9 of histone 3 (H3K9me2), transcription of the gene is inhibited[21].

Non-coding RNAs also play a significant role in the regulation of gene expression. Depending on the number of nucleotides forming them they are classified as miRNAs if they have less than 200 nucleotides, generally 21–25, or long non-coding RNAs with 200 or more nucleotides. In general, miRNAs inhibit the transcription of target genes or decrease the stability of messenger RNA (mRNA), preventing its translation[22].

Epigenetic changes in systemic lupus erythematosus

The main epigenetic changes reported in SLE patients include hypomethylation in promoter regions of autoimmune-associated genes expressed in $CD4^+$ T cells, resulting in their overexpression. Hypomethylation is generated by inhibition of DNMT1, due to several mechanisms, one being the action of miRNAs, including miR-148a and miR-126, both of which are overexpressed in $CD4^+$ T cells in SLE patients[22].

Other genes in which hypomethylation has been observed are related to the overproduction of interferon, including *KIR* in T cells. Overexpression of IL-4 and IL-6 is also associated with hypomethylation of CpG islands in SLE patients; several regulatory enzymes of histone acetylation and deacetylation are overexpressed in $CD4^+$ T cells from patients with active SLE, including *Sirtuin 1* (SIRT1), a type of histone deacetylase. Overexpression of cytokine genes such as TNF-α and IL-17 in SLE are associated with increased histone acetylation. The level of expression of miR-146a is decreased in peripheral blood mononuclear cells from SLE patients and correlates inversely with disease activity. The expression of miR-15a in regulatory B cells shows a positive correlation with serum levels of anti-double-stranded DNA (anti-dsDNA) autoantibodies in a mouse model of lupus, whereas miR-155 correlates significantly with proteinuria and disease activity in SLE[23].

Epigenetic changes in rheumatoid arthritis

In RA, epigenetic modifications have been documented at the level of the synovial fibroblasts, which show hypomethylation secondary to low DNMT expression. However, the gene for CD40L is overexpressed in $CD4^+$ T cells, synovial fibroblasts and synovial tissue show overexpression of miR-155 and miR146, respectively, and high levels of IL-6, all of which are associated with overexpression of miR-203 in the synovial fibroblasts[22]. High levels of miR146 associated with increased proinflammatory cytokines and TNF-α have been reported in peripheral blood mononuclear cells, while overexpression of miR155 is associated with elevated C-reactive protein, TNF-α, IL1, erythrocyte sedimentation rate, and disease activity[24].

Epigenetic changes in systemic sclerosis

In SSc there are low levels of DNA methylation at the level of *CD40L, CD11a* and *CD70* gene promoters, which results in their overexpression. However, hypermethylation in the promoter region of the *Forkhead box P3* (*FOXP3) gene* decreases proliferation of regulatory T cells and leads to elevated levels of JMJD3 in $CD4^+$ T cells, which is associated with decreased methylation in H3K27[25].

Epigenetic changes in Sjögren's syndrome

In SS, decreased methylation has been reported in salivary gland epithelial cells and $CD4^+$ T cells; in addition to the participation of multiple miRNA, including miR146 and miR155, that have been found to be overexpressed in T lymphocytes and salivary gland epithelial cells of SS patients[26,27].

Monogenic inheritance in autoimmune rheumatological diseases

Cases of autoimmune rheumatological diseases, such as SLE and RA, have been described where the aetiology does not result from the association of variants in multiple genes, but instead is due to mutations in a single gene. A mutation, unlike a polymorphism, occurs in less than 1% of the population and is a change in nucleotide sequence that usually affects phenotype or function and causes disease; they are mostly Mendelian inherited, i.e., autosomal dominant, autosomal recessive or X-chromosome linked[28].

The main genes capable of causing monogenic SLE are:

Deoxyribonuclease I-like 3 (DNASE1L3): encoded in region 3p14.3, homozygous mutations in this gene are responsible for early-onset autosomal recessive SLE, which presents with anti-dsDNA antibodies and low complement. The gene encodes an endonuclease, necessary for chromatin degradation during apoptosis, and therefore chromatin microparticles are targets of autoantibodies when deficient in this enzyme[2,29].

Three prime repair exonuclease 1 (TREX1): encoded in region 3p21.31, heterozygous mutations cause familial chilblain lupus, with autosomal dominant inheritance. It encodes an exonuclease, which degrades short DNA fragments, and therefore, if there is a deficiency of this enzyme secondary to the mutation, these DNA fragments accumulate and stimulate the production of IFN I and thus autoimmunity[30].

SAM and HD domain containing protein 1 (SAMHD1): encoded in region 20q11.23, it encodes a hydrolase that degrades deoxynucleotide triphosphates at the intracellular level. Its deficiency leads to IFN I production in response to the accumulation of undegraded DNA, also causing autosomal dominant familial chilblain lupus[31].

Other genes associated with monogenic SLE are involved in the complement pathway (*C1Q, C2*, *C3* and *C4*), apoptosis, self-tolerance (*FAS*, *FASLG* and *PRKCD*), and degradation of nucleic acid (*RNASEH2A*, *RNASEH2B* and *RNASEH2C*)[32].

Influence of environmental factors on the genome

Environmental factors that favour the expression of autoimmune rheumatological diseases in a genetically predisposed individual act at various levels, many directly on the genome, mainly by inducing hypomethylation. For example, ultraviolet B (UVB) radiation, associated with SLE, induces decreased activity of DNMTs causing hypomethylation of peripheral blood mononuclear cells, especially $CD4^+$ T cells, with increased production of IL1 and TNF-α. Elevated urinary levels of cadmium, an element present in cigarette smoke and diet, were found to be up to 7 times

higher (7.4 ug/l) compared to those not exposed (1.0 g/l) ($P < .001$) and were associated with hypomethylation of genes encoding for MGMT (0-6-methylguanine DNA methyltransferase). Zinc and selenium are components of antioxidant enzymes, lower levels of which were found ($P = .001$) in a study in SLE patients compared to healthy controls; zinc in particular increases DNA methylation, and therefore its deficiency contributes to the hypomethylation that is characteristic in this group of patients. Similarly, silica favours the development of SLE, RA and scleroderma by decreasing DNA methylation; Epstein-Barr virus infection is a further example, also associated with hypomethylation of CpG islands[33,34].

Influence of sex

Autoimmune rheumatological diseases are more frequent in women, which has been related to hormonal factors and to the dosage of genes present on the sex chromosomes. The female to male ratio in SLE is 9:1[35]; in RA it is 4:1 and 2:1 under the age of 50 and over the age of 60, respectively[36]; for antiphospholipid syndrome (APS) it has been reported to be 5:1 in secondary presentation, associated with another autoimmune rheumatological disease, and 3.5:1 in primary presentation[37]; in primary SS it has been reported as 14:1 (frequency [female] = .93, 95% CI .89–.96)[38]; and in SSc the ratio is 3–4:1[39].

X chromosome

The sex chromosome component in females is XX, whereas it is XY in males, which means there is a double dosage of X chromosome genes in the female sex. To compensate for this excess dosage in females, one of the 2 X chromosomes is randomly inactivated in embryonic development. However, approximately 15%–25% of the genes escape X inactivation, which means that they will be expressed in double dosages, while those that are inactivated will only be expressed in one dosage, that of the allele present on the active X chromosome[40].

Several immune response-associated genes are found on the X chromosome, including Interleukin 9 receptor (IL9R), Interleukin 2 receptor gamma (IL2RG), which code for the interleukin 9 and 2 receptors, respectively[41]. Toll-like receptor 7 (TLR7) escapes X inactivation and together with toll-like receptor 8 (TLR8) is associated with increased IFN-α production in women with SLE. C-X-C motif chemokine receptor 3 (CXCR3) and CD40 ligand (CD40LG) are hypomethylated and overexpressed on $CD4^+$ T cells, whereas Forkhead box p3 (FOXP3) is overexpressed on $CD8^+$ T cells from SLE patients[42].

However, there is evidence of the influence of the number of X chromosomes as a factor of susceptibility to autoimmune rheumatological diseases that predominate in the female sex. The low frequency of these diseases in patients with Turner syndrome, who have only one X chromosome (45,X) and an increased risk for males with a diagnosis of Klinefelter syndrome, who have one or more extra X sex chromosomes (47,XXY; 48,XXXY; 49,XXXXY), the risk being higher the greater the number of extra X chromosomes[43].

The prevalence for SLE in males with Klinefelter syndrome has been reported to be up to 14 times higher compared to males with a 46,XY karyotype, and cases of males with SLE with a 46,XX karyotype have even been reported. It is worth mentioning that although patients with Turner syndrome are at lower risk because they have only one X chromosome, there are exceptions, such as patients with 45,X/46,XX/47,XXX mosaic, who have cells with 2 and even 3 X chromosomes, conferring higher risk for SLE and SS, or women with karyotype 47,XXXX, who have 2.5 times higher risk for SLE compared to women with karyotype 46,XX[44,45].

Patients with Turner syndrome due to X long arm isochromosome (46,X,i(X)(q10)) are at increased risk of autoimmune diseases as they have a normal X chromosome plus another X chromosome that lacks short arms and only consists of 2 long arms, meaning that there is triple dosage of the genes present on the q arm of the X chromosome[46].

Sex hormones

Both endogenous (oestrogens, progesterone, androgens, prolactin) and exogenous (oral contraceptives and hormone replacement therapy) sex hormones modify the immune system response. Oestrogens are considered to have a pro-inflammatory function and androgens have an anti-inflammatory function, making women more susceptible to autoimmune rheumatological diseases. Cells of the immune system have receptors for oestrogens and androgens which in turn activate transcription factors. In the case of oestrogens, they induce overexpression of IRF5, increasing levels of IFN1 and increase the expression of intracellular TLRs in peripheral blood mononuclear cells (PBMCs). Testosterone inhibits lymphocyte proliferation and natural killer cell activity; progesterone inhibits Th1 and Th17 differentiation and stimulates the Th2 response; and prolactin increases the survival of autoreactive B cells[36,41].

Sex hormone levels vary between life stages, which influences the age of onset or severity of disease. SLE mainly affects women of reproductive age and pregnancy may increase disease activity by increasing Th2 response and autoantibody production; oral contraceptive use, hormone replacement therapy and early menarche are considered risk factors for SLE[34]. In contrast, in RA, a peak incidence has been observed in the postmenopausal stage, mainly in the fifth decade of life, whereas premature menopause, before the age of 45 years, is considered a risk factor for RA. Decreased disease activity has been observed with pregnancy, and increased incidence of RA in the first 3 months postpartum (OR: 5.6; 95% CI: 1.8–17.6), associated with increased prolactin and decreased progesterone. An association has also been found between oral contraceptive use and the presence of positive anti-citrullinated protein antibodies (ACPA) (OR: 1.7; 95% CI: 1–1–2–6) and increased conversion of androgens to oestrogens by aromatase, activated by inflammatory mediators[36].

Future perspectives

Advances in molecular techniques and bioinformatics are making it possible to obtain, capture and analyse a large amount of useful data for the generation of biomarkers to stratify patients into groups and design clinical trials to provide personalised treatment for patients suffering from one of these autoimmune rheumatological diseases. The PRECISESADS project (Molecular Reclassification to Find Clinically Useful Biomarkers for Systemic Autoimmune Diseases) is a European Union project that began in 2014 and aimed to reclassify the different systemic autoimmune diseases based on their molecular characteristics through genomic studies, mainly using GWAS; transcriptomics, through RNA sequencing in peripheral blood and specific tissues; epigenomics through methylation analysis, and proteomics through mass spectrometry, liquid chromatography, measurement of cytokines and autoantibodies[1].

This is evidenced by the studies conducted by Alarcón-Riquelme et al., who formed groups of SLE patients based on the percentage of neutrophils and lymphocytes that were related to disease activity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). In a subsequent exploratory analysis using transcriptomics and the CLUE platform, which enables the analysis of drug-induced gene expression signals, they evaluated the ability of several drugs to reverse these signals and observed that mTOR inhibitors reversed the signal in the lymphocyte-directed subgroup, while TNF inhibitors reversed the signal in the neutrophil

subgroup. Experimental pharmacodynamic studies are required to corroborate the effectiveness of these drugs in each group. The results could direct therapeutic decisions to provide each patient with personalised treatment[47].

Conclusions

Knowledge of the genetic factors involved in the aetiology of autoimmune rheumatological diseases enables a better understanding of the pathophysiology of each disease. In the case of polygenic or multifactorial presentations, HLA class II genes contribute to the heritability of the disease. However, polymorphisms in other non-HLA genes such as *IRF5*, *IRF7*, *PTPN22*, *STAT4*, *BANK1*, *BLK*, *FCGR*, and *NCF* also contribute significantly, through increased interferon expression. In the case of SLE, monogenic forms have been described with autosomal dominant Mendelian inheritance mainly due to mutations in the TREX1 and SAMHD1 genes; and an autosomal recessive form due to mutations in the DNASE1LB gene.

DNA hypomethylation is the main mechanism involved in relation to epigenetic alterations, which confers overexpression of genes related to the immune response. The sex chromosome component is considered another risk factor for females, since 15%–25% of genes escape X inactivation, which represents excess gene dosage of several loci associated with autoimmunity compared to males, including TLR7, which increases IFN-α levels, as well as susceptibility conferred by the hormone component, mainly oestrogens, which in general have a pro-inflammatory effect. Advances in molecular techniques and bioinformatics provide a better understanding of the physiopathology and management of a large amount of data, resulting in molecular classification of these diseases and thus in specific treatment for each patient.

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Conflict of interests

The authors have no conflict of interests to declare.

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