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To Review the Key Aspects of Pathogenesis of Systemic Lupus Erythematous Autoimmune Diseases.

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ABSTRACT

Over the past few years, remarkable advancements have been made in understanding how nearly The expression of systemic autoimmunity is influenced by every facet of the immune system. Within In parallel, research has clarified the processes that lead to organ damage and inflammation. Novel strategies that tackle the complex interplay among genetic variations,Sex, the environment, and epigenetic processes have the potential to shed light on the various pathways leading to systemic lupus erythematosus. Every patient isanticipated topossesses a distinct "interactome" that will determine the course of treatment.[1]A. Understanding the molecular mechanisms underlying the pathophysiology of autoimmune illnesses is essential for the development of effective, target-directed, and well-tolerated therapies. In this review, we highlight recent studies that emphasise the importance of epigenetic modifications in autoimmune disorders, with a focus on systematic lupus erythrematosus[2]

Introduction

Autoantibodies are a characteristic of the autoimmune rheumatic disease known as systemic lupus erythematosus (SLE). Although SLE can affect almost any organ or system, it typically skin, joints, kidneys, lungs, central nervous system, and haematopoietic system.[3]The first example of a multi-organ autoimmune disease is systemic lupus erythematosus (SLE). The pathogenesis of SLE is multifactorial, involving both innate and adaptive immune system abnormalities as well as genetic and environmental factors, as is the case with a number of other autoimmune disorders. Each of these elements plays a part in the development, maintenance, and advancement of the illness.The pathophysiology of SLE is complex, involving both innate and adaptive immune system disorders as well as hereditary and environmental variables. Each of these elements has a part in the development, maintenance, and advancement of the illness. It is commonly acknowledged that SLE develops in stages over a period of time that may include years.

The following actions have been recommended

i) genetic predisposition,

ii) gender as an additional risk factor

iii) environmental stimuli that initiate immune responses

iv) autoantibody appearance

v) autoantibody regulation, T and B cell failure with the development of the clinical disease

vi) oxidative damage and chronic inflammation as causes of tissue damage in uencing morbidity[4]

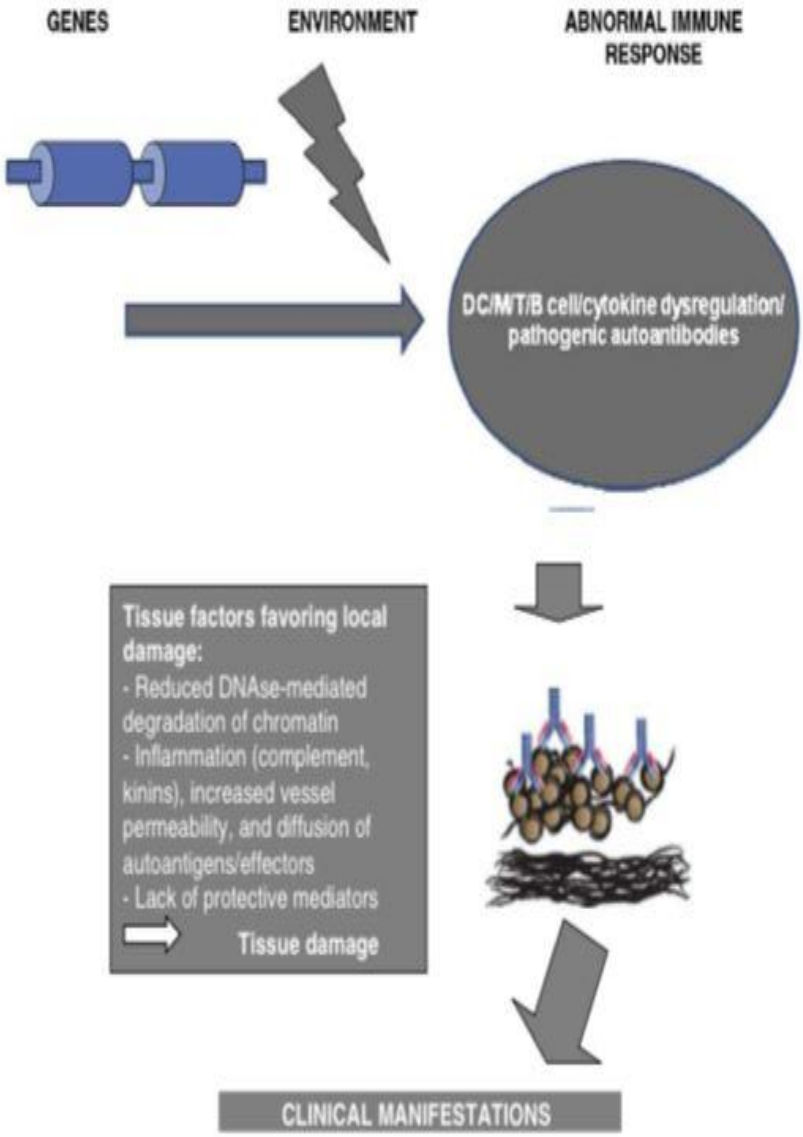
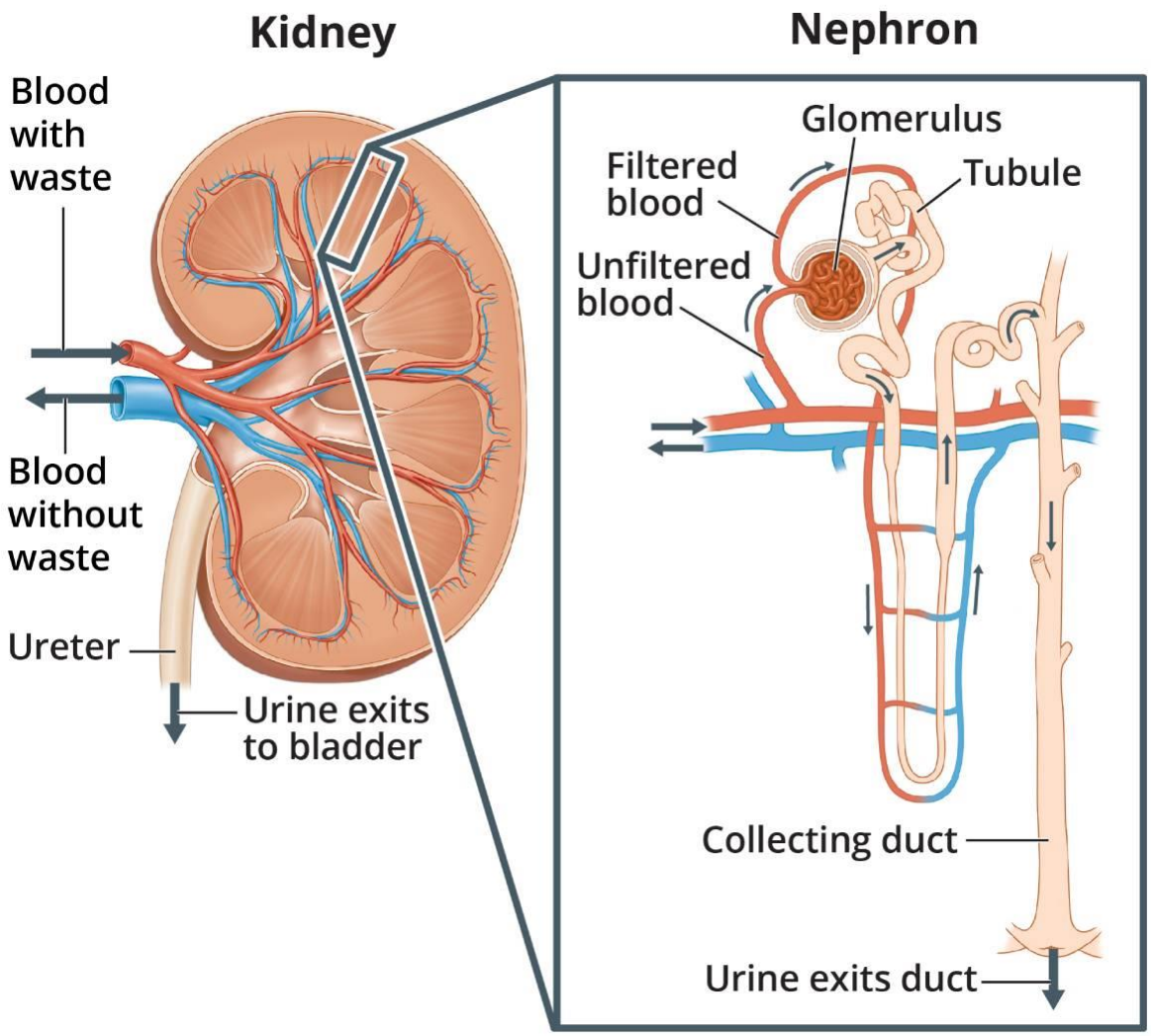
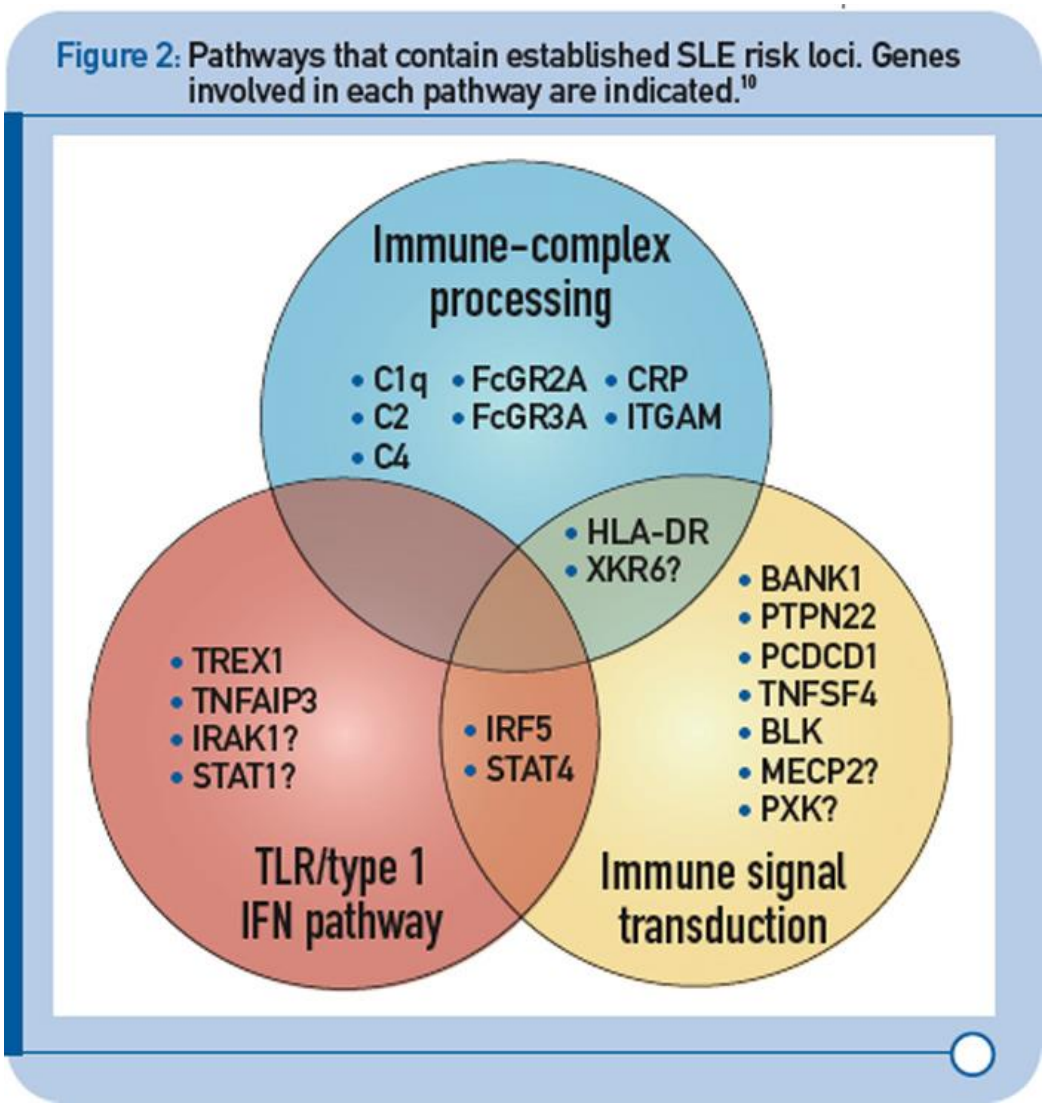


Fig. 1. Pathogenic steps in SLE.



GENETIC SUSCEPTIBILITY OF SLE

Over 90 SLE susceptibility loci have been discovered in the past ten years by a genome-wide association study (GWAS), including numerous single nucleotide Over 90 SLE susceptibility loci have been identified in the past ten years by a genome-wide association study (GWAS), with numerous single nucleotide polymorphisms functioning in concert. There have also been reports of uncommon monogenic types of SLE [9]. Of the 730 polymorphisms linked to SLE, 21 result in changes to amino acids, 484 leave gene coding areas, and the remaining variations are intergenic, indicating a substantial impact on gene regulation rather than protein sequence. The reviewed SLE risk genes are arranged according to important disease pathways. However, because of their many roles, these genes may contribute to the pathophysiology of disease through[5]Genetic polymorphisms are inherited changes in the DNA sequence that affect gene expression and function, potentially determining a person's vulnerability to disease. More than 20 loci harbouring lupus-associated genes and their chromosomal locations are reported in recent reviews of lupus genetics [6]



ENVIROMENTAL FACTOR OF SLE

Numerous environmental factors, including chemicals, viruses, and cigarette smoke, have been shown to cause oxidative stress. Oxidative stress has also been shown to inhibit and/or lower Dnmt1 levels, which in turn lowers DNA methylation in CD4+ T-cells and increases autoimmunity.

ULTRAVIOLET LIGHT

In SLE patients, ultraviolet (UV) radiation, specifically UV-A1 and UV-B, can cause illness flare-ups and initiate the start of SLE. Additionally, it seems that UV light's capacity to trigger SLE or lupus flare-ups is dose dependant. It is clear that UV-B causes keratinocytes and other skin cells to undergo apoptosis. This process releases a significant quantity of autoantigens and pro-inflammatory cytokines into the bloodstream, which causes autoimmune-related systemic inflammation. Keratinocytes have been shown to undergo typical cascade-dependent apoptosis in response to low levels of UV-B, although DNA fragmentation, an increase in IL-1α production, and keratinocyte necrosis have been reported in response to moderate and high amounts.[7]

VITAMIN DEFICIENCY

Hypovitaminosis D is common in the general population. Many studies that have been conducted to show the association between vitamin D deficiency and systemic lupus erythematosus (SLE) reveal that deficiencies in vitamin D are common in this group of patients. Our aim was to study the relationship between 25(OH)D and disease activity in patients with SLE.[8]

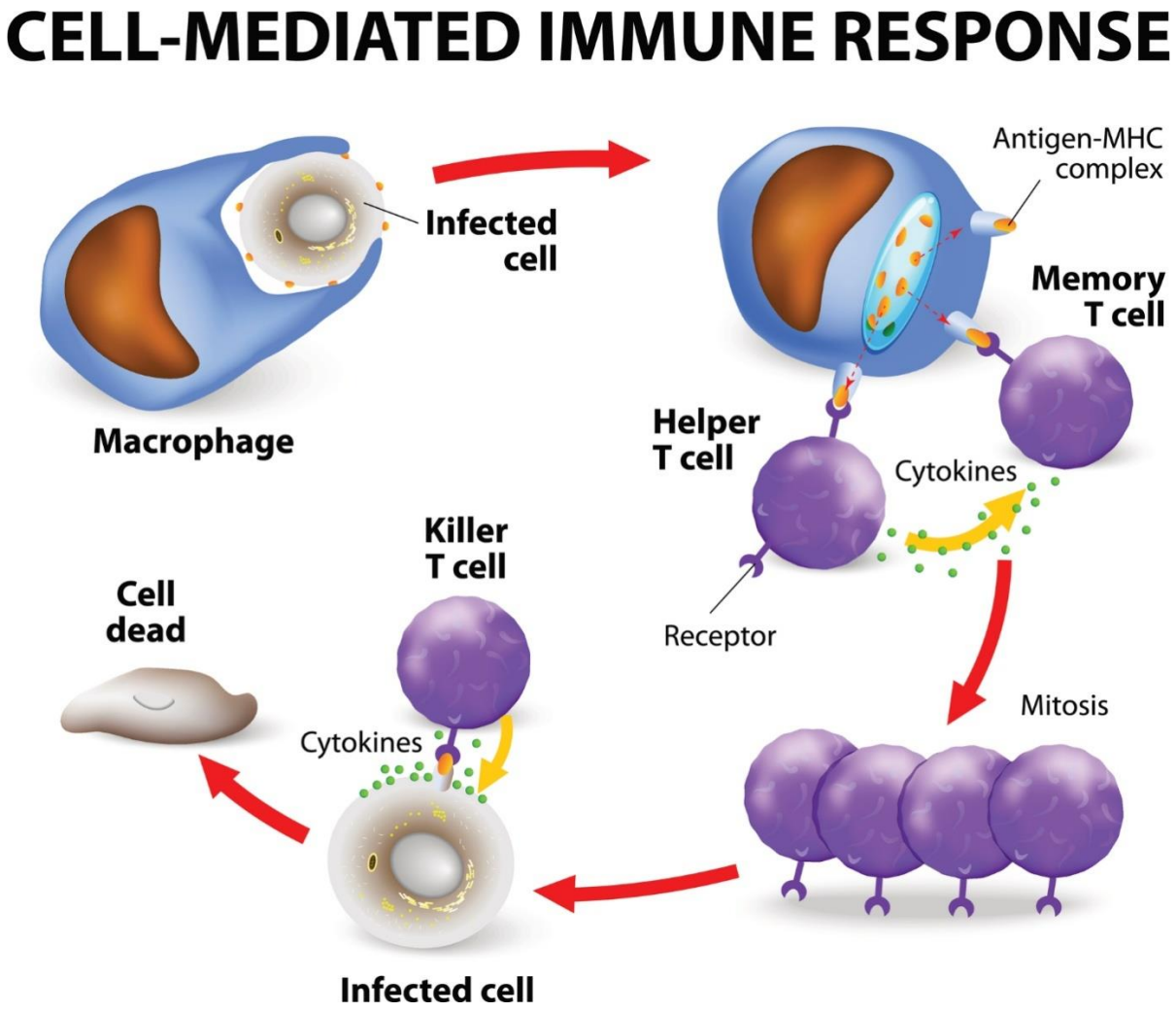
SMOKINGThe classification of SLE subtypes by autoantibody has been a significant advancement in the research of environmental exposures and SLE risk. SLE is a diverse illness marked by the presence of autoantibodies as well as clinical symptoms. Anti-dsDNA risk was closely linked to smoking. The risk of anti-dsDNA+ SLE increased by 60% in those who had smoked for more than ten pack-years and nearly doubled in current smokers. Perhaps because the development of these antibodies is highly specific for SLE, a more recent study did not find correlations between cigarette smoking and anti-dsDNA antibodies among healthy individuals and those at increased risk for developing SLE due to a strong family history [9]

IMMUNE DYSNFUNCTION AND SLE

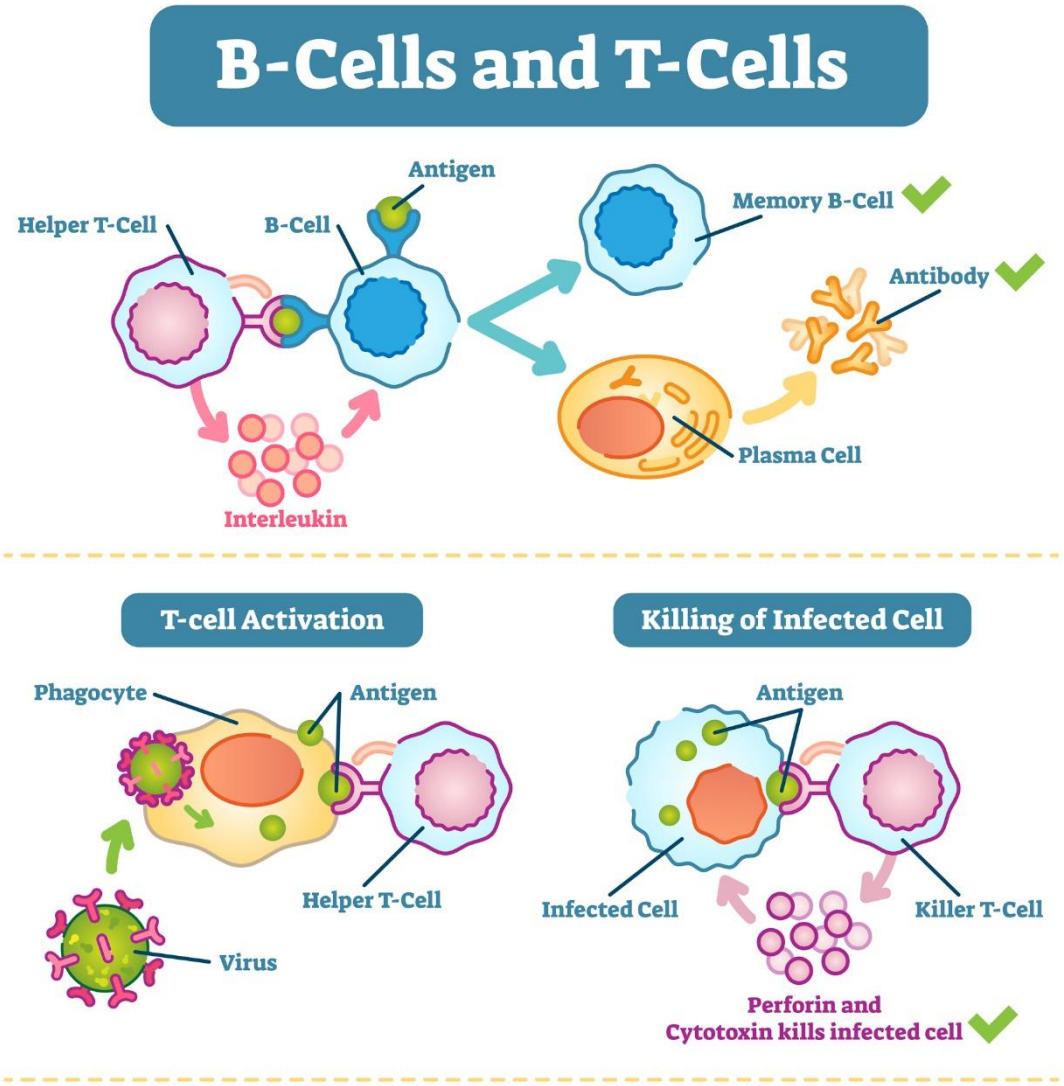
Inflammation and blood vessel abnormalities, such as band or occlusive vasculopathy, vasculitis, and immune complex deposition, are the fundamental pathological characteristics of SLE. The kidney has the most well-characterized organ pathophysiology.

Renal biopsies from SLE patients show mesangial cell growth, inflammation, abnormalities of the basement membrane, and immune complex deposition, which includes immunoglobulins and complement components, according to light and immunofluorescence microscopy. These deposits are visible under electron microscope coin the mesangium and on the basement membrane's subendothelial or subepithelial surface. Although clinical signs are occasionally mild, organ systems affected by SLE typically exhibit non-specific inflammation or vascular abnormalities. Patients with long-term SL may exhibit atherosclerosis and tissue damage brought on by hypertension, corticosteroids, and other medications.[10]

BETA AND T CELL

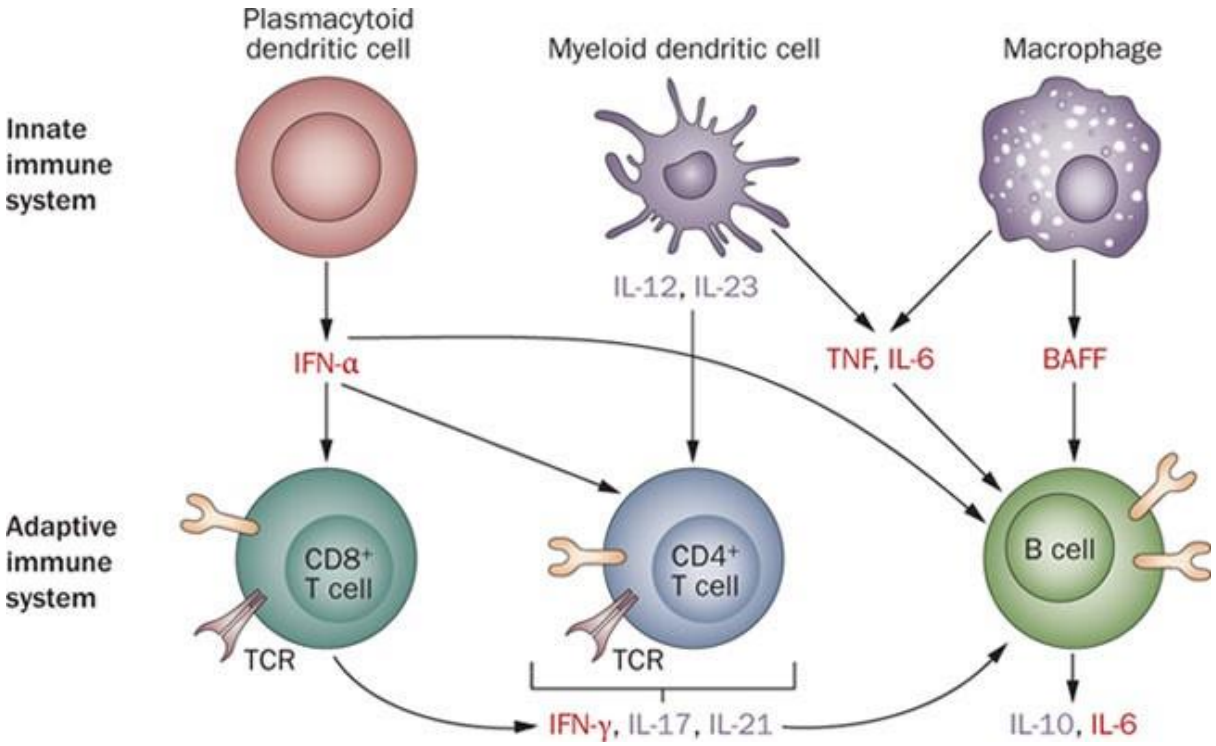


SLE has been described as a mosaic of anomalies due to the disease's multifaceted appearance in human patients. Considerable research has long been focused on disruptions in the T lymphocyte compartment due to the widespread infiltration of T cells at sites of inflammation, such as the skin and kidneys, the IgG isotype of auto-Ab, and the presence of somatic mutation in the variable genes of these Ab. Although the participation of B lymphocytes was acknowledged, it was limited to the production of auto-Ab under instruction from self-reactive T lymphocytes. SLE was frequently defined as a disease of faulty T cell censoring. Numerous recent investigations into the biology of B lymphocytesHowever, these cells have attracted a lot of attention since they contain a number of traits that could lead to the development of monorgan-specific autoimmune disease, in addition to their capacity to produce and release Ab[11]



CYTOKINESIS OF SLE

Although it is commonly known that SLE patients have impaired IL-2 production, little is known about the underlying process. IL2 transcription is modulated by a number of transcription factors. However, an imbalance between cyclic AMP responsive element-binding protein (CREB) and -modulator (CREM) is especially relevant in SLE patients. In the IL2 promoter, CREB and CREM vie for a binding site. While CREM is a negative regulator, CREB has a positive influence. CREB occupies the binding site in resting T cells and is phosphorylated during activation, which causes the production of IL2. CREB levels are decreased and CREM levels are abnormally high in SLE patients (Solomou and others 2001).[12]

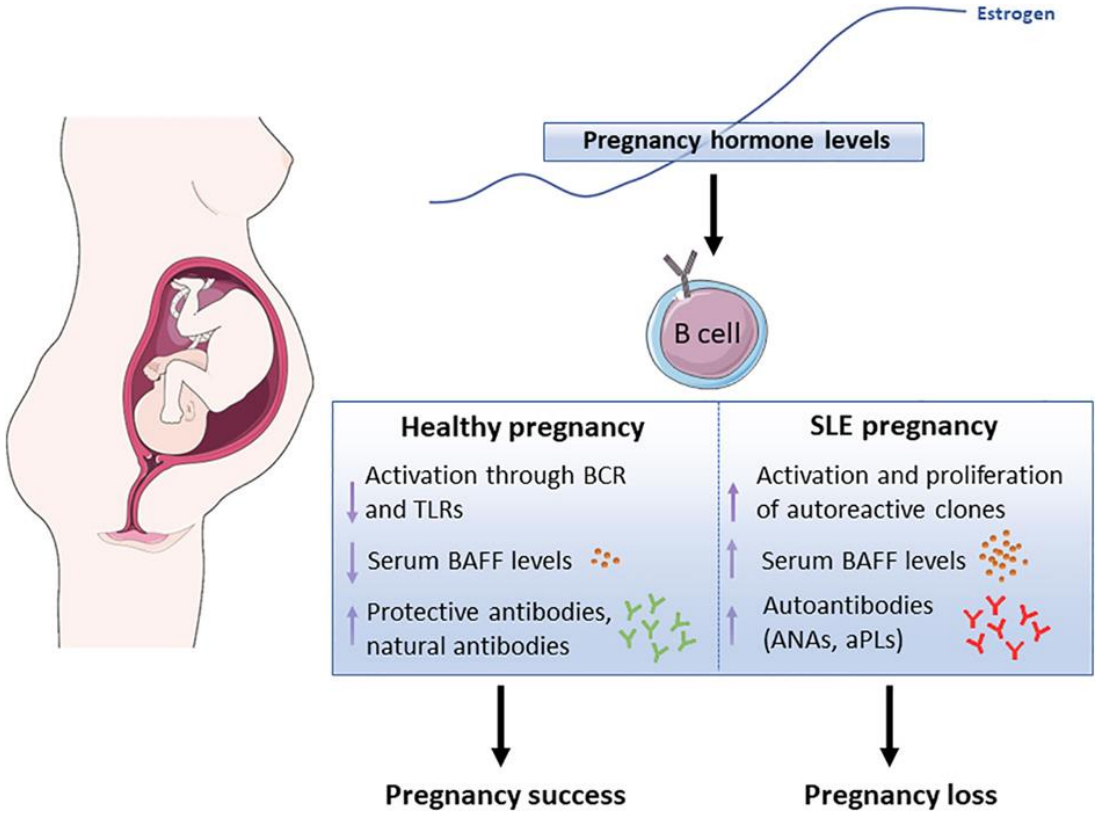


HORMONAL FACTOR OF SLE

The acute and chronic autoimmune inflammatory illness known as systemic lupus erythematosus (SLE) is more common in women and peaks throughout the reproductive years.The higher female-to-male ratio of SLE patients indicates that sex variables influence the predisposition and development of the disease; see for further information. The female predisposition to SLE and other illnesses may be caused by a variety of sex-related variables. According to a recent assessment, there are genetic (X and Y chromosome-mediated), endocrinologic, metabolic, and environmental biologic variations between the sexes. However, the 1944 discovery of SLE flare-ups linked to menstrual cyclicity sparked a period of research into the possible roles of prolactin, oestrogens, and androgens in the onset of SLE. The idea that sex hormones affect the prevalence and severity of disease in SLE patients is supported by substantial evidence of the immunoregulatory effects of 17-estradiol (oestradiol), testosterone, progesterone, and prolactin[13].It is debatable if pregnant women are more likely non-pregnant women to experience lupus flare-ups. Since the 1960s,number of retrospective and uncontrolled studies have documented SLE aggrIt is debatable if pregnant women are more likely than non-pregnant women to experience lupus flare-ups. Since the 1960s, a number of retrospective and uncontrolled studies have documented

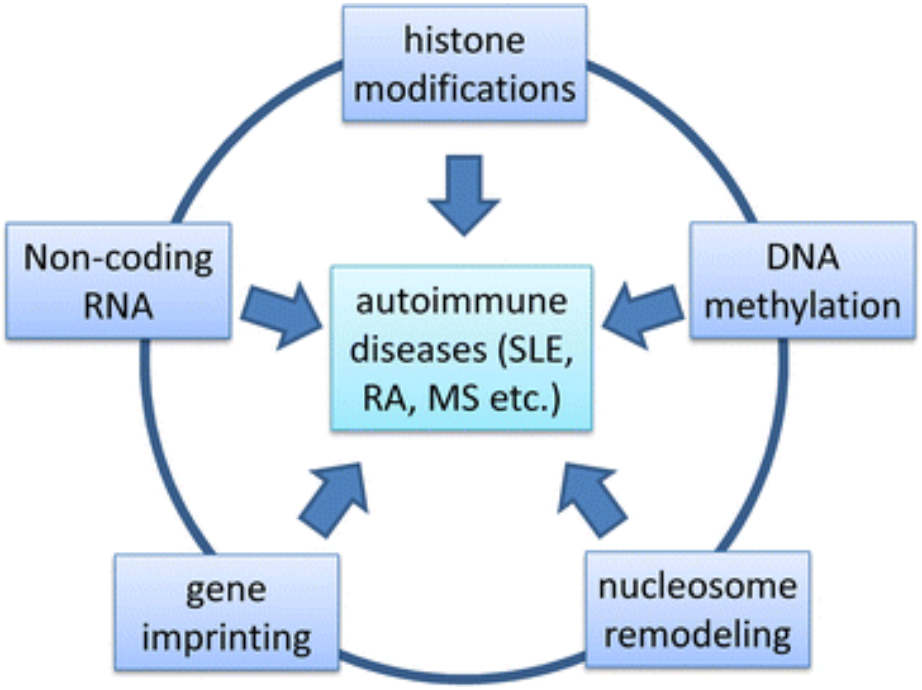
Box 1: Pregnancy and flares of SLE

- Whether flares of SLE are more frequent during pregnancy remain controversial.
- Lupus flares during pregnancy do not seem to be exceedingly more serious than those occurring in non-pregnant patients.
- Lupus may flare at any trimester and the postpartum period.



EPIGENETICS ALTERATION IN SLE

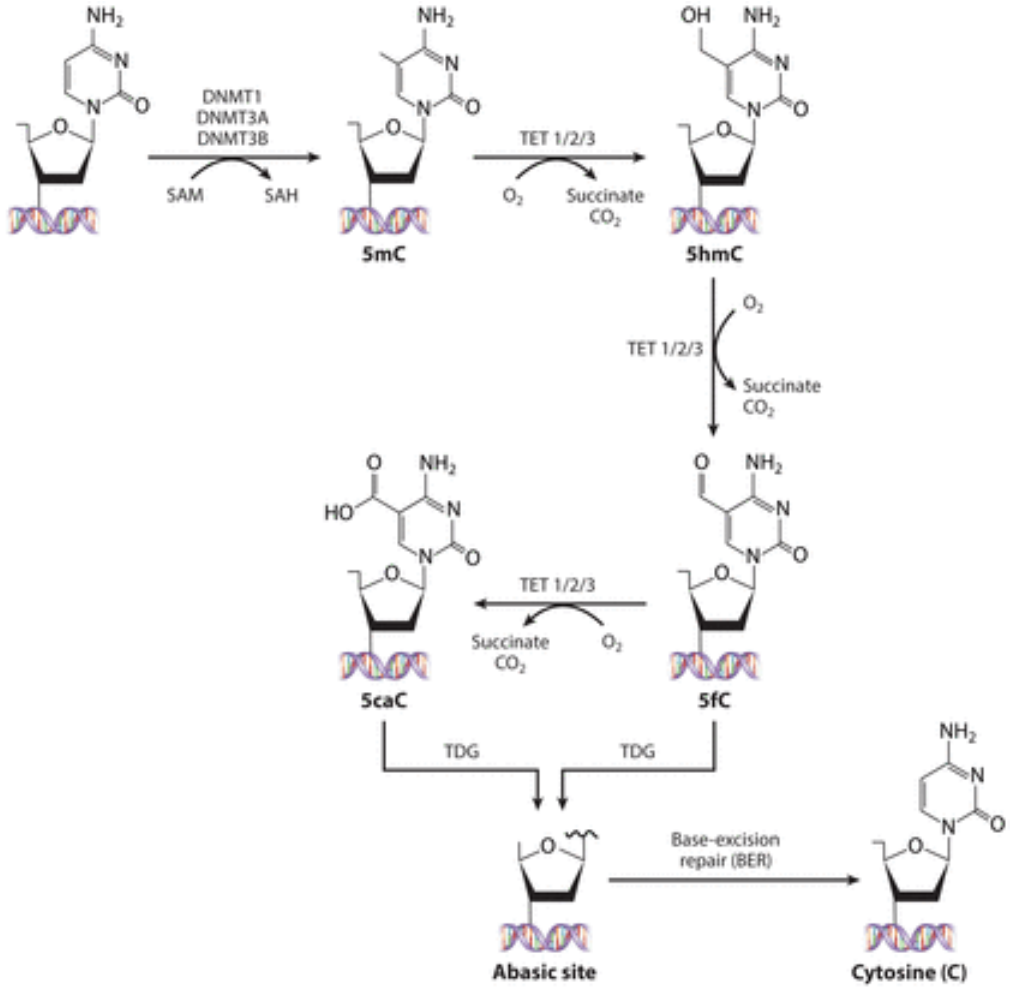
DNA methylation, histone modifications, noncoding RNAs (ncRNAs), and RNA methylation are examples of epigenetic alterations that are believed to be important signalling mediators between the environment and the genome. According to Richardson et al., CD4+ T cellstreated with 5-azacytidine, a DNA methylation inhibitor, showed an increase in self-reactivity Since then, numerous investigations have determined the role of DNA demethylation in SLE[15]



DNA METYLATION

To control gene transcription, transcription factors must attach to matching cis-DNA regions. Therefore, transcription factors need an accessible DNA structure, and preventing transcription factors from attaching to DNA is the most effective method of silencing genes. DNA methyltransferases (DNMTs) can hinder binding by adding methyl groups to the 5′ carbon position of cytosine in cytosine-phosphate-guanosine (CpG)-dinucleotides. DNA methylation

patterns are maintained by DNMT1, which re-methylates hemimethylated CpGs during cell division; de-novo methylation is produced by DNMT3a and b. Depending on a person's genetic background and genomic location, dysregulation of DNA methylation has been connected to the manifestation of several disorders [16]



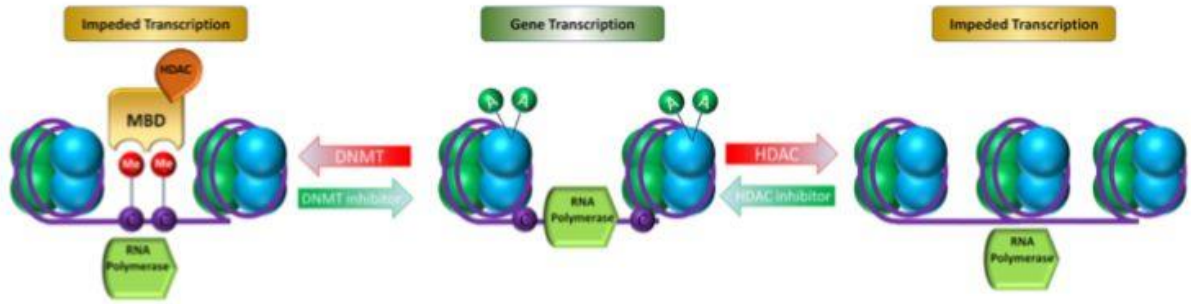
Martin EM, Fry RC. 2018.
Annu. Rev. Public Health. 39:309–33

MICRO -RNA

At the transcriptional and post-transcriptional levels, ncRNAs control the expression or silencing of genes. While lncRNAs work on the controlled complex of growth and differentiation from various immune cells through the synthesis of active protein, miRNAs control over 60% of mRNA and are linked to a number of ADs, including SLE and AR (1). They are currently thought to be effective treatment targets and biomarkers in ADs .

The significance of miRNAs in lupus pathogenesis has been examined in a number of preclinical and clinical investigations, but lncRNAs have not received much attention up to this point. As a result, we have updated the primary ncRNA epigenetic changes linked to SLE [17]A class of post-transcriptional regulators known as micro-RNAs is involved in numerous biological processes, including development, differentiation, proliferation, and death.

The roughly 22 nucleotides that make up micro-RNAs reduce translation by attaching to mRNA and ultimately causing the target mRNA to degrade. Similar to regular protein-coding RNAs, they are encoded by the genome and transcribed by RNA polymerase II. They have lately been investigated in autoimmune illnesses and chronic inflammatory states . Since most miRNA genes are intergenic, they should be transcribed as distinct units. Nearly 40% of miRNA genes can be found in non-protein-coding genes, as well as in the exons or introns of lengthy non-protein-coding transcripts.[18]



HISTONE METYLATION

By altering their three-dimensional organisation, post-translational changes to the N terminal amino acids of histone proteins control the accessibility of regulatory areas to transcription factors and RNA polymerases. Histone proteins aggregate in octamers with two copies of each of the histones H2A, H2B, H3, and H4 in eukaryotic cells. 147 base pairs of DNA are wrapped around histone octamers when they form complexes with genomic DNA. Nucleosomes are the name given to these DNA:histone complexes [2,6,8,12]. Acetylation, phosphorylation, citrullination, and methylation are only a few of the numerous histone modifications.[19]The impact of histone acetylation on genes linked to SLE pathophysiology is still unknown, despite its early identification as the first epigenetic modification linked to biological activity. However, global mapping from earlier studies has shown that CD4? T cells with active lupus had hypoacetylation of H3 and H4 histones [62]. By influencing the transcriptome of SLE patients, H3K4 trimethylation at transcription start sites plays a significant role in transcription regulation [63]. In monocytes from SLE patients, H4 has also been demonstrated to be markedly hyperacetylated [62]. Additionally, there has been evidence of aberrant expression of chromatin-transforming genes and global hypomethylation of H3K9 but not H3K4 histones in CD4 T cells of both active and passive lupus phases.[20]

AUTOANTIBODY PRODUCTION

High circulating autoantibody titers, dysregulation among T, B, and myeloid cell compartments, and immune-complex deposition that causes inflammatory damage in various organs and organ systems, such as the skin, haematopoietic and lymphoreticular organs, joints, lungs, cardiovascular structures, nervous system, and kidneys, are characteristics of SLE, which is arguably the archetypal systemic autoimmune disorder. The formation of circulating autoantibodies is practically universal, despite the fact that the clinical and laboratory symptoms of SLE are extremely varied and exhibit a great degree of variability. As a result, autoantibodies have historically been used as indicators of disease activity and as diagnostic and prognostic criteria.[21]Nearly every organ in the human body is affected by the multi-systemic autoimmune illness known as systemic lupus erythematosus (SLE). An enormous number of autoantibodies accompany the wide range of clinical manifestations in SLE (from mild arthritis through pericarditis and nephritis to potentially fatal neuropsychiatric manifestations). However, the autoantigen in SLE is yet unknown, unlike other classical autoimmune illnesses. Furthermore, it is unknown if every distinctive autoantibody in SLE is harmful. Although patients with polymyositis or rheumatoid arthritis have high levels of antibodies, no other autoimmune disease has as many autoantibodies as SLE[22].

ANTI-DNA AUTO-ABS

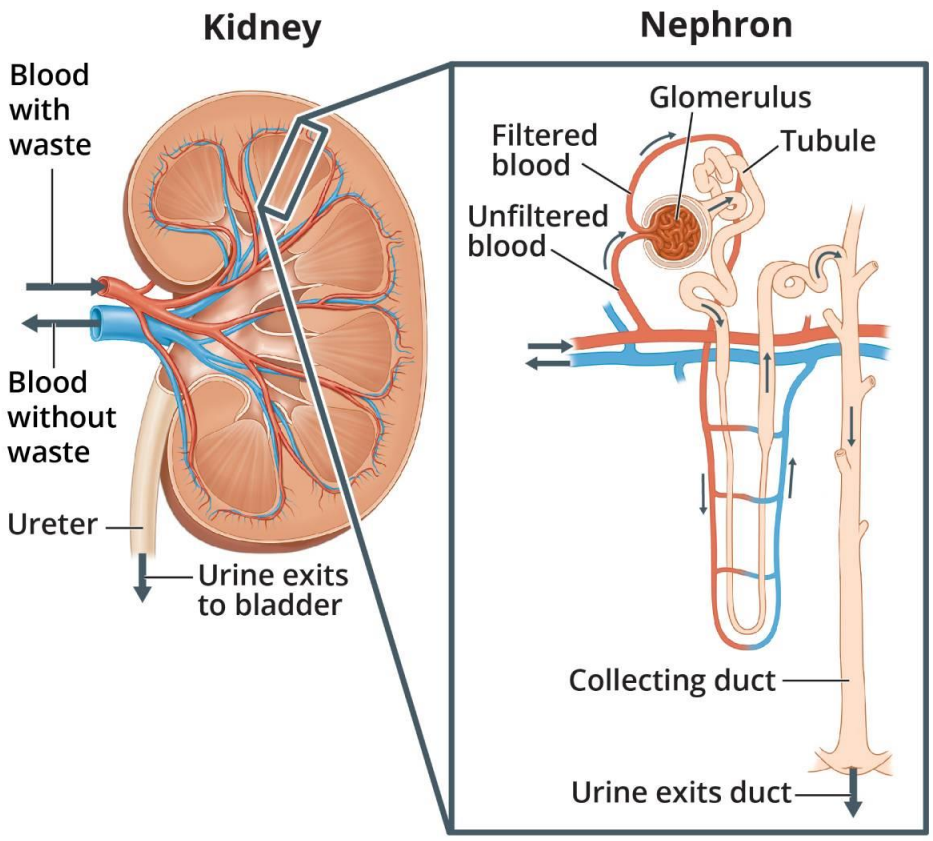
When lupus erythematosus (LE) cells were found in the bone marrow of SLE patients in 1948, anti-chromatin auto-Abs were first discovered Later research revealed that these cells were phagocytic cells with foreign nuclei. Haserick's 1950 in vitro experiment, in which leucocytes from healthy controls and blood plasma from SLE patients were co-incubated, gave the first indication that SLE patients had plasma components that bonded to the cell nuclei . In order to determine that the SLE factor was an Ab to chromatin, the LE assay was crucial.[23]antibodies. The one-step glutaraldehyde coupling approach was used to couple sheep and goat antibodies to human immunoglobulins IgG, IgA, and IgM that were extracted by passing antiserum over immunoadsorbents. These antibodies were acquired from Institut Pasteur. SDS-polyacrylamide gel electrophoresis was used to examine each antigen, and it was discovered that all of them were pure with little to no chance of lipid contamination[24]

Table 1. Clinical, biological and histological findings of SLE patients

				Biological activity					
				Complement			Antibodies		Classification of nephritis
Patient	Sex	Age	Clinical activity	CH50	C3	C4	Nuclear	DNA	
1	F	28	No	L	N	L	No	No	Vc
2	F	19	No	N	N	N	No	No	IVd
3	F	40	No	N	N	N	Yes	No	IIIc
4	F	17	Yes	L	N	N	Yes	Yes	IVb
5	F	29	Yes	N	N	N	Yes	Yes	IIIa
6	F	30	No	L	N	L	No	No	V
7	F	53	No	N	N	N	No	No	IVa
8	F	16	Yes	L	L	L	Yes	Yes	IVb
9	F	41	No	L	N	L	Yes	Yes	IVa
10	M	20	Yes	L	L	L	Yes	Yes	I
11	F	44	No	L	N	L	No	No	IIIa
12	F	40	No	L	L	L	Yes	No	IVa
13	M	43	Yes	N	N	N	Yes	Yes	Vb
14	M	38	No	N	N	N	Yes	No	IVb
15	F	38	Yes	L	N	N	Yes	Yes	Va
16	F	56	Yes	N	L	L	Yes	No	IVb
17	F	33	Yes	L	L	L	Yes	Yes	IVb
18	M	76	No	N	N	N	Yes	ND	IVa
19	F	19	Yes	N	N	N	Yes	Yes	IIa
20	F	32	No	L	N	L	Yes	Yes	IIIa
21	F	39	No	N	N	N	No	No	IIb
22	M	30	Yes	N	N	L	Yes	Yes	Vb
23	F	27	Yes	L	L	L	Yes	Yes	IVb
24	F	21	Yes	L	L	L	Yes	Yes	IVa
25	F	30	Yes	L	N	L	Yes	Yes	IIIa

LUPUS NEPHRITIS

A loss of tolerance to self-antigens and the generation of large titers of autoantibodies against native DNA and other cellular components are the hallmarks of Systemic Lupus Erythematosus (SLE) A chronic inflammatory disease. Roughly 90% of people with SLE are women, most of whom are of reproductive age. Patients with SLE may have a broad range of clinical symptoms affecting several organ systems[25]In SLE patients, the five IFN-inducible genes were significantly expressed, and elevated levels were linked to disease activity as determined by several techniques. Patients with lupus nephritis, particularly those with active renal illness, as well as those with anti-dsDNA antibody positivity and hypocomplementemia, had higher IFN scores, or LY6E levels. LY6E levels or IFN scores could be helpful as a biomarker for lupus nephritis treatment.[26]



GENETICS OF LUPUS NEPHRITIS

Although there are few genetic studies that explicitly assess LN, a number of risk alleles linked to SLE have also been linked to LN. Risk genes in LN, such as apolipoprotein L1 (APOL1), platelet-derived growth factor receptor alpha (PDGFRA), typically observed in SLE patients without nephritis. LN is also linked to genetic changes in HLA alleles. While HLA-DR3 and HLA-DR15 enhance risk, HLA-DR4 and HLA-DR11 seem to protect against LN. More than 50 genetic variants linked to several physiological systems known to be abnormal in LN were found in a recent genome-wide association research.[27]About 40% of lupus patients have lupus nephritis (LN), one of the most prevalent manifestations of systemic lupus erythematosus (SLE). Ten percent of people with LN may develop end-stage kidney disease (ESKD), making it a significant risk factor for morbidity and mortality. The search for novel clinical biomarkers with a more precise correlation with lupus activity and the redefining of the histological classification into various subgroups in order to direct a customised treatment are thus two areas for improvement in the field of LN.[28]

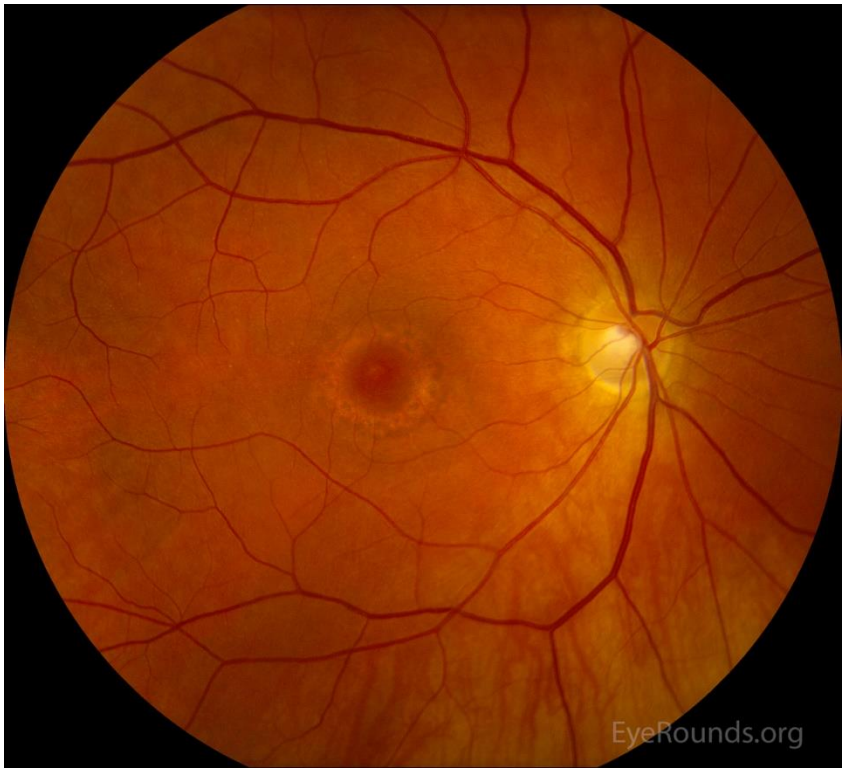
CLINICAL STUDIES

A weak androgen with mild immune modulatory effects is dehydroepiandrosterone (DHEA). 5 Early research revealed that SLE patients had lower circulating DHEA levels than healthy controls, and that these levels were associated with higher SLE disease activity. 6, 7 These findings prompted researchers to look into using DHEA supplements to treat SLE[29].Patients with SLE now have survival rates of over 95% and 90%, respectively, after five and ten years of cumulative illness. 40, 41. Therefore, irreversible harm to the affected organ systems as well as impairment and/or loss of health-related quality of life (HRQOL), as determined by the patient, are the best ways to describe long-term outcomes. Clinical trials of possible treatment drugs for SLE have usually used patient and physical global assessments. Although they are sometimes used independently, physician global assessments are part of the LAI and SLAM. Physicians' assessments, which are based on measurements of disease activity and damage, frequently diverge from patients' judgements of disease activity and/or overall healthWekking demonstrated that while patients' opinions of the severity of their illness were continuously linked to psychosocial stressors, there was no substantial correlation between these perceptions and physical symptoms associated with SLE69. Patients and doctors were frequently asked by Aranow et al. to rate SLE disease activity using a visual analogue scale70 and to classify it into four categories: remission, stable active, mild/moderate flare, or severe flare. When patients thought their SLE was active or the doctor thought it was in remission, there was the best agreement. Only 51% of respondents agreed overall.It seems suitable to use a patient global assessment of disease activity in SLE clinical trials when taking into account outcomes that are significant to the patient.[30]The Stanford Immunology Clinic and rheumatologists in the San Francisco Bay area recruited patients with SLE who met the American College of Rheumatology's (ACR) criteria. Informed consent forms approved by the IRB were signed by every patient. The following criteria have to be met by the patients: severe renal, haematological, or serosal lupusIf additional immunosuppressive medicine was started during the clinical trials due to therapeutic need, all other patients were likewise deemed non-responders.SLAM scores, SLE-DAI scores, global assessments by patients and doctors, prednisone dosage, global health evaluation by health (HAO), and pertinent laboratory data were secondary outcomes.[31]All underwent normal general physical examinations by a certified internist, as well as medical

interviews and documented medical histories. For the immunological tests, a serum sample was taken from each patient. All of these patients' clinical and serological details were gathered in a protocol format. This protocol's salient features included: (1) age at onset of the disease; (2) age at diagnosis, which is defined as the age at which the patient met four or more of the 1982 revised ARA criteria for the classification of SLE; (3) time of evolution of the disease, which is defined as the time from the onset until the current study; (4) clinical manifestations at onset; (5) cumulative clinical manifestations during the evolution of the disease; and (6) laboratory features at diagnosis. Data entered into the protocol forms was sent to a computerised database software (DBASEIV).[32]

SIDE EFFECT

Chloroquine's Ocular Side Effects in Patients with Scleroderma, Systemic Lupus Erythematosus, and Rheumatoid ArthritisAn antimalarial medication called chloroquine is frequently used to treat musculoskeletal and mucocutaneous issues in a variety of connective tissue conditions, including scleroderma (Scl), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). It is unclear how chloroquine works. Chloroquine contains anti-inflammatory properties, reduces enzyme activity, affects immunological activities, and interferes with intracellular processes.[33]



BULL'S EYE MACULOPATHY DUE TO HYDROXYCHLOROQUINE TOXICITY

Cardiovascular side effectOne uncommon yet dangerous side effect of HCQ is cardiotoxicity. Clinical manifestations of cardiotoxicity typically include restricted or dilated cardiomyopathy or anomalies of the conduction system, such as bundle branch block and atrioventricular block. Non-specific chest pain, however, could be a symptom . Older age, female gender, longer medication duration (>10 years), higher daily dose per kilogramme, pre-existing cardiac illness, and renal insufficiency are risk factors for the development of HCQ-induced cardiotoxicity . Although the pathogenetic role of HCQ has been questioned, endomyocardial buildup of pathologic metabolic products may result from lysosomal dysfunction brought on by HCQ.[34]

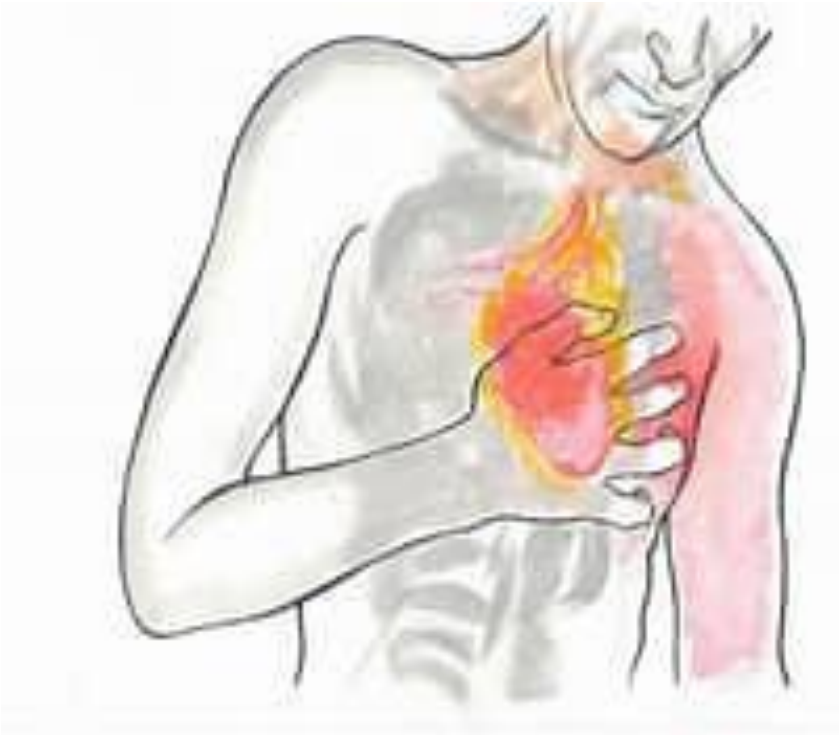
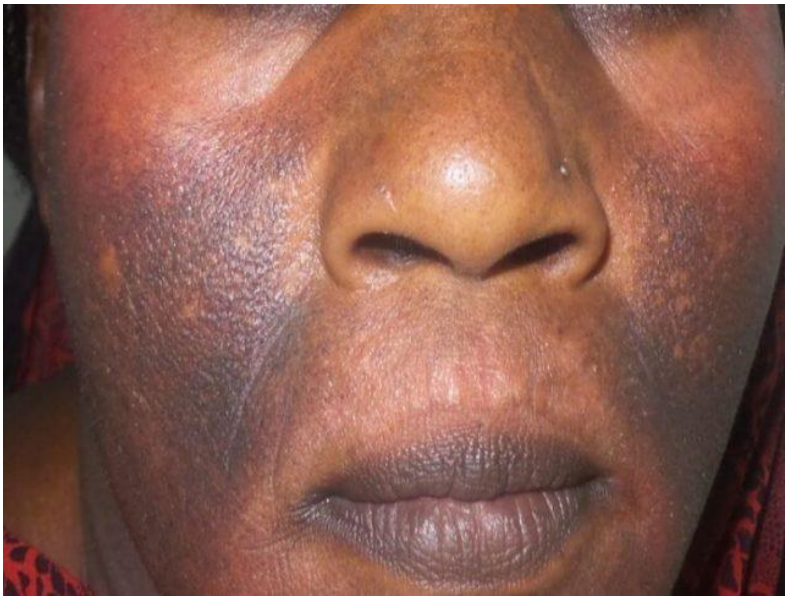


Fig: localización más frecuente del dolor de perfil anginoso

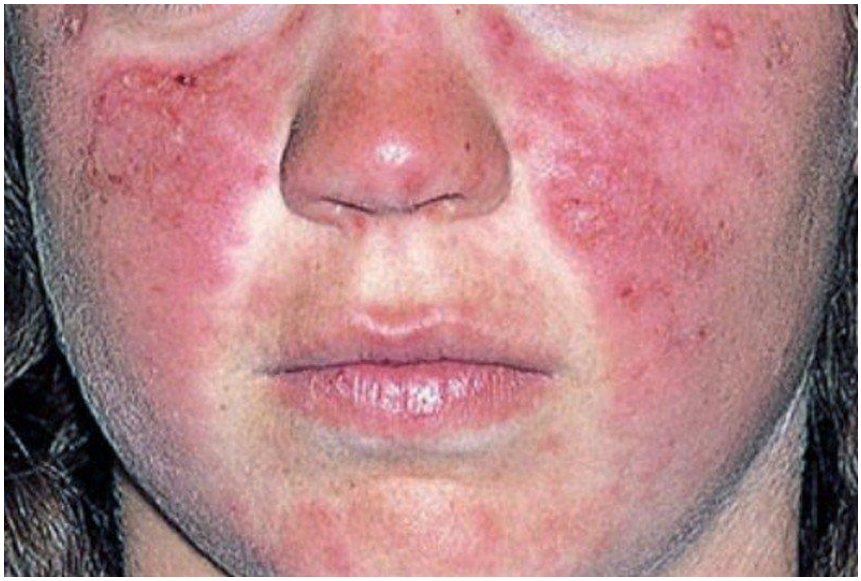
Safety evaluationHCQ is regarded as a safe medication. However, HCQ can have a variety of side effects, just like any other medication. Many adverse events are caused by purposeful or inadvertent overdosing, and HCQ side effects are typically dose-dependent. Cutaneous side effects are more common in patients with psoriasis, alcoholism, porphyria, and allergies. Children are especially susceptible to the negative consequences of even a slight chloroquine overdose. Given its resemblance to chloroquine, HCQ should also be regarded as potentially dangerous at small doses in the paediatric population . There is little information on paediatric HCQ overdoses and no reports of toxicity from 1-2 pills. Generally speaking, patients taking HCQ for an extended period of time should continue to monitor adverse effects.Generally speaking, patients taking HCQ for an extended period of time should continue to monitor adverse effects.Considering that not all of the documented issues happened in individuals without SLE, we provide here the most severe side effects of HCQ[35]



THIS IS WHAT HAPPEN WHEN YOU GET TOO MUCH HYDROQUINONE

Rash is a common cutaneous symptom in people with systemic lupus erythematosus (SLE), but little information is available about its frequency or connection to illness symptoms. This may be because rash is a common but non-specific symptom. 48 out of 81 (59%) SLE patients had a rash. Individuals

with rashes showed lower completion levels, lymphadenopathy, higher levels of antibodies to double-stranded DNA, and more cutaneous symptoms and indicators. Additionally, they were taking prednisone at a higher dosage. Regarding renal or central nervous system disorders, there was no difference between patients with and without rash. Clinical indicators of illness aggravation and the disease activity index did not link with rash.When evaluated by the physician, rash was defined clinically as the occurrence of any unidentified cutaneous eruption or as occurring concurrently with a variety of specific cutaneous manifestations, such as discoid lesions, skin vasculitic ulcers, malar rash, the typical rash of subacute cutaneous lupus (papulosquamous or annular), or cutaneous vasculitis (palpable purpura, microinfarcts, livedo reticularis), which were monitored independently. The patient's medical history was also used to evaluate the rash. We used the doctor's assessment of the rash for the various evaluations (35).



CONCLUSION

Much progress is being made in increasing our knowledgeof the aetiopathogensis of this complex disease. Thisunderstanding has brought with it the potential targeting ofkey molecules and the reasonable hope that this specificitywill reduce the side effects associated with more generalimmunosuppression. Although the mortality associatedwith SLE has substantially reduced in the last decade, itremains a serious, potentially life-threatening condition,and careful long-term follow-up of patients with SLEremains paramount

Rather thanrepresenting chronological events evolving a single gentic events , the above four pathologenics mechanisms are likely to represent independent entitites . through several of above -enumerated factors that feed into these four event may be genetically determined,other may well be subject to environmental or hormone influence .Over the last decades, as ongoing studies methodiology unravel the suspectibility genes and pathogenic mechanisms underlying this diseases ,the mystery enshrounding lupus will slowly but surely ,vanish.

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