Etiology and Pathogenesis of Systemic Lupus Erythematosus

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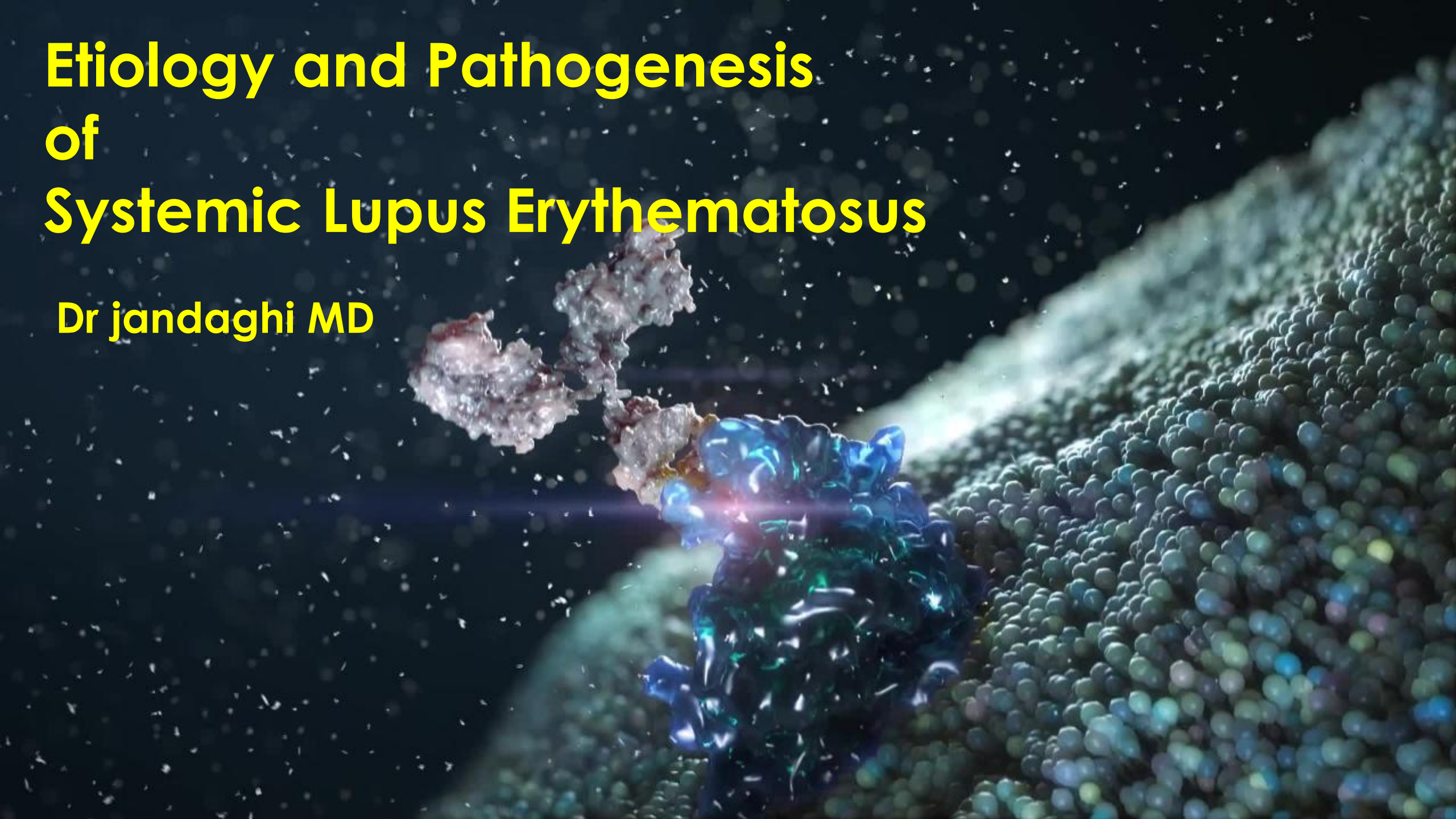


Introduction

- Systemic lupus erythematosus (SLE):
  - ✓ Predominantly a disease of young women in their childbearing years
  - ✓ significant physical disfigurement, morbidity, and occasionally mortality

- Pathogenesis:
  - ✓ significant contribution of the innate immune system and autoantibodies and T cells
  - ✓ vasculature is a target of the immune system

- genetic diversity with environmental triggers amplifies immune system activation

⟹ organ vulnerability and classic manifestations of lupus and significant comorbidities

Introduction

- **Mechanisms that related to the underlying genetic profile :**
  - excessive production or impaired clearance of stimulatory nucleic acids
  - increased generation of products of the innate immune response, particularly type I interferon (IFN)
  - altered threshold for activation or efficiency of signaling of cells of the adaptive immune response

- intra-cellular nucleic acids

  Or

- exogenous triggers, such as a virus or debris derived from damaged or dying cells

=initiation of disease:

Introduction

IFN-a is produced by plasmacytoid dendritic cells (pDCs).

INF –a:

I. activation of **self-reactive T cells** → express CD154 (CD40 ligand) and produce interleukin-21 (IL-21) → differentiation of **B cells** and generate antibody-producing plasma cells.

II. production of **B cell–activating factor** (BAFF, also known as B lymphocyte stimulator):survival and differentiation factor for B cells

immune complexes amplify immune activation by accessing **endosomal Toll-like receptors** in pDCs and B cells → depositing them directly in the vicinity of blood vessels → complement activation, inflammation, and tissue damage

monocytes and macrophages contribute to tissue damage Reactive → **oxygen species (ROS)** and **pro-inflammatory cytokines** → poor vascular repair and sclerosis.

Historic View of Lupus Pathogenesis

- Toll-like receptors (TLR) :
  - play a role in lupus pathogenesis
  - Nucleic acids are the most relevant TLR ligands for amplification of immune system activation and autoimmunity in SLE

- Additional sensors of DNA and RNA present in the cytosol
- TLRs or the cytosolic receptors, or both, contribute to :
  - Initiation of innate immune system activation ?
  - augment immunologic activity that is initiated by other molecular pathways.?

- both TLR and cytosolic sensors ⟹ signal new gene transcription and production of pathogenic mediators, such as type I interferon (IFN

Historic View of Lupus Pathogenesis

- The lupus erythematosus (LE) cell:
  - important concept in considerations of lupus pathogenesis, was active at sites of inflammation.
- antibodies directed at cellular components,particularly cell nuclei ⟹ lupus reflected an autoimmune process:

glomerular deposition of immunoglobulin and complement components, combined with the elution of anti-DNA autoantibodies from lupus kidneys

Historic View of Lupus Pathogenesis

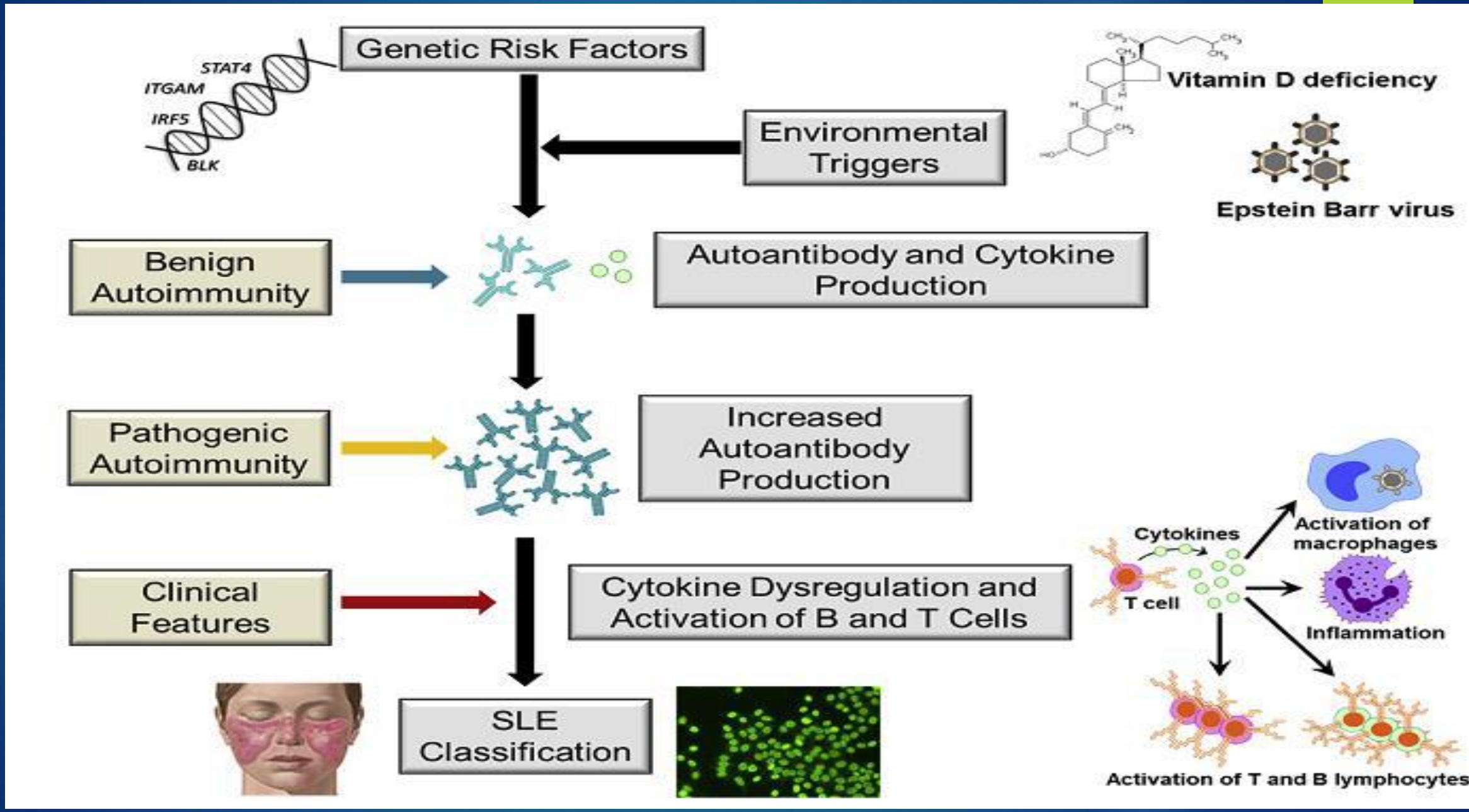
- exposure to sunlight, microbial infection, and certain drugs as factors that can lead to initiation or exacerbation of lupus

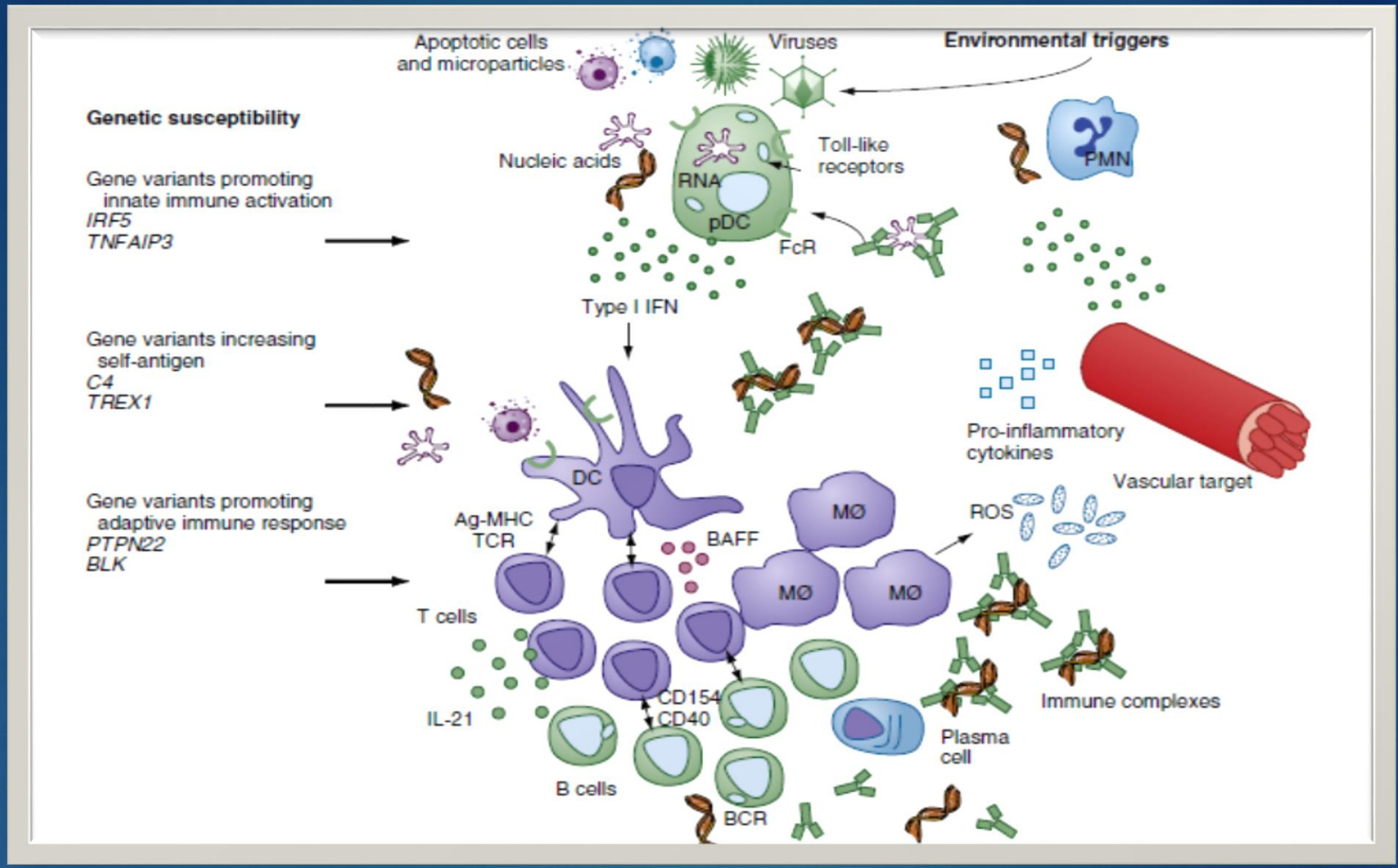
- molecular change induced by these environmental triggers ?
  - not clear

- ultraviolet (UV) light:
  - DNA damage:

    modification of DNA methylation

    oxidation of mitochondrial DNA or other cell components


Genetic Risk Factors
STAT4
ITGAM
IRF5
BLK
Environmental Triggers
Vitamin D deficiency
Epstein Barr virus
Benign Autoimmunity
Autoantibody and Cytokine Production
Pathogenic Autoimmunity
Increased Autoantibody Production
Clinical Features
Cytokine Dysregulation and Activation of B and T Cells
Cytokines
Activation of macrophages
T cell
Inflammation
SLE Classification
Activation of T and B lymphocytes



SYSTEMIC LUPUS ERYTHEMATOSUS PATHOGENESIS

Genetic Contributions to Lupus Pathogenesis

- high frequency of concordance of SLE in identical twins, have pointed to a strong genetic contribution to SLE

- A study based on the ImmunoChip SNP platform identified :
  - more than 50 non- HLA risk variants
  - some of the variants differ between Caucasians and African-Americans
  - Many of the lupus associated SNPs are near genes encoding proteins implicated in immune system function → supporting the centrality of the immune system in disease pathogenesis

Genetic Contributions to Lupus Pathogenesis

- In parallel to the requirements for immune system activation stimulated by foreign antigens, SLE-associated genes are involved in:
  - generation or impaired clearance of self-antigen
  - activation of the innate immune response
  - activation of the adaptive immune response
- Additional genetic variants may impact target organ vulnerability

Genetic Contributions to Lupus Pathogenesis

TABLE 84.1 Genetic Variants Associated With Systemic Lupus Erythematosus—Major Histocompatibility Complex Genes

Major Histocompatibility Complex Genes Associated With SLE

Homozygous deficiencies of early complement components (C2, C4A, C4B) increase risk five- to 10-fold
HLA-DR2 increases relative risk twofold to threefold
HLA-DR3 increases relative risk twofold to threefold
DR2/DRX associated with anti-Sm antibodies
DR3/DRX associated with anti-Ro and anti-La antibodies
DR2/DR3 associated with anti-Ro, anti-La, and/or anti-Sm and also associated with anti-dsDNA antibodies
DR3/DR3 associated with anti-Sm antibodies

Genetic Contributions to Lupus Pathogenesis

Gene[a]	Protein
European	
ATG5	Autophagy related 5
BANK1	B-cell scaffold protein with ankyrin repeats 1
BLK	B-lymphocyte–specific tyrosine kinase
CLEC16A	C-type lectin domain containing 16A
DEF6	DEF6, guanine nucleotide exchange factor
DGKQ	Diacylglycerol kinase theta
ETS1	ETS proto-oncogene 1
FCGR2A	Fc fragment of IgG receptor IIa
GRB2	Growth factor receptor bound protein 2
GTF2I	General transcription factor IIi
IFIH1	Interferon induced with helicase C domain 1
IKZF1	IKAROS family zinc finger 1
IKZF3	IKAROS family zinc finger 3
IL10	Interleukin 10
IL12A	Interleukin 12A
IRF5	Interferon regulatory factor 5
IRF7	Interferon regulatory factor 7
IRF8	Interferon regulatory factor 8
ITGAM	Integrin subunit alpha M
JAZF1	JAZF zinc finger 1
MSRA	Methionine sulfoxide reductase A
NMNAT2	Nicotinamide nucleotide adenylyltransferase 2
OLIG3	Oligodendrocyte transcription factor 3
PKIA	CAMP-dependent protein kinase inhibitor alpha
PTPN22	Protein tyrosine phosphatase nonreceptor type 22
PTTG1-MIR146A	Pituitary tumor-transforming 1
PXK	PX domain containing serine/threonine kinase like
SLC15A4	Solute carrier family 15 member 4
SLC17A4	Solute carrier family 17 member 4
STAT4	Signal transducer and activator of transcription 4
TMEM39A-TIMMDC1	Transmembrane protein 39A-translocase of inner mitochondrial membrane domain containing 1
TNFAIP3	TNF induced protein 3/A20
TNFSF4	TNF superfamily member 4/Ox40 ligand
TNIP1	TNFAIP3 interacting protein 1
TYK2	Tyrosine kinase 2
UBE2L3	Ubiquitin conjugating enzyme E2 L3
WDFY4	WDFY family member 4

Gene[a]	Protein
African	
BLK	B-lymphocyte-specific tyrosine kinase
IRF5	Interferon regulatory factor 5
ITGAM	Integrin subunit alpha M
PLAT	Plasminogen activator, tissue type
PTTG1	Pituitary tumor-transforming 1
Hispanic	
CLEC16A	C-type lectin domain containing 16A
GALC	Galactosylceraminidase
IRF5	Interferon regulatory factor 5
ITGAM	Integrin subunit alpha M
NCF2	Neutrophil cytosolic factor 2
TNIP1	TNFAIP3 interacting protein 1
STAT4	Signal transducer and activator of transcription 4

Genetic Contributions to Lupus Pathogenesis

- **lupus susceptibility :**
- impairing clearance of cellular debris and deficiencies in complement pathway gene products, including C2, C4, and C1q

- C1q plays an additional role in inhibition of IFN-a:

  C1q deficiency can augment IFN-a and promote broad immune dysregulation

- Increased availability of nuclear debris and induction of self-reactive T cells

Genetic Contributions to Lupus Pathogenesis

- MHC 8.1 haplotype block,HLA B8/DR3/DQw2/C4AQO encodes the alleles B8 and DR3 and bears a short *C4B* gene
  - relative risk related to the *C4A* null allele is twice that of either HLA-B8 or DR3:significance of the C4 genes in disease risk

- this risk haplotype is associated with accelerated disease in :
  - HIV,insulin-dependent diabetes mellitus, and several other autoimmune diseases

Genetic Contributions to Lupus Pathogenesis

- C-reactive protein(CRP) contributes to clearance of apoptotic debris.
- Polymorphisms in *CRP* have been associated with SLE and with decreased levels of CRP

- mutations in genes that regulate the integrity or degradation of endogenous DNA or RNA can result:
- excess stimulatory nucleic acid
- innate immune system activation
- excessive production of type I IFN

Genetic Contributions to Lupus Pathogenesis

- absence of **DNase1** and **DNase1-like 3** is associated with:

  vascular occlusions due to the accumulation of intravascular NET clots

- mutation in the ***DNASE1L3*** gene:

  aggressive lupus and anti-DNA antibodies or hypo complementemic urticarial vasculitis syndrome

- biallelic mutations in ***DNASE2*** :

  membranoproliferative glomerulonephritis, anti-DNA antibodies, and high levels of IFN-a

Genetic Contributions to Lupus Pathogenesis

- Aicardi-Goutières syndrome (AGS):
- A lupus like syndrome induce by mutations implicated in control of nucleic acid integrity
- Mutations in :
  - ***TREX1*** : increased levels of IFN-β
  - ***SAMHD1***: triggering a DNA damage response and type I IFN production
  - ***RNASEH2*** family : remove ribonucleotides from RNA-DNA hybrids also activate an innate immune response
  - Parents of AGS patients who were heterozygous for the variant ***RNASEH2***: anti-nuclear antibodies
  - ***ADAR***: encodes an RNA-specific adenosine deaminase
- these gene products ppears to be important for avoiding aberrant activation of an innate immune response characterized by IFN pathway activation
- skin lesions, autoantibodies, CNS disease, and high levels of type I IFN

Genetic Contributions to Lupus Pathogenesis

- An additional form of AGS:
  - genetic variants of ***IFIH1***, encoding the RNA sensor MDA5: production of type I IFN
  - termed *interferonopathies* and provide important clues to pathogenic mechanisms relevant to SLE
- *TREX1* mutations in approximately 0.5% of SLE patients

Genetic Contributions to Lupus Pathogenesis

- SLE or systemic sclerosis develops in young children :
  - Skin rash, a livedo-like vascular pattern, distal extremity ulcerations, interstitial lung disease, markers of systemic inflammation, and low-titer autoantibodies

- Mechanism:
  - mutations in *TMEM173*, encoding STING , that functions downstream of recognition of cGAS
  - increased transcription of IFN-β and IFN-stimulated genes
  - constitutive phosphorylation STAT 1

- In vitro studies that use a JAK inhibitor support targeting the effector arm of the IFN pathway

Genetic Contributions to Lupus Pathogenesis

- **Lupus associated SNP:**

- IFN regulatory factor 5 (IRF5) and IRF7 are cytoplasmic proteins that translocate to the nucleus after effective activation of the endosomal TLRs by DNA or RNA → initiate transcription of IFN-α and other pro-inflammatory mediators.

- *TNFAIP3* encodes A20 → activate NF-κB

Genetic Contributions to Lupus Pathogenesis

- **gene variants contributes to adaptive immune system activation:**
  - altering thresholds for lymphocyte activation or efficiency of cell signaling

- **MHC 8.1** haplotype strongly associated with a diagnosis of SLE, influence the early stages of immune system activation

- lupus-associated variants that alter adaptive immune system activation are:
  - ***STAT4***: involved in cytokine signaling
  - ***PTPN22***: efficiency of signaling downstream of the T and B cell surface antigen receptors

Genetic Contributions to Lupus Pathogenesis

- **oxidative damage** is less well developed than the role of genetic variants in altered immune system function in SLE.

- risk of lupus nephritis :

  - ***TNIP1***, encoding a protein associated with TLR signaling
  - ***MTMR3***, encodes myotubularin-related protein
  - link between alleles of ***APOL1***, involved in cholesterol transport(end-stage renal disease) particularly in African-Americans

Genetic Contributions to Lupus Pathogenesis

- statistical association of sequence variations in genes or genetic loci (GWAS)with a diagnosis of SLE
- nucleic acid–containing immune complexes are important stimuli that act through endosomal TLRs such as TLR7 and TLR9, those TLRs that mediate cell signals through the IRF5 and IRF7 transcription factors
- risk alleles for *IRF5* and *IRF7* are associated with increased serum type I IFN activity and autoantibodies targeting DNA or RNA-associated proteins

Genetic Contributions to Lupus Pathogenesis

- The strong support for activation and altered regulation of the TLR pathway, point to potential therapeutic targets for future study

- associated **anti-dsDNA antibodies** with:
  - HLA-DR3, *STAT4,* and *ITGAM*
  - *PTPN22, IRF5,* and *PTTG1*
  - *FCGR2A, OX40L, IL10, PXK, UHRF1BP1, PRDM1, BLK,* and *IRAK1*.

- some of these variants are associated with distinct autoantibody specificities, general immune system activation, inflammation, or tissue damage.

Female Predominance of Systemic Lupus Erythematosus

- dramatic 9:1 female predominance of the disease

- Hormonal contributions to immune system activation:
  - estrogen modulate lymphocyte and pDC activation
  - prolactin is expressed at increased levels in lupus serum
- Klinefelter's syndrome(47,XXY) is increased 14-fold among men with SLE compared with men without SLE:
  - X chromosome gene dose effect as an important contributor to SLE pathogenesis

- **duplications of portions of the X chromosome that encode the *TLR7* gene activate of the innate immune system → production of type I IFN,and generation of autoimmunity**

Female Predominance of Systemic Lupus Erythematosus

- **altered methylation**
  - generalized immune activation, with a particular focus on type I IFN–stimulated genes

- **ovulation** as factors contributing to lupus pathogenesis:
  - The onset of SLE most typically occurs in the childbearing years, after menarche and before menopause.
  - positive association between early menarche and SLE
  - breastfeeding confers a protective effect

- **germ cells and associated somatic cells**
- might provide a source of stimulatory nucleic acid– containing complexes that could access TLR-dependent or TLR independent pathways and result in immune activation

Environmental Triggers of Lupus

- in development of SLE:
  - genetic(44%)
  - environmental factors and stochastic events

- Socioeconomic factors have been demonstrated to contribute to poor outcomes in lupus patients

Environmental Triggers of Lupus

- possible role for EBV virus in SLE pathogenesis(increased EBV DNA in blood and higher frequency of anti-EBV antibodies)

- Several mechanisms, including:

  1-EBV encoded **small RNAs, or EBER**(expressed in cells latently infected with EBV)

  - EBERs induce expression of type I IFN and activating signaling through a TLR-independent pathway
  - Sustained production of type I IFN and a shift from expansion of T effector cells to expansion of T follicular helper cells accompanies the organ inflammation and damage

Environmental Triggers of Lupus

2-EBNA2, encoded in the EBV genome, can bind to genomic loci ,regulating the expression of relevant genes that can alter immune system function

- antibodies specific for the virus-encoded EBNA-1 protein can also react with dsDNA

- This phenomenon was also other autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis

3-Latent membrane protein 1, encoded by EBV, can act as a mimic of CD40 and promote B cell dysfunction and autoimmunity

4-T cell responses specific for EBV to be deficient

Environmental Triggers of Lupus

- **endogenous bacteria** can initiating or exacerbating autoimmunity and SLE.
- Mechanism:
  - **T cell** and **antibody cross-reactivity/molecular mimicry** between commensal bacteria expressing Ro-related epitopes and the human Ro antigen
  - translocation of commensal gut bacteria (*Enterococcus gallinarum)* to the liver in lupus susceptible mice induced **anti-DNA antibodies**, an **IFN signature**, and tissue inflammation.
- *Ruminococcus gnavus* → association of that microbe with disease activity and anti-DNA antibodies
- *interactions between our microbiome and the immune system of genetically susceptible individuals will require additional study and confirmation*

Environmental Triggers of Lupus

- **current smoking :**
  - risk factor for SLE
  - dose response relating pack years of smoking to risk
  - relationship between smoking and anti-dsDNA+ SLE
  - might provide an inflammatory stimulus to epithelial or mononuclear cells in the lungs, promoting protein modification or nonspecific inflammation

- moderate **alcohol consumption** is a negative risk factor for SLE

Environmental Triggers of Lupus

- **Hormone:**
- early menarche (≤ age 10), use of post-menopausal hormones, and use of oral contraceptives as associated with a significant relative risk of incident SLE
  - placebo-controlled trials showed that oral contraceptives did not increase rate of lupus flare, and hormone replacement therapy in post-menopausal women did not increase rate of severe flare over 12 months and only modestly increased risk of a mild or moderate disease flare

- **obesity** during teenage years with later diagnosis of SLE
- less than 7hours/night **sleep** as associated with transition to SLE

- **residential pesticides :**contributor to SLE in African-American women
- **silica**

Environmental Triggers of Lupus

- UV induces :
  - DNA breaks
  - alter gene expression or lead to apoptotic or necrotic cell death.
  - DNA breaks or prolonged maintenance of DNA-protein cross-links might provide an adjuvant or antigenic stimulus to the immune system
  - generation of cyclobutane pyrimidine dimers and induction of IFN-stimulated genes in cells from individuals heterozygous for mutations in *RNASEH2* genes

Environmental Triggers of Lupus

- drug-induced lupus:

  - Altered DNA methylation
  - hydralazine: inhibits ERK pathway signaling, resulting in decreased expression of DNA methyltransferase(DNMT) 1 and DNMT3a

Innate Immune System Activation in Systemic Lupus Erythematosus

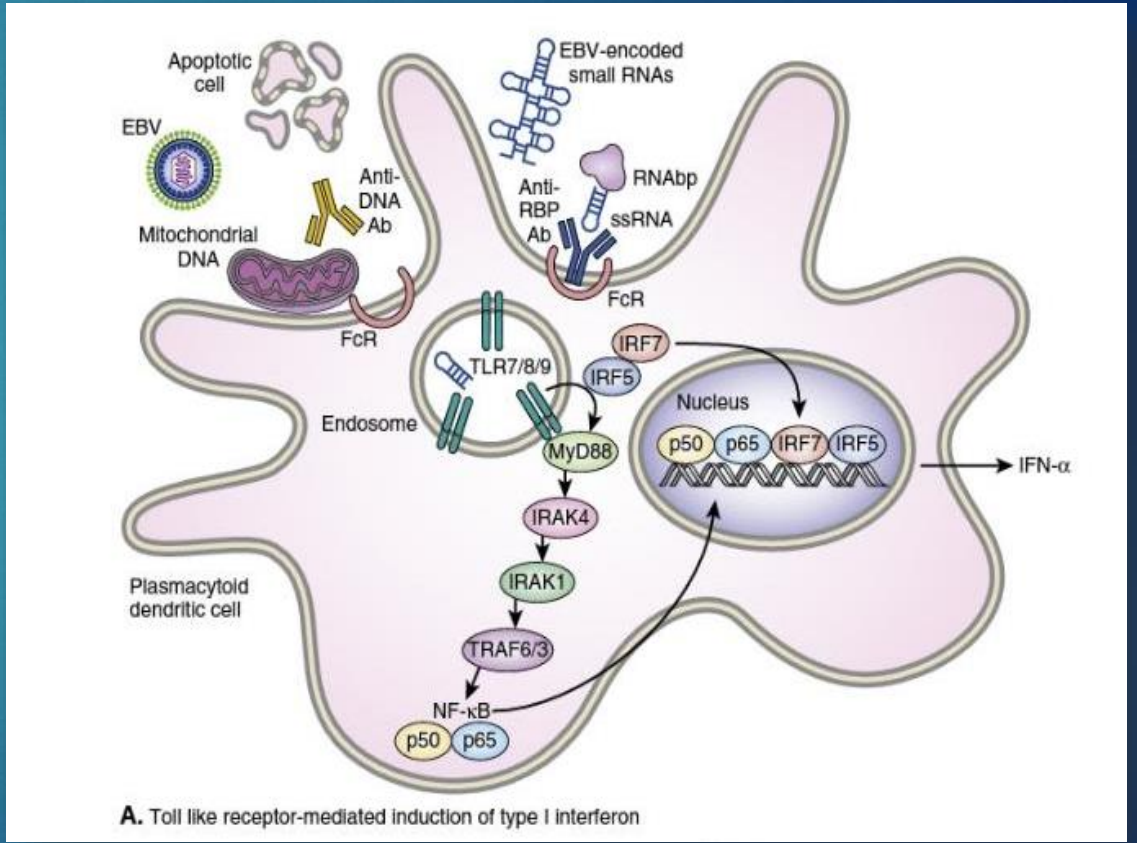
- innate immune system activation has central role for regulation of the adaptive immune response,inflammation, and tissue repair
- innate immune activation can be initiated by :

❖ TLRs dependent :

- associates with adaptor molecules that initiate signaling, resulting in activation of members of the IFN-regulatory factor family(**NF-κB**) and (**MAPK**)

Toll like receptor-mediated induction of type 1 interferon

Plasmacytoid dendritic cells are the most active producers of INF-1 induced by activation of endosomal TLRs(TLR7 and TLR9 in pDCs,TLR8 in monocyte)
single –stranded RNAs associated with RNA-binding proteins and anti –RBP antibodies
or
double strand DNAs associated with anti –DNA antibodies
access TLR7 or TLR9,respectively, in an FC receptor-dependent manner.
A signaling sascade involving MyD88 ,IRAK4, IRAK1, TRAF6 and TRAF3, along with IRAF5 and IRAF 7 ⟹ activation and translocation of NF-κB and IRF5 to the nucleus and transcription of **IFN -α**



A. Toll like receptor-mediated induction of type I interferon

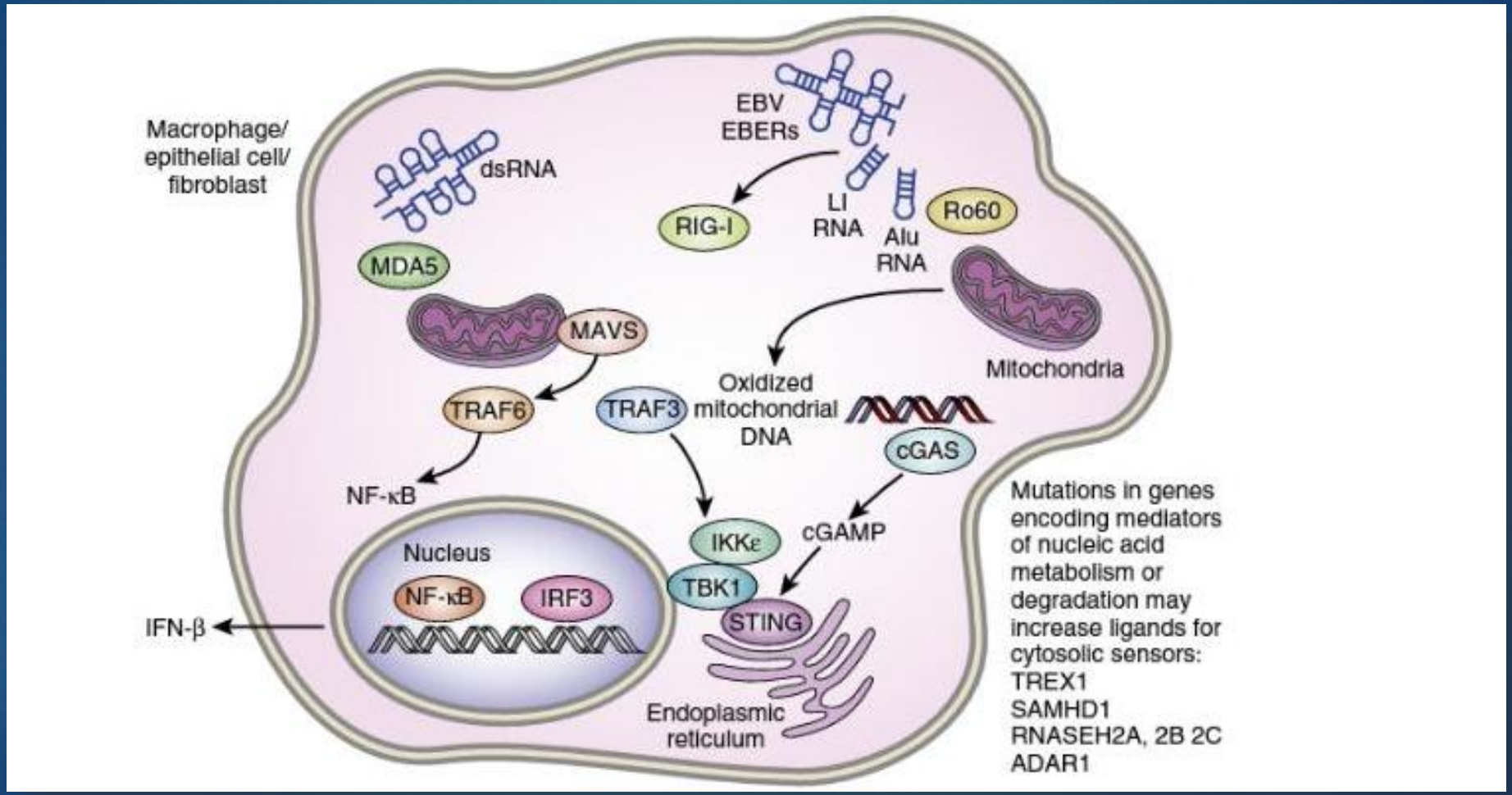
Innate Immune System Activation in Systemic Lupus Erythematosus

- **TLR-independent**
- Small RNAs (Alu RNA, [L1]-RNA, EBV-encoded small RNA–EBERs, viral RNA) may bind directly to RNA sensors RIG-I or MDA5 → increased permeability of mitochondria and release of oxidized mitochondrial DNA into the cytosol → Cytosolic DNA interact with the DNA sensor cGAS. generate of cGAMP, and activate of STING and TBK1/IKKε

- The RNA sensing pathway activate mitochondria-associated MAVS → activating TRAF3, TRAF6, TBK1/IKKε, and NF-kB
- **both RNA and DNA leads to activation of IRF3 as well as NF-κB transcription factors that generate IFN-β and other pro-inflammatory mediators**

- Aicardi-Goutières syndrome:
- Mutations in genes (TREX1, SAMHD1, RNASEH2A, RNASEH2B, RNASEH2C, and ADAR) may augment available cytosolic nucleic acids and drive increased signaling through RNA and DNA

Cytosolic sensor-mediated induction of type I INF



Innate Immune System Activation in Systemic Lupus Erythematosus

- association of autoantibodies with specificity for RNA-binding proteins (such as Ro, La, Sm, and RNP) with high expression of IFN-induced genes → significant role for RNA-containing immune complexes in innate immune activation and IFN production.

- TLR pathway activation :
  - lupus pathogenesis
  - production of particular autoantibody specificities

Innate Immune System Activation in Systemic Lupus Erythematosus

- **pDCs :**
  - major producers(type I INF)
- **Macrophages**
- expression of type I INF –stimulated genes ➡ lupus disease activity and lupus flares
- Platelets :
  - promoted IFN production by pDCs through signals mediated by CD40 ligand (CD154) on activated platelets and CD40 on the pDCs

Innate Immune System Activation in Systemic Lupus Erythematosus

- Keratinocytes :
  - produce IFN-κ that can promote expression of IFN-stimulated gene products and contribute to recruitment of inflammatory cells, potentially important for the pathogenesis of cutaneous lupus.
- bone marrow :
  - produce IFN-β
- neutrophils and their products:
  - IFN pathway activation
  - low-density granulocytes in the circulation of lupus patients
- mutations in *TMEM173,* encoding STING, suggest that epithelial cells might be additional producers of type I IFN

Innate Immune System Activation in Systemic Lupus Erythematosus

- ***NETosis:***
  - aggregates of nuclear or mitochondria-derived DNA and its associated histones, HMGB1,LL37, elastase, and myeloperoxidase into the extra-cellular
  - induced by interaction of neutrophils with vascular endothelial cells, activated platelets, or various cytokines, nucleosomes and RNA-containing immune complexes
  - induce production of type I IFN by pDCs
  - serve as a source of relevant self-antigens for presentation to T lymphocytes
  - mediate vascular damage and thrombosis

Innate Immune System Activation in Systemic Lupus Erythematosus

- decrease complement components (C1q, C2, and C4) in SLE:
  - ⬇ clearance of apoptotic debris BY complement components
  - ⬇ capacity of complement to solubilize immune complexes

Adaptive Immune System Alterations in Systemic Lupus Erythematosus

- in vitro experiments support the capacity of cytokines such as: **BAFF/BLyS** and **TLR ligands** To mediate antibody production by B cell

  T cells are recognized as the most efficient drivers of B cell differentiation

- Lupus T cells :
  - express **CD40 ligand (CD154)** after activation leading to augmented help for activation and differentiation of B cells exposed to those T cells
  - produce **less IL-2** , perhaps one factor that contributes to impaired generation of IL-2–dependent T regulatory cells,is of individuals carrying the HLA 8.1 haplotype
  - relative depletion of Tregs and increased Th17 cells and IL-17
  - inhibitor of IL-12 and IL-23 may provide support for the relevance of the T cell populations supported by those cytokines

Adaptive Immune System Alterations in Systemic Lupus Erythematosus

- The T follicular helper population, characterized by expression of ICOS,CXCR5, and Bcl-6, and by production of **IL-21** ➡ mediates important signals that promote differentiation of autoantigen-specific B cells

- "exhausted" CD8 T cell phenotype has been associated with relatively **good prognosis**

- Rapamycin(inhibitor of the serine/threonine kinase mTOR) ➡ relative depletion of CD8+effector-memory Tcells as a predictor of response

Adaptive Immune System Alterations in Systemic Lupus Erythematosus

- B cell regulation is also impaired in SLE, contributing to production of autoantibodies and cytokines
- B cell population, the so-called *ABCs* (age-associated B cells), is dependent on the transcription factors **T-bet and IRF5** and is enriched in patients with lupus and other autoimmune diseases

- altered B cell function is strictly secondary to :
  - Increased availability of T cell help
  - B cell survival
  - proliferation and differentiation factors
  - signaling through TLRs

- **BAFF/BLyS,IL-10, and IL-21 are among the candidate therapeutic targets that can modify the B cell differentiation program**

Adaptive Immune System Alterations in Systemic Lupus Erythematosus

- **Long-lived plasma cells** are proposed as sources of anti-Smith (Sm) and anti-Ro : refractory to modulation by immunosuppressive or B cell depletion therapy

- **circulating preplasma cells** or **plasmablasts** are sources of anti-dsDNA antibodies:
  - fluctuate in some patients in association with variations in disease activity
  - more amenable to anti–B cell therapy

- Increased production of type I IFN and presence of anti-nuclear antibodies in healthy family members of lupus patients likely reflect the consequences of genetic variations that are among the factors that predispose to SLE

Autoimmunity in Systemic Lupus Erythematosus

- Virtually all lupus patients demonstrate a positive **anti-nuclear antibody** test
- anti-dsDNA and anti-Sm are most specific for SLE
- **microbiome** might provide endogenous triggers of autoantibody specificities Anti-Ro, anti-La, and anti-RNP antibodies are characteristic of SLE but are also seen in other systemic autoimmune diseases.

Autoimmunity in Systemic Lupus Erythematosus

- The characteristic autoantibodies in SLE can be categorized in relation to their targets:

  - DNA and DNA binding proteins: aggregated in nucleosomes that contain histones
  - RNA and RNA-associated proteins: aggregated in cytoplasmic or nuclear ribonucleoprotein (RNP) particle
  - β2-glycoprotein 1:exposed in plasma membranes

- some patients with a clinical picture characteristic of SLE do not have significant titers of those autoantibodies :undefined autoimmunity targeted at unspecified antigens

Autoimmunity in Systemic Lupus Erythematosus

- differentiation of B cells by :

- activation of low-avidity self reactive T cells

  or

- direct activation of self reactive B cells in the presence of activating TLR ligands together B cell differentiation factors such as an BLyS/BAFF

=starting points for development of pathogenic autoimmunity

Autoimmunity in Systemic Lupus Erythematosus

- The presence of autoantibodies can be observed more than 5 years before clinical manifestations of disease appear:
  - **Anti- Ro** antibodies typically present earliest
  - **anti-dsDNA** antibodies appear several years later
  - **anti-Sm**:most specific for a diagnosis of SLE, appears approximately at the time of clinical diagnosis.
  - **Anti-C1q antibodies** :associated with lupus activity and with proliferative lupus nephritis

Autoimmunity in Systemic Lupus Erythematosus

- **important determinants of the antibody's capacity to bind to Fc receptors** :

- Ig class
- amino acid sequence and charge of the antigen binding site
  - Arginines in the CDR3 region of anti-dsDNA antibodies are characteristic
- complement-fixing capacity

Autoimmunity in Systemic Lupus Erythematosus

- The role of SLE autoantibodies in the pathogenesis of the disease:

- deposition of immune complexes in skin, renal glomerulus, and other sites of tissue injury
- nucleic acid–containing immune complexes can directly induce cell signaling and new gene transcription after accessing endosomal TLRs

Correlations Between Clinical Manifestationnof Systemic Lupus Erythematosus and Autoantibodies, Immune Complexes, and T Cells

Manifestation	Autoantibodies	Immune Complexes	T Cells
Nephritis	Anti-dsDNA Anti-Ro Anti-C1q Ids 16/6, 3I, and GN2	+	+
Arthritis	?	+	+
Dermatitis	Anti-Ro Anti-dsDNA Id 16/6		+
Vasculitis	Anti-Ro	+	+
CNS	Antiribosomal P Antineuronal Anti-NR2	+	
Hematologic			
Lymphopenia	Antilymphocyte		
Hemolysis	Antierythrocyte		
Thrombocyto-penia	Anti-platelet	+	
Clotting	Antiphospholipid		
Fetal loss	Antiphospholipid		
Neonatal lupus	Anti-Ro		
Sicca syn-drome	Anti-Ro		+
Mild disease	Anti-RNP without other autoantibody except anti-nuclear antibody		

RNP, Ribonucleoprotein.

Autoimmunity in Systemic Lupus Erythematosus

- the best-developed characterization of the mechanisms by which an autoantibody mediates disease is the role of maternal derived anti-Ro antibody in the neonatal lupus syndrome

- After transplacental transfer of anti-Ro antibody, RNA-containing immune complexes, activating the production of cytokines that contribute to fibrosis of the cardiac conduction system

Autoimmunity in Systemic Lupus Erythematosus

- **Anti-Ro** and **anti-La** antibodies:
  - sicca symptoms, subacute cutaneous lupus, and, neonatal lupus
- **Anti-RNP** antibodies :
  - SLE and mixed connective tissue disease.
- **Antiphospholipid antibodies**:
- placental damage and vascular thrombosis, thrombocytopenia in the antiphospholipid syndrome and lupus.
  - activate of the complement system and induce tissue damage and thrombosis
- Similar mechanisms might be relevant in forms of lupus renal disease characterized by microangiopathy.

Mechanisms of Target Organ Damage

- **tissue damage :**

- autoimmunity and immune system activation, along with an exaggerated or aberrant repair response:
- activation of the complement system by immune complexes deposited in tissue
- release of products of phagocytes, including enzymes released from neutrophil granules
- reactive oxygen intermediates from macrophages
- granulocytes and pro-inflammatory lipids

Mechanisms of Target Organ Damage

- **vasculature** role as a significant target organ contributing to disease in lupus has once again come to the fore
- potential role of **type I IFN** on endothelial cells and endothelial cell progenitor cells and impaired vascular repair
- Degos disease: association of activation of the IFN pathway with vascular sclerosis and endothelial damage

Mechanisms of Target Organ Damage

- Altered structure and function of both venous and arterial vessels include:
  - periarteriolar concentric onion skinning in th spleen
  - microangiopathy and associated microthrombi in some organs
  - endothelial dysfunction associated with premature atherosclerosis

Mechanisms of Target Organ Damage

- **Renal damage:**
  - monocyte populations that mediate inflammation and contribute to sclerosis and organ dysfunction
  - Infiltrating T and B cells in the kidney interstitium, with in situ production of autoantibodies specific for vimentin
  - IFN-a can also contribute to development of crescents in lupus kidneys

- **Podocytes damage** :proteinuria and lupus nephritis

- **CNS damage:**
  - autoantibodies with dual specificity for DNA and the NMDA receptor
  - cytokines

conclusion

- central role for innate immune system activation, including the role of type I IFN in lupus pathogenesis

- The products of the immune system, including:
  - autoantibodies and their immune complexes
  - cytokines
  - complement components
  - pro-inflammatory mediators
  - reactive oxygen products released from neutrophils and macrophages

conclusion

- alterations in molecular pathways that regulate genome integrity, nucleic acid degradation, TLR-dependent and -independent innate immune signaling, and lymphocyte activation thresholds ➡ important concepts that can guide future therapeutic approaches

- combination therapies that target components of both innate and adaptive immune systems may be required to achieve improved patient outcomes

- prevention of disease is an important goal:
- Efforts to apply the many lessons learned relevant to pathogenic mechanisms of SLE to assessment of patients at risk for disease development might result in design of preventive strategies.


مطرب بگو که کار جهان شد به کام ما
ساقی به نور باده برافروز جام ما
هرگز نمیرد آن که دلش زنده شد به عشق
ثبت است بر جریده عالم دوام ما
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