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Immunogenetics of some connective tissue disorders

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Abstract

Connective tissue diseases (CTDs) are systemic autoimmune disorders characterized by a large spectrum of clinical features and multisystemic involvement. Connective tissue disease is any disease that has the connective tissues of the body as a target of pathology.
Connective tissue is any type of biological tissue with an extensive extracellular matrix that supports, binds together, and protects organs. These tissues form a framework, or matrix, for the body, and are composed of two major structural protein molecules: collagen and elastin.

Autoimmunity involves the loss of normal immune homeostasis such that the organism produces an abnormal response to its own self tissue. The hallmark of autoimmune diseases generally involves the presence of self-reactive T cells, autoantibodies and inflammation

Introduction

Connective tissue diseases (CTDs) are systemic autoimmune disorders characterized by a large spectrum of clinical features and multisystemic involvement. CTDs include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), systemic sclerosis (SSc), dermatomyositis (DM) and polymyositis (PM) However, undifferentiated connective tissue disease is observe in some patients who cannot be assigned to a single disease category. overlap syndrom is observe when manifestations from two or more CTDs are identified in the same patient.[(1)]

Systemic lupus erythromatosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with complex etiology. Genetics plays an important role in lupus pathogenesis through its influence on clinical and autoantibody phenotype of the disease. [(2)]

The incidence rates of SLE range from approximately 1 to 10 per 100,000 person-years, and prevalence rates generally range from 20 to 70 per 100,000[(3)]

SLE, like many autoimmune diseases, affects females more frequently than males, at a rate of about 9 to 1 [(4)]

The X chromosome carries immunological related genes, which can mutate and contribute to the onset of SLE. The Y chromosome has no identified mutations associated with autoimmune disease[(5)]

Childhood-onset systemic lupus erythematosus generally presents between the ages of 3 and 15 and is four time more common in girls [(6)]

The disease appears to be more common in urban than rural areas. Sixty-five per cent of patients with SLE have disease onset between the ages of 16 and 55 years, 20% present before age 16, and 15% after the age of 55 [(7)]

The prevalence of late-onset systemic lupus erythematosus (SLE) diagnosed in patients over the age of 50 years is estimated at 10% to 20%. [8]

Aetiology

The aetiology of SLE includes both genetic and environmental components with female sex strongly influencing pathogenesis. These factors lead to an irreversible break in immunological tolerance manifested by immune responses against endogenous nuclear antigens.

Genetic factors

Siblings of SLE patients are approximately 30 times more likely to develop SLE compared with individuals without an affected sibling.

For instance Tranducer And Activator Of Transcription 4Signal (STAT4) a genetic risk factor for rheumatoid arthritis and SLE, is associated with severe SLE. One of the key components of these pathways is TNFAIP3, which has been implicated in at least six autoimmune disorders, including SLE [9]

Epigenetic effects

The most well understood type of epigenetic factor is DNA methylation, which plays a role in a variety of human processes, such as X chromosome inactivation and certain cancers. Previous research has also implicated the importance of DNA methylation in SLE. Differences in the methylation status of genes may explain, at least in part, the discordance observed in some identical twins that are discordant for SLE. Epigenetic mechanisms may represent the missing link between genetic and environmental risk factors [9]

Environmental factors

Anumber of environmental triggering factors have been associated with SLE, including UV light and cigarette smoking, some of which trigger lupus through epigenetic mechanisms [10]

Epstein–Barr virus (EBV) and cytomegalovirus (CMV), have been linked to the pathogenesis of SLE by several reports). Commensal microbes residing inside the host, in return, have been shown to maintain and expand CD8+ memory T cells during CMV infection, supporting the notion that microbiota and CMV cooperatively augment immune activation[11]

It is well established that certain drugs induce autoantibodies in a significant number of patients, most of whom do not develop signs of an autoantibody associated disease. These drugs may alter gene expression in CD4+ T cells by inhibiting DNA methylation and induce over-expression of LFA-1 antigen, thus promoting autoreactivity[12]

Antibiotics, which can remove gut bacteria, are known to trigger lupus flares. These include sulfa drugs such as trimethoprim– sulfamethoxazole (Septra), tetracycline-related antibiotics such as minocycline, and penicillin-related antibiotics such as amoxicillin [13]

Recently, several groups have found that metabolites produced by gut bacteria, especially butyrate produced by Clostridia, can promote the differentiation of regulatory T cells (Tregs) in the colon, spleen, and lymph nodes to suppress inflammation [14]

Hormonal factors

More than 90% of systemic lupus erythematosus (SLE) patients are female, suggesting an important role for sex hormones. Epidemiological data suggests both pregnant and postmenopausal women are more susceptible to developing SLE [5]

Disease activity in female SLE is associated with low testosterone, androstenedione,anddehydroepiandrosterone (DHEA). Moreover, immune cells express estrogen receptors, and lymphocyte activation by estrogen is associated with SLE disease activity [15]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that affects approximately 1% of the population. Initial symptoms include joint swelling, stiffness, and tenderness, which are all causes of disability. The diagnosis of RA is based on patient history of joint pain and stiffnes[16]

RA affects between 0.5 and 1% of adults in the developed world with between 5 and 50 per 100,000 people newly developing the condition each year [17]

The incidence rate ratio among ever smoking patients was 1.96 after 30 pack-years, and 1.034 per year of smoking implying a doubling of risk after 20 years regardless of sex and smoking intensity [18]

Genetic and Environmental Factors

Rheumatoid arthritis involves a complex interplay among genotype, environmental triggers, and chance. Twin studies implicate genetic factors in rheumatoid arthritis, with concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins [19]

The long-established association with the human leukocyte antigen (HLA)–DRB1 locus has been confirmed in patients who are positive for rheumatoid factor or ACPA.[20]

These findings suggest that some predisposing T-cell repertoire selection, antigen presentation, or alteration in peptide affinity has a role in promoting autoreactive adaptive immune responses. [21]

Genetic risk factors for ACPA-negative disease appear to be not less important than those for ACPA-positive disease. However, they are less well established and involve different HLA alleles (e.g., HLA DRB1*03), interferon regulatory factors (e.g., interferon factor 5), and lectin-binding proteins (e.g., C-type lectin domain family 4 member A) [22]

Moreover, smoking and HLA-DRB1 alleles synergistically increase one's risk of having ACPA.[23]

Several citrullinated self-proteins are recognized in anti-CCP assays, including α-enolase, keratin, fibrinogen, fibronectin, collagen, and vimentin[24]

Infectious agents (e.g., Epstein-Barr virus, cytomegalovirus, proteus species, and Escherichia coli) and their products (e.g., heat-shock proteins) have long been linked with rheumatoid arthritis.[25]

Finally, the gastrointestinal microbiome is now recognized to influence the development of autoimmunity in articular models, and specific clinical bacterial signatures that are associated with autoantibody positive rheumatoid arthritis are emerging [26]

Systemic sclerosis

Systemic sclerosis (SSc) (scleroderma) is a complex autoimmune disease that clinically manifests as progressive fibrosis of the skin and internal organs. Anti-centromere antibodies (ACAs), anti-topoisomerase antibodies (ATAs), and anti-RNA polymerase III antibodies (ARAs) are three mutually exclusive SSc-associated autoantibodies that correlate with distinct clinical subsets characterized by extent of cutaneous involvement and pattern of organ involvement [27]

Scleroderma is a chronic sclerosing disease of the connective tissues. Hidebound skin is an important and characteristic feature of this disease [28]

Scleroderma exists in two forms: morphea (circumscribed scleroderma) and generalized/progressive(diffuse scleroderma). [29]

Systemic sclerosis is a rare disease. Systemic scleroderma has an incidence of 0.3–2.8/100,000/year and a prevalence of 1–15/100,000. The distinct female predominance is seen in the female: male ratio of 3:1 [30]

Type of Systemic Sclerosis

Diffuse Scleroderma

Affects the skin as well as the heart, lungs, GI tract, and kidneys.

Limited Scleroderma

Mostly affects the skin of the face, neck and distal elbows and knees and late in the disease causes isolated pulmonary hypertension. CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, Telangiectasias) is associated with limited scleroderma [31]

The diffuse form of systemic sclerosis (DSSc) occurs equally in males and females. The limited form of systemic sclerosis (LSSc) has a strong female predominance, with a female-to-male ratio of 10:1. [32]

Systemic sclerosis usually appears in women aged 30-40 years, and it occurs in slightly oldermen.Pulmonary hypertension leads to 12% of systemic sclerosis–related deaths.

Lung fibrosis and heart changes are responsible for 9% of systemic sclerosis–related deaths. [33]

Family and twin studies

The disease can occur in families in which a member has already been diagnosed with SSc or another autoimmune disease. Having a sibling with SSc is one of the highest risk factors [34]

Candidate-gene studies

Multiple candidate-gene studies of SSc have been carried out. Most often, the candidate genes and single-nucleotide polymorphisms (SNPs) were selected on the basis of their involvement in the susceptibility to other autoimmune diseases [35]

Genome-wide association studies

GWAS identifiedthat IRF8 is specifically associated with lcSSc. The same study also demonstrated that HLA-DQB1 is associated with anti-centromere autoantibodies (ACA) positivity,whereas HLA-DPA1/B1 was associated with anti-topoisomerase autoantibodies (ATA) positivity. Less discriminating was NOTCH4, which was associated with the presence of both ACA and ATA [36]

GWAS show that T cell signalling and interferon signalling pathways are involved in SSc susceptibility, and reveal roles in apoptosis, DNA or RNA degradation and autophagy [37]

The role of epigenetics in SSc

The environment can affect the breakage of immune tolerance and the development of fibrosis and SSc in certain genetic backgrounds. This concept is supported by numerous studies indicating that different environmental factors, including occupational exposure to silica dust, vinyl chloride or drugs such as bleomycin, can induce SSc-like symptoms[38]

Interestingly, no clear association between smoking and the risk of developing SSc has been established.Potential mechanisms for environmentally induced systemic autoimmunity include interference with immune tolerance, activation of the immune system, induction of genetic alterations and dysregulation of epigenetic patterns [39]

Dermatomyositis and polymyositis

Dermatomyositis (DM) and polymyositis (PM) are autoimmune myopathies characterized clinically by proximal muscle weakness, muscle inflammation,extramuscularmanifestations and frequently, the presence of autoantibodies. Although there is some overlap, DM and PM are separate diseases with different pathophysiological mechanisms [40]

The estimated incidence of dermatomyositis is 9.63 cases per million population. The estimated incidence of amyopathicdermatomyositis (AMD) is 2.08 cases per million [41]

Immune mechanisms in PM and DM

The strongest support for an immune-mediated myopathy is the presence of cellular infiltrates of both the adaptive and innate immune systems in muscle biopsies and the frequent presence of autoantibodies. [42]

Autoantibodies

To date a majority of patients with PM and DM has at least one myositis specific antibody (MSA) if sensitive techniques to identify autoantibodies are utilized. Other autoantibodies can also be found, so-called myositis-associated autoantibodies (MAAs), which may also be present in other autoimmune diseases such as SLE and SS. The most frequently present MAAs in PM and DM are anti-SSA or anti Ro-52 and anti-PMScl[43]

Sjögren's syndrome

Sjögren's syndrome (SS), a systemic autoimmune disease, is characterized by inflammation of exocrine tissues accompanied by a significant loss of their secretory function. Clinical symptoms develop late and there are no diagnostic tests enabling early diagnosis of SS [44]

Sjögren syndrome affects 0.1-4% of the population. This wide range, in part, reflects the lack of uniform diagnostic criteria [45]

The female-to-male ratio of Sjögren syndrome is 9:1. Sjögren syndrome can affect individuals of any age but is most common in elderly people. Onset typically occurs in the fourth to fifth decade of life

One of the consequences of the stimulation of innate immunity is the activation of nuclear factor κB (NFκB), which can occur in a number of different cell types. In salivary gland epithelial cells from patients with pSS, hyperactivation of NFκB has been associated with decreased expression of one of the regulators of NFκB activation, A20 (also known as TNF α-induced protein 3 [TNFAIP3]) [46]

Furthermore, the first GWAS in pSS identified an association between this disease and a gene (TNIP1) encoding TNFAIP3-interacting protein 1, a protein that interacts with A20 and is involved in the regulation of NFκB activation.[47]

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