Review Article

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Microorganisms and Autoimmunity

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Abstract

Autoimmume diseases occur when the host's immune system reacts against own or self antigens. Many microorganisms can trigger and initiate autoimmunity by various mechanisms.These things are very interesting to note and study. Hence here we try to present relevant information about epidemiology and pathogenesis behind microbes causing autoimmunity.

Keywords: Autoimmune, infection, vaccination.

Introduction

Microbes play a role in induction of autoimmunity. Microbes, both pathogenic and commensal, can stimulate production of autoantibodies that bind to brain and can influence behaviour in susceptible hosts.[1] This is now a very interesting and hot topic of research. Any disruption of normal microbiome may trigger autoimmunity. Non-pathogenic microorganisms found in various parts of body are called commensal microbiota. There are three major features of host–commensal interactions. Mechanisms of central tolerance, or deletion and inactivation of self-reactive lymphocytes and their inhibition by regulatory T cells (Tregs) exist to minimize autoimmunity. Potentially autoreactive immune cells are always found in the host.[2]

Autoimmune diseases can be broadly divided into two large groups: Group I consists of diseases that need innate–adaptive immunity connection, and Group II, or those for which this connection is not important. Group II diseases occur due to the loss of control over one of the principal mechanisms controlling adaptive immunity, like negative selection or generation of Tregs.[2]

Conventional commensal microbiota is free of specific pathogens. However they can harbour microbes that are not pathogenicnormally. This category of commensal microorganisms can confer protection against autoimmunity.[2] Bonafide pathogens can either suppress or provoke autoimmunity. Coxsackie B3 viruses can induce type 1 Diabetes mellitus in the mouse model.[3]

Mechanisms by which microbes induce autoimmunity

Microbes can initiate or precipitate autoimmunity in many ways. Firstly, molecular mimicry can be important for autoimmunity. Acute Rheumatic fever is a disease caused by destruction of myocardium due to cross-reactivity or molecular mimicry with Group AStreptococcal antigens.[4] Klebsiellapneumoniae,can carry antigens mimicking MHC class I molecule HLAB27 and, hence can possibly induce Ankylosing spondylitis.[2]

Secondly, there can be induction of co-stimulation and cytokine production by APC (Antigen presenting cell) activated by infection, which also presents self-antigens, activating autoimmunity. This is called "bystander activation.[2] Thirdly, specific commensal bacteria induce production

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of cytokines affecting autoimmunity. Segmented filamentous bacteria stimulate generation of Th17 and Th1 types of T-cell responses.[2] Whereas Th17 cells are critical for defence against somepathogens, they also contribute to autoimmunity. Th17 cells induced by SFB (Segmented filamentous bacteria) can affect autoimmune reactions in remote organs, likejoints.[2]

In this chapter the author has tried to present in a concise manner all available information in this respect.

Evidence in illnesses

Neuropsychiatric illnesses

An increased prevalence of familial autoimmunity, exposure to pathogens prenatally and postnatally, and findings of anti-brain antibodies are common in schizophrenia, obsessive-compulsive disorder and autism. So differences in exposure timing and genetic vulnerability are important determinants of neuropsychiatric outcomes.[5]

Diabetes mellitus

A initially high level of amyloid-producing E. coli in the intestine, followed by their depletion, most likely due to prophage induction, can lead the initiation of autoimmunity and T1D progression. The diabetogenic role of E. coli prophagesis supported by activation of E. coli prophages with mitomycin C resulting in pronounced amyloid release from preformed microbial biofilms. Together with metagenomics data, these findings suggest that same process might occur in gut of children who develop autoimmunity and T1D.[6] Enterovirusescan also causeT1D in humans.[7] Seasonal incidence of T1Dare documented afterEnterovirus infections. However the etiological link is enigmatic.[7] A higher frequency of enterovirus infections has been found in siblings with type 1 diabetes as compared to nondiabetic controls.[7] Additionally, higher titres of enterovirus antibodies are seen in pregnant mothers whose children later develop T1D.[7]

Protein produced by common gut bacteria trigger the onset of autoimmune diseases like multiple sclerosis (MS), rheumatoid arthritis, and ulcerative colitis.

Some patients with autoimmune disorders display higher than normal levels of a "mimic protein" (ubiquitin) produced by Bacteroidesfragilis, a Gram negative anaerobe normally found in gut.[8] Ubiquitin tagging (ubiquitylation) of proteins affects nearly every eukaryotic cell function. Ubiquitin is also involved in the development and function of immune system.[9] B. fragilis is unique in being the only bacterium to encode an ubiquitin homologue. B. fragilis is produces and exports a eukaryotic ubiquitin which is closely related to mammalian ubiquitin and is structurally similar.The B. fragilis gene sequence indicates a past horizontal gene transfer from an unknown eukaryotic source. It encodes a protein with 63% identity to human ubiquitin.[9] B. fragilis ubiquitin can cross human gut lining and generate immune response. People with lupus and RA are more likely than healthy volunteers to have antibodies to BfUbb (B. fragilis ubiquitin). Interestingly, another role of Bacteroides spp. is also important. Some B. fragilis strains produce a capsular polysaccharide that stimulates dendritic cells to alter ratio of T helper cells and producesIL-10, which reduces production of proinflammatory IL-17.[9]

Autoimmunity in HUS

Haemolytic uraemic syndrome (HUS) is a severe disease with renal failure, microangiopathicanemia and thrombocytopenia. Several mechanisms leading to HUS are identified, like infections with enterohaemorrhagic Escherichiacoli, and genetic mutations of complement genes, which result in defective complement control on surface of host cells. In atypical HUS, autoantibodies that bind complement inhibitor Factor H are important.[10] Susceptibility to reactive arthritis, an acute inflammatory joint disease after intestinal bacterial infection, is associated with MHC class-I genes, notably HLA-B27. The disease follows infection with intracellular bacteria, including Chlamydia, Salmonella, Shigella, and Yersinia species. This association is established based on isolation and analysis of antibody responses. These bacteria enter body through mucosa and invade cells. Yersinia enterocolitica is taken up by M cells in Peyer's patches through interaction between bacterial surface invasin and host β1-integrins. Yersinia can use phagocytes to translocate through endothelium, reaches bloodstream and synovium.[11] Reactive arthritis and ankylosing spondylitis have a very strong association with the MHC class I allele HLA-B27. HLA-B27 is found in about 80% of cases with reactive arthritis and in over 95% of cases with primary ankylosing spondylitis. Ankylosing spondylitis can be preceded by reactive arthritis. Several studies indicate persistence of bacteria and bacterial antigens in patients with reactive arthritis. These patients have continued IgA antibody responses against the triggering microorganisms. Mononuclear phagocytes carrying antigens of arthrogenic microorganisms

(LPS, heat shock proteins) can enter peripheral circulation. They are the major source of microbial antigens reachingsynovium. In Yersinia-induced arthritis, LPS, 60-kDa heat shock protein, and urease β-subunit have been detected in joint by immunohistochemistry or immunoblotting.[11]

Guillain-Barre syndrome (GBS)

GBS or autoimmune demyelinating radiculoneuropathy is an inflammatory disease of the peripheral nerves that can follow infection with Campylobacter jejuni, Epstein-Barr virus, cytomegalovirus, and Mycoplasma pneumoniae. GBS shows lymphocytic infiltration and demyelination in peripheral nerves. The onset is sudden and limb weakness progresses to maximum disability within 1 week of onset. C. jejuni is the principal agent associated with GBS. Campylobacter, the commonest cause of bacterial diarrhea in the US, are Gram-negative bacilli that readily invade the intestinal mucosa.[11] In GBS, involvement of C. jejuni has been documented by serology,and direct isolation from GBS patients. In astudy, C. jejuni is found in 26% of GBS patients and 2% of household controls.[12] Infection with C. jejuni stimulates formation of antibodies cross-reacting with peripheral nerve antigens. Patients with GBS develop antibodies specific for LPS of C.jejuni thatcrossreactwith gangliosides from peripheral nerves. Gangliosides are membrane-anchored glycosphingolipids. The outer polysaccharide of LPS from Campylobacter bear structural similarities to gangliosides of peripheral nerves. The Campylobacter O:19 serotype shares an identical tetrasaccharide with GM1 ganglioside and a pentasaccharide with GD1a ganglioside.[11] Serotypes O:23 and O:36 share a branched tetrasaccharide with GM2 gangliosides. Patients with GBS develop antibodies against LPS of certain C. jejuni strains that crossreact with gangliosides from peripheral nerves. Gangliosides are membrane-anchored glycosphingolipids with hydrophilic extracellular oligosaccharide. Serotypes O:23 and O:36 share a branched tetrasaccharide with the GM2 ganglioside.[13]

GBS can also occur after CMV infection. CMV-related GBS has a different clinical pattern from other GBS groups. Patients are significantly younger, and initially have a severe course with a high frequency of breathlessness, and frequently develop cranial nerve involvement and severe sensory loss. This is in contrast to C. jejuni infection, which causes motor GBS.[14] Studies have reported the presence of IgM anti-GM2 antibodies in GBS patients after CMV infection.[15] CMV related GBS is also associated with increased soluble adhesion molecules and interleukin-2 receptor in blood, suggesting activation of T cells. The histological picture of the AIDP form of GBS is similar to experimental autoimmune neuritis, which is T cell–driven. Similarities between CMV and Schwann cell or myelin proteins has also been noted.[15]

Miller-Fisher syndrome(MFS) is a less severe and rarer variant of GBS. The worldwide incidence of GBS is 1 to 2 in 100,000, with the MFS variant producing a subsetof cases (1 to 2 in 1,000,000). MFS affects more men than women and has a mean age of 43.6 years at onset of symptoms. MFS presents with at least 2 of the following features: ataxia, areflexia, and ophthalmoplegia. It is commonly associated with the involvement of lower cranial and facial nerves and does not involve motor weakness of limbs.[16] MFS is thought to result from aberrant acute autoimmune response to prior infection by Campylobacter jejuni, Cytomegalovirus, EBV, or HIV. A cross-reaction between peripheral nerve antigens and microbial components is said to drive the inflammatory process of MFS.[15] Several studies report that IgG anti-GQ1b antibody, isfound in MFS. The feature of ophthalmoparesis in MFS occurs from direct action of anti-GQ1b antibodies on the neuromuscular junction between the cranial nerves and ocular muscles.

Role of microbiome in autoimmune disease

The human microbiomerefers to the entire habitat, including microorganisms, their genomes and the surrounding environmental conditions. When the equilibrium between microbial habitat and host is disturbed, dysbiosis is caused. Commensal microorganisms play a central role in maintaining homeostasis and health, not only by blocking microbial activity but also by reinforcing immune system through specialized mechanisms.[17]

Oral microbiota

The oral microbiome (OMB) is responsible for the manifestation of many intra- and extraoral diseases. A dysbiotic shift of oral host microorganisms triggers disease entities, like dental caries, periodontal diseases, periimplant inflammation and halitosis.[17] There are oral bacteria which prevent pathogenic colonization by other microbes (colonization resistance). Also, the antagonistic or synergistic interaction between commensal and pathogenic microorganisms is responsible for eliciting oral diseases. Sjogren's syndrome or SS is a systemic chronic autoimmune disease,

characterized by B-cell hyperactivity, that produces antibodies and lymphocytic infiltration of exocrine glands resulting in their destruction. Salivary and lacrimal glands are primarily attacked, leading to a significant reduction in saliva and tear production, which then leads to the most prominent symptoms of the disease, oral and ocular dryness. Firmicutes have a significantly higher frequency in patients, but Spirochaetes are significantly depleted in SS. Streptococcus and Veillonella show almost a two-fold increase in SS. Also, Veillonellaatypica and Veillonellaparvula dominate in patients, but Prevotellamelaninogenica dominates in controls. So, the microbiome is less diverse and richn in patients, where a depletion of nearly 17% in number of genera is detected.[17] A microbial protein (von Willebrand factor type A) carrying the peptide Ro60 , is present in the commensal oral bacteria Capnocy to phagaochracea. It can activate T cells with a receptor for Ro60 (SSA) through dendritic cells. SSA autoantibodies might be produced when activated Ro60-reactive T cells activate B cells into plasma cells. If next-generation sequencing methods for analyzing OMB in patients with SS reveal an increased relative abundance of C. ochracea in the mouth, the microbiome–SS connection can be explained by molecular mimicry theory.[17]

Rheumatoid Arthritis (RA) is a chronic systemic disease of the synovium characterized by inflammation, hyperplasia and formation of autoantibodies, like the rheumatoid factor and anticitrullinated protein antibodies. This leads to symmetric polyarthritis and destruction of cartilage and bone. The OMB may trigger RA. There is evidence to suggest that periodontal pathogens Aggregatibacteractinomycetemcomitans and Porphyromonasgingivalis are autoimmunity triggers for RA. A. actinomycetemcomitans produces leukotoxin A, which forms pores on neutrophil membranes, producing neutrophil hypercitrullination, which leads to the release of citrullinatedautoantigens in gum. Research has also shown that 47% of patients with RA have had previous A. actinomycetemcomitans infection as compared with 11% in controls.[17]

Microbiome in other parts of body

Recently, scientists have found that autoantibodies formed against the cell wall mannan of the yeast Saccharomycecerevisiae , were detected in several autoimmune diseases with different manifestations, like RA, SLE and Anti-phospholipid syndrome. Anti-S. cerevisiae antibodies (ASCAs) are a serological marker of Crohn's disease (CD) in about 32% cases. Also, S. cerevisiae is used as adjuvant in vaccines. This has led to a hypothetical risk of developing abnormal immune activation after an autoimmune/inflammatory syndrome induced by adjuvants (ASIA).[18] Inflammatory bowel diseases (IBD) ,is an example of how alteration of gut microbiome can induce disease. Both CD and UC are associated with a reduced complexity of the commensal microbiota and shiftto a dysbiotic state. In a similar manner to that observed during acute mucosal infections, both CD and UC are characterized by the outgrowth of proteobacteria, in particular Enterobacteriaceaeand Fusobacteriaceae.[18] Moreover, adherent-invasive E. coli, Yersinia and Clostridium difficile are more common in patients affected by Crohn's disease than healthy individuals and, in mouse models, these bacteria have been shown to be contributors to IBD.

Enterococcusgallinarum, SLE and other autoimmune diseases

The events before establishment of infectious-related autoimmunity depend on microbiome changes of an individual with time. Enterococcus gallinarum, a Gram-positive gut pathobiontcan translocate, in gut barrier breakdown, into any systemic organ like liver and induce experimental autoimmune disease in genetically susceptible mice; namely, Systemic lupus erythematosus (SLE).[19] So Enterococcus gallinarum, present in the gut of lupus-prone (NZW x BXSB) F1 mice, has emerged as a candidate pathobiont for triggering SLE.[20] The same can happen in man and should be explored.In lupus patients, autoantibodies target many antigens, like double-stranded DNA (dsDNA), phospholipids, cardiolipin, and b, 2-glycoprotein. Genome-wide association studies have identified a definite genetic risk for SLE. However disease onset can occur in response to environmental insults of a biological, chemical, or physical nature.[21] In fact, E. gallinarum has also been isolated from stool samples and liver biopsies from patients having autoimmune hepatic disease and lupus patients with hepatic involvement.[20] SLE patients with Ribosomal P autoantibodies have higher anti-E. gallinarum IgGtitersthan healthy controls. In addition to anti-Ribosomal P antibody, higher anti-E. gallinarum titersare also significantly found to be associated with presence of anti-ds DNA and anti-Sm (anti- smooth muscle) autoantibodies.[20] Also, anti-E. faecalis IgGtiters are significantly higher in patients positive for antibodies to dsDNA, Sm, chromatin, and

RNP(Ribonucleoprotein) autoantigens.Growing usage of broad-spectrum antibiotics has increased prevalence of infections caused by E. gallinarum, slowly leading to multi-drug resistance and nosocomial infections of urinary tract, abdominal and biliary tracts.[19] Liver-resident E. gallinarum induces hepatic overexpression of ERV gp70 (Endogenous Retroviral Glycoprotein 70) that causesanti-ERV immune complex formation and systemic autoimmunity. This can also drive lupus kidney disease viaTLR-7.[22] E. gallinarum can induce expansion of plasmacytoid dendritic cells (pDCs) in lamina propria of small intestine of mice. These pDCs are potent producers of type I IFNs(Interferons), linked to SLE.[21] AlthoughE. gallinarum is a relatively minor component of the gut microbiome of lupus mice, it is prominent in internal organs, like liver. Hence, hepatocytes from lupus mice were co-cultured with E. gallinarum, E. fecalis, and B. thetaiotaomicron. Among these, E. gallinarum efficiently induces the transcription of IFNα and the lupus autoantigens b, 2-GPI and Erv gp70.[21] A specific antagonist blocking AhRsignaling reduces the levels of serum anti-dsDNA autoantibodies in E.-gallinarum-monocolonized mice, supporting the role of AhR-Th17 axis in inducing autoimmune inflammation.[21] Also, this autoimmune activity may be via the TLR 7 expression. SLE is found more in women (90%) then men, and the TLR7 locus is among X-linked genes that might promote disease in females. If further studies confirm a specific anti- E. gallinarum antibody signal in patients, this could be a very useful biomarker for SLE.[21]

Link of SLE with other gut bacteria and parasitic tissue infections

Infections caused by other pathogens, or the lack of them are associated with development of SLE . Epstein–Barr virus (EBV) and CMV, for example, have been linked with SLE by many reports.[23] Other studies have identified hepatitis B virus (HBV) as protective against SLE.[23] About 2.5% of SLE patients were found positive for presence of HBV-core antibody, compared to 10.7% from normal controls, which suggests a potential benefit of HBV infection. Helicobacter pylori seronegativitywas found to be associated with an increased risk and also earlier onset of SLE in African Americans, indicating a protective role of the bacterium.[23] Antibiotics, which can remove commensal gut bacteria can trigger lupus flares in humans. These include Trimethoprim–Sulfamethoxazole,Tetracycline derivatives and aminopenicillins.[23] Butyrate produced by Clostridium spp. can promote differentiation of regulatory T cells (Tregs) in colon, spleen, and lymph nodes to suppress inflammation. Also, removal of certain gut commensals with antibiotics can lead to decreased bacterial metabolites, such as homoserine lactone, N-acetylmuramic acid, and N-acetylglucosamine which are immunosuppressive, causing SLE progression. Dietary components influence SLE by changing composition and function of gut microbiota, immunomodulation, and by exerting epigenetic changes.[23] Lipopolysaccharide (LPS) is a Gram-negative cell wall component recognized by TLR4. In SLE, soluble CD14 (sCD14), released by monocytes in response to LPS, is increased in blood.[23] The level of sCD14 can be correlated with disease activity. Enhanced TLR4 signalling by LPS stimulation can induce SLE. LPS can do so by inducing neutrophil activation and migration, which promote development of SLE.[23] Inhibition of TLR4 reduces autoantibody production and diminishes glomerular IgG deposits in kidney in lupus-prone mice.

Lipoteichoic acid (LTA), an important component of Gram-positive bacterial wall, is also important in lupus pathogenesis. LTA is a ligand for TLR2, whose expression is increased in T cells, B cells, and monocytes in blood in SLE. Another bacterial antigen and component of bacterial biofilms, amyloid fiber (curli), is reported to induce autoantibody production in mice.[23] Amyloid fibers can tightly bind to extracellular DNA in bacterial biofilms. These Amyloid-DNA composites are strong stimulators of both innate and adaptive responses, and promote IL-6 and TNFα production and type I interferon response in mice models.[23] Injection of curli-DNA composites greatly increase autoantibody level in lupus-prone mice, and stimulate autoantibody production in wild-type mice.

Lactobacilli are known to be beneficial to the host when administered in adequate amounts. Health benefits provided by consumption of Lactobacilli are: prevention of constipation, hepatic disease, infections, allergies, and as recently suggested, inhibition of autoimmune diseases such as IBD and T1D.[23] Some Lactobacillus strains canmodulate host microbiota, inhibiting the formation of NETs (Neutrophil Extracellular Trap), improving antioxidant status, and increasing expression of genes that encode for junction and adhesion proteins. Thus some strains of Lactobacillus can be used for managing SLE.

Toxoplasma gondiiinfection may be beneficial for SLE. IFNγ and IL-10 expression are reduced

in the spleen of mice in the presence of T. gondii, suggesting the suppression of T helper 1 (Th1) and Th2 responses, respectively, both shown to be pathogenic for murine lupus.[23] Studies have found that female SLE patients have more active monocytes with enhanced TLR4 responsiveness than male patients, which can explain the gender preponderance of SLE.

Role of microbes in Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune demyelinating disease, caused by a complex interaction of genetic and environmental factors. MS is the commonest cause of non-traumatic neurological disability in young adults.Numerous causative factors have been postulated, including exposure to several bacteria.[24] Mycobacterium spp., Chlamydia pneumoniae, Helicobacter pylori, and other bacteria are risk factors for MS with different mechanisms of action. Bacteria express specific pathogen-associated molecular patterns (PAMPs), which are recognized by cells of the innate immunity equipped with pattern-recognition receptors (PRRs). Human MyD88 is most important adaptor protein for inflammation used by all TLRs (except TLR 3). Helminth antigens modulate immune responses in B cells and dendritic cells isolated from parasite-infected MS patients by TLR2, through signalling pathways including MyD88-dependent pathway.[24]

Nod-like receptors (NLRs) are intracellular proteins that bind peptidoglycans of bacterial cell wall.[25] Nucleotide binding oligomerization domain (NOD)1 detects gram-negative bacteria like Chlamydia or Helicobacter pylori, whereas NOD2 is involved in recognizing mycobacteria.[25] NLR family members are positive and negative regulators of inflammatory responses; mutations in NLRP1 gene are linked to MS.[24] Microglia are resident macrophages of CNS that are the first line of defence in response to pathogens. Circumventricular organs are structures permitting substances like hormones to leave brain without disrupting BBB and allow microglia to sense signs of infection via TLRs, NLRs, and scavenger receptors.[26] Mycobacterium tuberculosis, Streptococcus pneumoniae, and others can penetrate BBB or the blood–CSF barrier and enter into CNS, and release toxic cell wall components. This promotes further production of inflammatory factors by activated microglia, with neurotoxic or neuroprotective functions, depending on stage of disease.[24] The microbiota has an important impact in bidirectional interactions between enteric nervous system and the CNS. Some commensal Clostridia stronglyinduceTregs and maintain gut homeostasis, whereas others contribute to Th17 cell expansion in MS.[24] Another interesting study revealed that CD4 T cells were responsible for IL 17A activation and demyelination in mice models of EAE or Experimental autoimmune encephalomyelitis. Treating the mice with Ampicillin ameliorated these symptoms.[27] This further substantiates microbial pathogenesis theory in MS.

Lactobacillus spp. in gut may worsen MS.Research suggests that antibiotic or probiotic strategies that are developed to help prevent or treat multiple sclerosis should consider host genetics, pre-existing gut microbiome, and the timing or mode of intervention. Scientists found that Lactobacillus reuteri, commonly used in probiotics, can increase disease severity in mouse model of MS, in genetically susceptibleanimals.[28] Hence both genetic makeup and gut microbiotaare important.

Psoriasis and autoimmunity

Psoriasis is a chronic proliferative autoimmune disease with about 0.3-4.8% prevalence. Its aetiology is still undetermined, but genetic and environmental factors are important.[29] One of the considered environmental factors is infestation with Malassezia yeast. Malassezia's role in psoriasis is still not determined, but itmay be related.[29] Malassezia yeasts induce Th1 and Th2 related cytokine, chemokine, and PGE2 production in PBMCs from patients with psoriasis and atopic dermatitis.Malassezia have role in pathogenesis of atopic dermatitis and psoriasis by inducing allergic and inflammatory reactions. In a study on psoriasis skin biopsies with positive and negative Malassezia, TGF1 up regulation, Integrin chain and HSP70 expression in keratinocytes due to Malassezia was proven. So Malasseziahelps in overproduction of molecules important in cell migration and hyperproliferation.[29] Malassezia also has a role in the psoriatic Koebner phenomenon by chemotaxis of PMNLs.M. furfur up-regulates TGF-β1, integrin chain, and HSP70 expression in keratinocytes. In biopsies of M. furfur-positive psoriasis-affected patients, an increase in TGF-beta1, integrin chains, and HSP70 expression was found.[30] M.furfur can exacerbatePsoriasis.[30] Malasseziaglobosais associated with exacerbation of scalp Psoriasis.[31] Chronic plaque psoriasis or psoriasis vulgaris is caused and aggravated by Malassezia. The association was first proposed in

1873. Narang et al., in 2007 also observed them in lesions and lesionsrespondedto fluconazole.

In psoriatic patients withscalp lesions, eyebrows, ears and seborrhoeic areas of trunk involvement, Malassezia has strong association.[32]

Vitiligo andautoimmunity

Vitiligo is anautoimmune disease characterized by hypo pigmentation of skin, and affects 0.5 to 1% people worldwide. There is loss of pigment resulting from the massive destruction of skin melanocytes. Patients exhibit progressive skin depigmentation after environmental triggers. Depigmentation is due to skin-infiltrating cytotoxic T cells,in genetically predisposed individuals, acting against melanosomal proteins.[33] Hereditary factors support autoimmune aetiology. In lesional skin, there is less diversity of skin microbiota and increase in Firm cutes. In non-lesional skin there is abundance of Actinobacteria.[34] Also, levels of serum metabolites like taurochenodeoxycholate and L-NG-monomethyl-arginine in vitiligo patients differ from healthy individuals and show significant correlations with microbial markers.

Gut dysbiosis influences systemic immunity and is implicated in autoimmune conditions. Microbial diversity helps maintain immune homeostasis, but individual species may be pathogenic, like Ro60-producing commensal bacteria in lupus.[33] Ampicillin can induce reactive oxygen species (ROS) formation in bacterial and human cells, affecting gut permeability. ROS formation is important in Vitiligo, where increased cytokine production correlates with increased ROS and reduced antioxidant levels.[33] Ampicillin use causes outgrowth of proinflammatory bacteria and provides antigens taken up by gut dendritic cells to activate T cells against melanocytes. Corynebacterium, Ruminococcus, Jeotgalibaca and Psychrobacter correlate with disease duration and serum IL-1β levels in vitiligo.[35] Vitiligo subjects harbour a skin microbiota that is unique. Notably, a previously uncultured Corynebacterium species appears moreinvitiligo than control subjects.[36]

Bacteria and antiphospholipid syndrome

Antiphospholipid syndrome (APS or APLA) is an immune disorder that increases risk of developing blood clots.[37] There are lung clots, strokes, heart attacks, and in pregnant women, miscarriages or still births in APS. It is an acquired autoimmune disorder that manifests clinically as recurrent venous or arterial thrombosis and/or fetal loss. Laboratory findings include persistently elevated levels of antibodies against membrane anionic phospholipids like anti-cardiolipin antibody, anti-phosphatidylserine or associated plasma proteins, like beta-2 glycoprotein I (β2GPI) or a circulating anticoagulant.[38] There is also a relationship between Roseburiaintestinalis, a commensal gut bacterium and APLA.[37] Roseburiaintestinalis triggers disease in genetically predisposed people. In them, T and B cells react to a blood protein involved in clotting, and similar amino acid antigens of the bacterium. Rose buriaintestinalis, an anaerobic Gram-positive bacterium common in gut of APS patients, has many homologous sequences to major B and T cell epitopes and stimulates lymphocytes. Over time, this ongoing "cross-reactive" response causes tissue damage and chronic disease. Other bacteria can also be implicated. Scientists showed that mice immunized with proteins from Haemophilusinfluenzae, Neisseriagonorrhoeae or tetanus toxoid develop antibodies that recognize Cardiolipin, β2GPI and the amino acid sequences contained in the proteins.

Systemic sclerosis(SSc)

SSc is a complex and heterogeneous disease, with clinical forms ranging from limited skin involvement (limited cutaneous systemic sclerosis) to diffused skin sclerosis and severe and often progressive internal organ involvement (like diffuse cutaneous systemic sclerosis). Moreover anti-nuclear antibody (ANA), anti-topoisomerase I (antiScl-70) antibody, anti-centromere antibody (ACA) and anti-RNA polymerase III antibody (anti-RNAPIII) are found in SSc.[38] SSc patients have decreased Faecalibacterium and Clostridium, and increased Fusobacterium and γ-Proteobacteria, as compared to healthy controls. SSc patients also have increased Bifidobacterium and Lactobacillus, which are typically decreased in inflammation. Patients with moderate to severe gastrointestinal symptoms have decreased B. fragilis and increased Fusobacterium compared with those with littlesymptoms. Dysbiosis (lower abundance of F. prausnitzii and Clostridiaceae and relatively high load of Lactobacillus) is pronounced in SSc with pulmonary fibrosis, oesophageal dysfunction and malnutrition. There is also abundance of Rhodotorulaglutinis in SSc. R. glutinis can activate immune system and lead to skin sclerosis.[39]

Microbes and Inflammatory bowel disease (IBD)

InIBD, anautoimmune disease where environmental triggers are important,there are dysregulated

immune responses against gut microbiota, leading to chronic gut inflammation. The major forms of IBD are ulcerative colitis (UC), limited to colon, and Crohn's disease (CD), which affects whole GI tract.[40] In IBD, there is reduction in potentially anti-inflammatory microbes like Bacteroidetes, Lachnospiraceae , and Faecalibacteriumprausnitzii alongside increases in inflammatory microbes (Proteobacteria and Ruminococcusgnavus). More mucosa-associated bacteria results in greater contact between gut microbes and immune system and leads to anti-bacterial immunity and IBD.[40] In IBD patients, specific bacteria, like the butyrate producers Faecalibacteriumprausnitzii and Roseburiahominis are decreased.[40]

In mice models, high fibre-rich diets or direct administration of SCFA are beneficial; loss of the SCFA receptor, Gpr43 is pathogenic. Tryptophan metabolites are ligands for the aryl hydrocarbon receptor (AhR), which activates IL-22 and IL-10 and is negatively associated with colitis.[40] A tryptophan-free diet exacerbates pathology. So, microbes can be used for treating IBD. Administration of probiotics has shown success in animal models and patients.[40] However, broad scale benefits are yet to be found.

Crohn's disease affects approximately 1.4 million North American people. Due to the similarities between Crohn's disease and Johne's disease, a chronic enteritis in ruminants caused by Mycobacterium aviumparatuberculosis (MAP), MAP can cause of Crohn's disease.[41] MAP is included in the Mycobacterium avium complex (MAC) along with M. avium and M. intracelluare. Like other mycobacteria, it contains a thick and hydrophobic cell wall that resists decolourization with acid- alcohol, leading cells to be acid fast.[41] The bovine immune response to subclinical MAP infection starts with a Th1 type, or cell mediated response against the infected macrophages. The major source of MAP in the environment is by shedding of MAP in the faeces of infected ruminants. MAP along with faeces is deposited onto pastures where runoff can contaminate ground or surface water.[42]

Secondarily infected animals include rabbits and wild deer, which also shed MAP into environment via faeces. MAP cannot replicate outside host cells. However, it survives in environment for 12 weeks to 1 year. MAP is hence also present in the human food supply, in dairy and meat products.[43] The thick lipid cell wall allows it to survive pasteurization; live MAP has been found in retail milk and cheese products.[41] Crohn's disease has symptoms like abdominal pain, diarrhoea, bleeding, bowel obstruction, as well as systemic symptoms. CD has an estimated annual healthcare cost of over 1.7 billion USD. Common clinical features between Johne's and Crohn's disease are intermittent diarrhoea, weight loss, primary site like the ileocecal area, mucosal ulcerations, and granulomas. So MAP can be the etiological agent of Crohn's disease.[41] The first report of a possible link between MAP and CD was made even before original descriptions by Crohn.[44] In 1913, T.K.Dalziel noticed that clinical and gross appearances in CD were very similar to those in cattle with Johne'sdisease. However not everyone with MAP develop CD.

Most calves exposed to MAP become subclinically infected and approximately 10% develop Johne's disease. Approximately 1/3rd of the world population is infected with Mycobacterium tuberculosis, but clinical disease occurs in 5–10% infected people.[41] A genetic association with CD was identified in the Nucleotide-binding Oligomerization Domain-containing protein2, or NOD2 encoded by the CARD15 gene. This protein functions as an intracellular pattern recognition receptor for Mycobacteriaceae. NOD2 activates NFkBsignalling following binding to microbial peptidoglycans. NOD2 mutations confer susceptibility to Crohn's disease by altering the receptors' recognition of pathogens or the downstream activation of NFkB in monocytes. The SLC11A1 (Solute carrier 11A1), formerly NRAMP (natural resistance-associated macrophage protein 1), is an ion transporter across phagosomal membranes and induces microbicidal functions in macrophages.[41] It plays a role in innate immune response to mycobacterial infections. Polymorphisms at locus 823 C/T are strongly associated with CD. Autophagy is an important component in innate immunity and contributes to clearance of intracellular microbes. The genes ATG16L1 and IRGM encode proteins involved in autophagy show a strong association with CD susceptibility.

Can microbes or microbial modulation cure autoimmune diseases?

Reports about faecal matter transplants (FMTs) or probiotic pills have given some hope that there can be an easy way to prevent or treat autoimmune diseases. For MS, treatment is a targeted dietary intervention that shifts the community from pro-inflammatory bacteria to anti-inflammatory type.[45] Scientists hope that better knowledge about gut microbiome during first 3 years of life, will lead to disease-preventing interventions. Those might

include giving babies well-defined compositions of microbes, so that a child's immune system develops optimal tolerance to self without sacrificing ability to fight infection. That is the kind of therapy that can have global impact because bugs or microbes are cheap.

Modulation of microbiota can help treat autoimmune diseases. Such approaches include prebiotic diets, antimicrobial interventions, faecal microbiota transplants, and selective probiotics. One new approach is the use of selective bacterial candidates to modulate the microbial composition. Use of single microbe for treatment is advantageous as microbes grow at different speeds and if needed, a single microbe is easy to target.[46]

Fungi in autoimmune diseases

Fungi do mediate immune disorders.Fungi contribute to auto-reactivity against self-antigens due to shared epitopes between fungal and human proteins like manganese superoxide dismutase ,thioredoxin, cyclophins and acid ribosomal proteins. The mechanism is thought to be molecular mimicry maintaining severe chronic allergic diseases such as atopic dermatitis.[47]

Currently, the evidence for fungal exposure being linked to the induction of autoimmune diseases is controversial. Studies suggest that fungal proteins have a role to play in autoimmune diseases. However, further studies are needed to establish the role of fungi in the immunopathology of autoimmune diseases.[47]

The involvement of microbial triggers in IBD, including Crohn's disease (CD), is increasingly evident with metagenomic sequencing that have identified dysbiosis in CD compared with healthy subjects. The vast majority of CD microbiome research has focused on complex bacterial communities and microbiome dysbiosis in the gut with 16S metagenomic sequencing. However, emerging data suggest fungal opportunistic pathogens are also associated with IBD pathogenesis and chronicity. CD patient populations display elevated antibodies against fungal targets, even before disease diagnosis.[48]

Parasites and autoimmunity: Chagas' disease (CD)

Chagas' disease is caused by Trypanosomacruzi, with reduviid bug as vector. That Chagas' disease has an autoimmune component, was based on finding of circulating antibodies against heart tissue antigens in patients and mice chronically infected with Trypanosoma cruzi. Later, T lymphocytes reactive with heart or nerve tissue antigens were found in chagasic mice and patients, extending the concept to include cell-mediated immunity.[49] Initial studies have showed presence of serum antibodies reactive to endocardial, vascular, and interstitial (EVI) antigens in a large proportion of chagasic patients. These antibodies can be removed by absorption with T. cruzi epimastigotes (suggesting cross-reactivity of some T. cruzi antigens with EVI antigens) and are absent in sera from normal individuals or patients with nonchagasic cardiovascular diseases. A later report described the presence of antibodies against Schwann sheaths of myelinated somatic and unmyelinated autonomic peripheral nerves in sera of patients with acute CD (aCD) and also chronic Chagas' heart disease (cCHD).

The anti-EVI antibodies were also present in sera from patients with malaria and VL , cross-reacted with Trypanosomarhodesiense antigens, and could bind a carbohydrate epitope expressed by cells from various species as well as several other heterologous antigens. Scientists identified a 160-kDa T. cruzi surface protein on flagellum, which they termed Fl-160. Normal mouse sera do not recognize the Fl-160 fusion protein.[50] Mouse anti-Fl-160 antibodies cross-react with a 48-kDa protein of axonal and myenteric plexus cells. Immunofluorescence studies reveal that Fl-160 is localized on flagellum of T. cruzi trypomastigotes. The antibodies cross-react with lysates of nerve and brain tissue but not from cardiac, skeletal muscle, liver, or kidney tissue. Also the finding that 44% of tested chagasic sera display reactivity with Fl-160 indicates that the anti-Fl-160 antibodies are involved in nerve damage, seen occasionally in patients with CD.[49] Peoplehave reported anti-heart and anti-skeletal muscle reactivity and anti-skeletal muscle glycolipid antibodies in CD.[51] Immunofluorescence studies showed positive staining by chagasic sera, which also has higher anti-glycolipid antibody titres than control sera. Also, the antibody titres were higher in patients with cCHD than in those with aCD.[51]

Viruses and autoimmunity

CMV or HCMV or Human Cytomegalovirus, can be important in precipitating GBS and MS. It can also initiate mononucleosis in adults. In autoimmune diseases with high levels of inflammation and chronic immune stimulation, such as RA, a causative role of HCMV has been hypothesized. After specific HCMVpp65 antigen-mediated long-term stimulation, increased anti-HCMV IgG antibodies and intracellular IFN-γ-

producing HCMVpp65-specific CD28-CD8+ T-cells are observed in RA and juvenile arthritis (JIA). This indicates a possible enhancement of inflammatory response following endogenous HCMV reactivation.[52] HCMV can induce or perpetuate autoimmunity through different ways like: (1) antigen-specific (like molecular mimicry) and (2) non antigen-specific (or bystander activation). From an immunopathological viewpoint, HCMV can trigger or sustain autoimmunity via the following 3 mechanisms: (i) autoantibody production, (ii) enhanced inflammation, and (iii) vascular damage.[52]

In systemic sclerosis also, HCMV issignificant. In recent years, workers have studied the interplay between HCMV and immunity in SSc and inflammation. In HCMV-infected human dermal fibroblasts, researchers found increased HCMV-specific CD8+ T-cell responses associated with disease development, and also enhanced expression of fibrosis and apoptosis-associated factors that are important in SSc.[52]

Discussion

Hence now it can be summarized that many different microorganisms can initiate and precipitate many autoimmune diseases by many mechanisms. Bacteria, fungi, viruses, parasites all can be responsible for these disorders. Diseases like Diabetes mellitus, Psoriasis, Systemic Lupus Erythematosus and Multiple sclerosis can all have possible or established microbial link. These things should be researchedmore. If microbial aetiologiesand link behind these autoimmune diseases are more and more explored, new strategies can be formulated to target these microbes flaring up autoimmunity.

A complex interplay of hosts genotype, host microbiota, environment, diet and microbial aetiology can help in developing myriad autoimmune diseases. Thus new avenues for therapy of debilitating autoimmune diseases might emerge. This could well be the topic of research of the future and can bridge the gap between understanding of communicable and non-communicable diseases also. Microbiologists and immunologists can work in tandem for more research in this very interesting field.

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