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Infection, vaccines and other environmental triggers of autoimmunity

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Abstract

The etiology of autoimmune diseases is still not clear but genetic, immunological, hormonal and environmental factors are considered to be important triggers. Most often autoimmunity is not followed by clinical symptoms unless an additional event such as an environmental factor favors an overt expression.

Many environmental factors are known to affect the immune system and may play a role as triggers of the autoimmune mosaic.

Infections: bacterial, viral and parasitic infections are known to induce and exacerbate autoimmune diseases, mainly by the mechanism of molecular mimicry. This was studied for some syndromes as for the association between SLE and EBV infection, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and more. Vaccines, in several reports were found to be temporally followed by a new onset of autoimmune diseases. The same mechanisms that act in infectious invasion of the host, apply equally to the host response to vaccination. It has been accepted for diphtheria and tetanus toxoid, polio and measles vaccines and GBS. Also this theory has been accepted for MMR vaccination and development of autoimmune thrombocytopenia, MS has been associated with HBV vaccination.

Occupational and other chemical exposures are considered as triggers for autoimmunity. A debate still exists about the role of silicone implants in induction of scleroderma like disease.

Not only foreign chemicals and agents have been associated with induction of autoimmunity, but also an intrinsic hormonal exposure, such as estrogens. This might explain the sexual dimorphism in autoimmunity.

Better understanding of these environmental risk factors will likely lead to explanation of the mechanisms of onset and progression of autoimmune diseases and may lead to effective preventive involvement in specific high-risk groups.

So by diagnosing a new patient with autoimmune disease a wide anamnesis work should be done.

Keywords: *Autoimmunity, autoimmune diseases, infection, vaccine, molecular mimicry*

Introduction

Autoimmune diseases can be classified into either organ-specific illnesses, such as thyroid disease, type 1 diabetes, and myasthenia gravis, or systemic illnesses, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and may be life threatening. Their etiology is still not clear but genetic, immunological, hormonal and environmental factors are considered to be important triggers. Most often autoimmunity is not followed by clinical symptoms unless an additional event such as an environmental factor favors an overt expression [1–4].

The etiology of autoimmune diseases is multifactorial. The degree to which genetic and environmental

factors influence susceptibility to autoimmune diseases is still ill defined. It is interesting to note that in almost all autoimmune conditions there are familial tendencies and an increased incidence of autoantibodies among healthy 1st degree relatives of affected patients [5].

The best hint derives from the concordance rates of these diseases in mono-zygotic twins. The rate is 25% in the case of multiple sclerosis (MS), and 40–50% in the case of type 1 diabetes [4].

The different clinical presentations of autoimmune diseases stem from various combinations of the above factors. A particular setup will evoke a certain manifestation, whereas in another member of the same family a different constellation will be associated with an involvement of completely different organs.

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Table I. Major pieces of the mosaic of autoimmunity (modified from Ref. [5]).

Genetic	Increased incidence of autoimmune diseases in families Increased incidence of autoantibodies in 1 st degree relatives of the patients Increased incidence of the disease in monozygotic twins HLA studies found increase incidence in HLA-B8, -DR3, -DR4 in some diseases Increased incidence of common idiotype of autoantibodies in the patients and their 1 st degree relatives Gm allotypes Complement compound deficiencies IgA deficiency
Defects in immune system	Complement compound deficiencies (C1q, C2 and C4) Defects in T suppressors, or decrease in T regulatory (CD4 + CD25 +) Defects in NK cells Defects in the IL-2 mechanism of action Defects in phagocytosis
Hormonal	Increased incidence of autoimmune diseases among females
Environmental	Increased incidence of autoimmune diseases in Klinefelter's syndrome Increased incidence of autoantibodies among females Exacerbation of autoimmune diseases during puberty, pregnancy, and post partum periods Association between hyperprolactinemia and autoimmunity The protective effects of testosterone like drugs Infections: viral, bacterial, parasites Drugs (I.g Drugs induced lupus: Hydralazine, Quinidine and Procainamide) Toxins (phthalate, etc.) UV light (induces SLE) Smoking Stress Nutrition

This phenomenon has been referred by us as *the mosaic of autoimmunity* [4–6]. This definition implies that by resembling the same pieces in a different order, another pattern or clinical picture will emerge.

The origin of autoimmunity is complex. Active suppression of one disease “opens the door” for other autoimmune disorder. Such switch from one abnormal immune balance to another is referred to by us as *the kaleidoscope of the autoimmune mosaic* [7]. For example, thymectomy in myasthenia gravis leads to SLE or antiphospholipid syndrome (APS), or splenectomy in ITP leads to chronic active hepatitis [8–10].

Many environmental factors known to affect the immune system may play a role as triggers of the autoimmune mosaic, and they are summarized in Table I.

In this review, we will concentrate on some of the major environmental factors leading to the emergence

of autoimmune diseases, such as infections, vaccines and others. Better understanding of these environmental risk factors will likely lead to a better understanding of the mechanisms for the onset and progression of autoimmune diseases and may lead to better preventive involvement in specific high-risk groups.

Infections as trigger of autoimmunity

Infection is a possible trigger for autoimmune diseases and may involve viral, bacterial and parasitic infections [2,11].

During the last four decades, it has been suggested that microbial antigens can play a significant role in the pathogenesis of the immune deregulation, leading to autoimmune disorders. Viral, bacterial or parasitic infection of subjects with specific genetic background, immune abnormalities, or hormonal constellation may trigger autoimmunity that leads to the development of an overt autoimmune disease [12].

Viral infections and autoimmune diseases

Viruses have been suggested as possible etiological factors for autoimmune diseases. For example, exposure to EBV is highly associated with the development of SLE [13]. The EBV has been examined as a potential candidate (both due to its ubiquitous nature and its ability to stimulate lymphoid responses) particularly in RA and SLE. Increased EBV reactivation has been demonstrated in some patients with SLE, as evidenced by increased viral DNA in their saliva and an increased number of EBV-containing B-cells circulating in their blood. These patients were also found to have modestly elevated anti-EBV antibody titers and altered antiviral T-cell responses. In a more recent study, EBV-DNA was demonstrated by polymerase chain reaction in the oropharyngeal secretions of SLE patients and the virus was isolated from most of these specimens [13].

Some examples of viral infections which may trigger MS include viruses of the human Herpes viruses family. One of the greatest challenges in confirming or refuting a role for herpes viruses (e.g. Epstein–Barr virus (EBV) and human herpes virus 6 (HHV-6)) in MS is their ubiquitous nature [14–18], i.e. these viruses are neurotropic, become latent and persist even with very limited genome expression, can be reactivated with the relapsing-remitting course of MS, and have been shown to induce demyelination [19]. Another example is the retroviruses family: (a) Human immunodeficiency virus (HIV) (b) MS-associated retrovirus. Only a few cases of HIV-positive patients with MS or MS-like lesions have been reported. The island of Sardinia has a high and increasing incidence of MS. While searching for environmental factors that may account for this

anomalously high incidence, MS-associated retrovirus (MSRV), was found. This virus accounts as an exogenous member of the human endogenous retrovirus family W (HERV-W) and was found in all patients with MS, in most patients with inflammatory neurologic diseases, and rarely in healthy blood donors. MSRV was found in the plasma and CSF of patients with MS, and was produced *in vitro* by their cells [19,20].

It has been suggested that MSRV may contribute to MS reactivation in Sardinia.

Also known is the human parvovirus B19 (PVB19), the etiologic agent of *Erythema infectiosum*, which causes transient and persistent immune derangements.

PVB19 infections have been reported to be associated with chronic immune-mediated disorders, including RA and SLE. PVB19 can invade the CNS, possibly resulting in encephalopathy and meningitis [19].

Except for infectious mononucleosis, which was a moderate risk factor, little association was found between the history of common viral diseases and risk of developing MS. However, a relationship between mumps and measles after 15 years of age and MS was found [20].

Systemic sclerosis (Scleroderma-SSc) is also associated with viral infections. The possible pathogenic role of two viruses, namely human cytomegalovirus (HCMV) and human parvovirus B19 (B19), has been recently proposed. Parvo B19 genomic sequences were demonstrated in 57% (12/21 patients) bone marrow biopsies from SSc patients and were never detected in the control group. It has been suggested that bone marrow may represent a reservoir from which the B19 virus could spread to SSc target tissues [21].

Human herpes virus 5 (HCMV), infection and its downstream effects on immune, vascular, and repair mechanisms could serve as an accelerating factor in SSc. The most direct link between HCMV and SSc is the high-titer antibodies to the polyglycine motifs of HCMV observed in a comparative study of EBV and HCMV in the sera of patients with several rheumatic and connective tissue diseases [22].

Pathogenesis of Coxsackievirus-induced myocarditis involves early viral and late autoimmune phases; the latter may lead to dilated cardiomyopathy, an important cause of cardiac mortality [23]. Dilated cardiomyopathy is one of the leading causes of heart failure and is most likely a sequel of myocarditis induced by infectious agents such as Coxsackievirus B (CVB) or cytomegalovirus [24]. Following the early stage of the infection with the virus, the disease continues and changes its nature. The A/J, A.SW/SnJ mice model is a susceptible strain for the development of this autoimmune myocarditis [25,26]. Rodent models have been developed to study the mechanisms underlying the progression of viral infection to autoimmune myocarditis and the subsequent

development of cardiac dysfunction and finally heart failure. These models include virus-induced (Coxsackievirus, encephalomyocarditis virus and cytomegalovirus) and cardiac antigen-induced (cardiac myosin or cardiac myosin-derived peptides) myocarditis. Important insights have been gained from the animal models regarding the role of the virus in triggering immune system activation and the role of different immune mediators in disease initiation and progression [23].

Bacterial infections and autoimmune diseases

Some common bacterial infections cause autoimmune diseases, as *Campylobacter jejuni* has been associated to Gullian Barre Syndrome (GBS) [27].

Approximately 30% of GBS cases are preceded by *C. jejuni* infections as detected by serologic tests. The presence of microbe-specific antibodies and T-cells with cross-reactivity to various nerve-sheath components initiates inflammatory demyelination and shedding of peripheral nerve auto-antigens.

More examples of autoimmune diseases linked to bacterial infections via molecular mimicry are summarized in Table II [28]. Classical autoimmune diseases, like Graves' disease and Hashimoto's thyroiditis, has been shown to be associated with a variety of infectious agents (e.g. *Yersinia enterocolitica*, retroviruses) [29]. Infections of the thyroid gland (e.g. subacute thyroiditis, congenital rubella) have been shown to be associated with thyroid autoimmune phenomena [29]. Such examples of molecular mimicry seem well accepted along with the observation that pathogens can aggravate disease.

Another example is PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) which is diagnosed in the presence of OCD and/or tic disorder, prepubertal age of onset, abrupt onset and relapsing-remitting symptom course, association with neurological abnormalities during exacerbations (adventitious movements or motoric hyperactivity), and a temporal association between symptom exacerbations and a Group-A β -hemolytic streptococcal (GAS) infection [30]. The working hypothesis for the pathophysiology

Table II. Autoimmune diseases which are linked to bacterial infections via molecular mimicry.

The autoimmune disease	The suggested bacterial etiology
RF	<i>S. pyogenes</i>
Ankylosing spondylitis	<i>Klebsiella pneumoniae</i>
RA	<i>Proteus mirabilis</i> and by <i>Mycobacterium tuberculosis</i>
Graves' disease	<i>Y. enterocolitica</i>

of PANDAS begins with a GAS infection in a susceptible host that incites the production of antibodies to GAS that cross-react with the cellular components of the basal ganglia, particularly in the caudate nucleus and putamen [30,31].

APS is characterized by the presence of pathogenic autoantibodies against β 2-glycoprotein-I (β 2GPI) [32,33]. Many infections may be accompanied by antiphospholipid antibody (aPL) elevations, and in some, these elevations may be accompanied by clinical manifestations of APS. The possible infectious origin of circulating anti- β 2GPI abs can be explained by molecular mimicry between common pathogen and anti- β 2GPI peptide epitopes as a possible origin for anti- β 2GPI Abs. However, development of APS requires the appropriate genetic predisposition in concert with exposure to the pathogen. The factors causing production of anti- β 2GPI remain unidentified, but an association with infectious agents has been reported [34]. Recently, we have shown infections as the etiological factors in APS. We identified a hexapeptide (TLRVYK) that is recognized specifically by a pathogenic anti- β 2GPI mAb. We evaluated the APS-related pathogenic potential of microbial pathogens carrying sequences related to this hexapeptide [35]. Following immunization, high titers of antipeptide [TLRVYK] anti- β 2GPI Ab's were observed in mice immunized with *Haemophilus influenzae*, *Neisseria gonorrhoeae* or tetanus toxoid.

Development of APS requires the appropriate genetic predisposition in concert with exposure to the pathogen [34].

Rheumatic fever (RF) and APS share partial common clinical features such as CNS and heart involvements. We assumed that it may be a consequence of a cross-reactive epitope between the M protein and the β 2GPI. The β 2GPI-related peptides TLRVYK and LKTPRV share homology with *Streptococcus pyogenes* M protein (mismatch = 2). β 2GPI-related peptide TLRVYK inhibited the binding of anti-M protein Abs from RF patients to M protein by 37%. Anti- β 2GPI could be inhibited by M protein for binding to β 2GPI by 23% [36].

Helicobacter pylori, one of the most common bacterial pathogens in humans, colonizes the gastric mucosa, where it appears to persist throughout the host's life unless the patient is treated. Colonization induces chronic gastric inflammation which can progress to a variety of diseases ranging in severity from superficial gastritis and peptide ulcer to gastric cancer and mucosal associated lymphoma [37].

Recently, a disappearance of APS after *H. pylori* eradication was reported. Using the Swiss protein database, we were able to find homology (mis1-2) between anti-2GPI peptides target epitopes and *H. pylori* structures [36].

H. pylori infection triggers the development of gastric autoimmunity [37-39]. Infection with *H. pylori*

results in an inflammatory influx of mononuclear cells, including T- and B-lymphocytes and macrophages, into the gastric mucosa. Then, under the influence of the predominant Th1 cytokine milieu raised in the host by *H. pylori*-infection, gastric epithelial cells would acquire properties essential for antigen-presentation [38,39]. Presentation of bacterial antigens by gastric epithelial/parietal cells and local professional APC may result in activation of *H. pylori*-specific FasL⁺ gastric T cells, that kill the antigen-presenting epithelial cells by *H. pylori*-antigen-dependent mechanisms (e.g. perforin-mediated lysis) or by inducing apoptosis.

A quite broad repertoire of culprit epitopes have been identified in both the pathogen and in the self gastric protein associated with AIG. The microbial cross-reactive epitopes were able to elicit vigorous responses in the same gastric T cells that responded at comparable levels to both self H⁺,K⁺ATPase epitopes and the entire self protein. Finally, cross-reactive T-cell clones quantitatively represented a significant component of the T-cell response at gastric level during the autoimmune disease and the concomitant *H. pylori* infection [40].

Higher prevalence of HP infection has been also found in SSc (78%) associated with elevated levels of anti-hsp65 but not of anti-hsp60 [21,41,42].

The relation between infection and spondyloarthropathies, predominantly reactive arthritis, is well established [43]. Bacteria clearly have an important role in the development of reactive arthritis. Epidemiological research has demonstrated that in its postenteric form, *Shigella*, *Salmonella*, *Yersinia* and *Campylobacter* species are arthritogenic [43]. Infection with *Klebsiella pneumoniae* has been proposed to be the underlying pathogen causing ankylosing spondylitis (AS). Different studies have shown that the anti-*Klebsiella* antibodies are higher in patients with AS compared to controls. An abnormal T lymphocyte response to *Klebsiella* infection has been reported, although these studies are difficult to interpret since considerable overlap exists between the response observed among patients and healthy individuals.

In B27 transgenic rats, disease is prevented when animals are kept in germ-free conditions. However, when they are moved into conventional facilities, they develop joint and gut inflammation [44]. Thus, at least in experimental conditions, the immune system must meet bacteria as a prerequisite in order for the inflammatory disease to ensue. In humans, evidence of previous infection is detectable in approximately 60% of patients with acute reactive arthritides. Several bacteria have been associated to reactive arthritis. However, Gram-negative bacteria in the intestinal (*Shigella flexneri*, *Salmonella*, *Yersinia*, *C. jejuni*) and urogenital (*Chlamydia trachomatis*) tracts are the classical triggering infections. Bacterial antigens (from *Chlamydia*, *Yersinia*, *Salmonella* and *Shigella*)

and DNA (from *Yersinia* and *Chlamydia*) have been found in synovial fluid and tissue of patients with reactive arthritis [43].

Parasites infections and autoimmune diseases

Observations that link autoimmunity and parasitic infections include: the presence of pathogenic autoantibodies and autoreactive cytotoxic T cells to heart and nerve cells in mice and in patients with Chagas' disease, the detection of antibodies directed against self antigens of the inner retina in the sera of patients with onchocerciasis and the development of complement-mediated hemolytic anemia associated with autoantibodies reacting with triosephosphate isomerase in patients with long standing malaria [45]. Autoantibodies associated with parasitic infections bind various self and foreign antigens (polyreactive antibodies) [46,47]. Autoantibodies to nuclear antigens detected in the sera of schistosoma infected mice bind DNA, polynucleotides and malaria and cercarial antigens. This pattern of autoantibody binding similar to that of human monoclonal anti-DNA antibodies derived from patients with SLE [45–47].

Various autoantibodies were detected in the sera of patients with malaria. Studies have found the sera of patients with malaria to bind: anti-nuclear antibodies (ANA), ssDNA, dsDNA, smooth muscle, parietal cells, cardiolipin, red blood cells (RBC), lymphocytes, IgG of Rheumatoid factor, neutrophil cytoplasmatic enzymes (ANCA) and ribonucleoproteins (RNP). Autoantibodies are detected in patients with acute malaria, chronic malaria, and in the sera of healthy subjects living in endemic malarious area [45].

A correlation was found between the presence of autoantibodies and high titers of anti-malarial antibodies, suggesting that acute malaria trigger the generation of ANA and possibly other autoantibodies. However, the persistence of these autoantibodies did not correlate with the level of parasitemia once the acute infection was treated, indicating that autoantibodies are associated with chronic infection [45].

As with malaria, sera of animals and humans with cutaneous and visceral *leishmaniasis*, recognize various autoantibodies including: nuclear antigens (ANA), native DNA, immunoglobulin (rheumatoid factor), Sm, RNP, SS/A, SS/B, cardiolipin, β 2-glycoprotein I, actin, tubulin, smooth muscle and others. The frequency and titers of autoantibodies were higher in the sera of patients with kala-azar compared with cutaneous leishmaniasis [48].

A pathogenic role for autoimmunity in leishmaniasis was reported. Three cases of pancytopenia in patients with kala-azar were described. Antiplatelet, antineutrophil and antierythrocytic IgG antibodies were documented on the cell surface of platelets, RBC and neutrophils in all three cases. Bone marrow suppression was not found, suggested that

pancytopenia resulted from rapid destruction of antibody-coated blood cells [48].

Schistosomiasis is a granulomatous disease characterized by the development of granulomas surrounding the helminth's eggs. Autoantibodies were detected in the sera of humans and animals infected with various schistosoma species including: Anti-DNA, ANA, RF, anti-Sm, anti-sperm, and anti-lymphocytic, anti-thyroid, anti-tubulin, anti-parietal cells. High levels of a pathogenic anti-DNA idotype (16/6 Id) and anticardiolipin antibodies were reported in the sera of patients with schistosomiasis [49].

Parasites may induce autoimmune activity by several mechanisms as we mention further on in this review.

Vaccines as trigger of autoimmunity

Vaccinations can provide an important protection from diseases like polio, rubella, measles, etc. However, there are several reports in the literature of onset of autoimmune disease within weeks or months from vaccination [50–52].

There are two kinds of vaccination: (1) Active vaccination—when a live, generally attenuated infectious agent (microbe or virus) is used, or an inactivated infectious agent (or constituents thereof), or products obtained by genetic recombination. Active vaccination may also be achieved when injecting a toxoid; (2) Passive vaccination—usually provides temporary immunity and consists of immune globulin preparations or antitoxins [53].

The same mechanisms that act in infectious invasion of the host apply equally to the host response to vaccination [1]. Based on these principles a killed vaccine would be less likely than a live attenuated vaccine to activate the innate immunity response [1]. Thus might be a risk that following a live attenuated vaccination an autoimmune disease or autoimmune symptoms may develop, using the same mechanism used by infections.

There have been over the last 15 years or so several reports of adverse autoimmune reactions to various vaccines. Mostly the connection between the vaccination and the autoimmune reaction was temporal and not causal. The vast majority of epidemiological studies could not find a causal link [54].

A causal relationship has been accepted by the institute of Medicine of the National Academy of Science in the USA for several different vaccines and three syndromes. These include (1) diphtheria and tetanus toxoid, polio and measles vaccines and GBS (2) MMR vaccines and thrombocytopenia (ITP like) and (3) rubella vaccine has been connected with acute and chronic arthritis in adult women [55]. The MMR vaccination has been associated also with IBD [55].

Many common infections can induce a transient rise in autoantibody production. A similar rise in

autoantibody production has been observed after various vaccinations. Such autoantibodies usually resolve within a period of 2 months [55] but can persist in rare cases. Several studies indicate that stimulation of autoantibody production has become one of the criteria of establishing the safety of vaccines. It is to be remembered, however, that although autoantibodies are a characteristic of autoimmune disease it is often unclear whether they are an epiphenomena or represent the causal agents of the illness.

The occurrence of arthritis has been described following administration of several vaccines and can be divided into *isolated* or *reactive arthritis* (poly or monoarticular) and arthritis as a symptom of a *systemic autoimmune* disease (such as SLE or RA) [56].

Three major neurological autoimmune manifestations have been addressed in conjunction with vaccination: the GBS, MS and autism.

GBS is a transient neurological disorder characterized by areflexic motor paralysis with mild sensory disturbances. GBS has been associated with the FLU vaccination [53].

Other vaccines that have been related with GBS include: Tetanus toxoid, Bacille Calmette–Guerin, Rabies, Smallpox, Hepatitis B, MMR, Diphtheria and Poliovirus [53].

MS has been connected to hepatitis B vaccine in one of the largest and most heated debates and law suites in France and the US. More than 600 cases of illnesses, many with MS-like symptoms have been reported in France among people who have received recombinant HBV vaccine [57,58]. The temporal association between MS and HBV vaccination has been reported on few occasions: neurological symptoms and signs as well as magnetic resonance imaging documenting CNS demyelination have been documented days to weeks after BV vaccination. On the other hand, a French government sponsored study in 1997 revealed that vaccinated individuals were less likely to have MS [19,53,56–58].

The vaccine most commonly associated with autism was the measles vaccine. The hypothesis suggested was that were an immunological assault to occur prenatally or post-natally (during infancy or early childhood) it could possibly result in poor myelination or abnormal function of the axon myelin. The hypothesis was supported by an association found in autistic children, between anti-viral and brain autoantibodies [59].

Another example of vaccine induced autoimmune symptoms is given by the broad use of BCG, as immunotherapy for bladder carcinoma. This treatment for TCC has proved itself both as efficient and safe. Nevertheless, several cases has been reported, regarding severe and long-term complications of BCG therapy—namely inflammatory arthritis and occasionally systemic autoimmune manifestations.

We summarized four cases of patients who received intravesical instillation with BCG for bladder carcinoma and developed long-standing inflammatory arthritis [60].

We are dealing with a valuable and effective treatment that has improved the prognosis of a serious disease. Yet, it can be a “double-edged sword” as it can trigger autoimmune phenomena and even full-blown autoimmune disease—though the incidence of these is very low. The patients developed polyarthritis, dactylitis, bursitis, elevated ESR, elevated CRP, Cutaneous psoriasis, seropositive RA, RF +, ANF +, and even Reiter’s syndrome (polyarthritis, balanitis, urethritis, prostatitis) [61,62].

We have addressed the issue of the “double-edged sword” of vaccination in our previous articles. We have referred to it as “vaccinosis” and we have shown that numerous vaccines are related—at least temporally—to the development of autoimmune phenomena, among which one of the more frequently encountered is inflammatory arthritis [62–64].

Silicone implants as trigger of autoimmunity

Another subject in debate is the connection between silicone implants and autoimmune diseases. The FDA still limits the use of silicone implants [65]. The silicone is considered as inert material without any biological reaction. However, literature review finds out about 120 autoimmune phenomena and around 70 autoimmune diseases which were regarded to be induced by silicone implantation in breast. The main autoimmune disease which is connected to silicone is systemic sclerosis.

Many autoantibodies were documented in patients with silicone breast implants. The autoantibodies were found in the serum of asymptomatic patients with augmentation as well as in patients with symptoms [66,67].

All the syndromes and autoimmune phenomena were more emphasized following rupture of the silicone implants. Women with silicone breast implants often report severe pain and chronic fatigue. Rupture of the implant is associated with an increase in symptoms of pain and chronic fatigue [68].

We described the appearance of transient “lupus-type” autoantibodies (anti-Sm and anti-RNP) with no clinical evidence of SLE, concurrent with the rejection of a silicone wrist implant inserted 4 years previously, in a woman with a 15 year history of primary Sjögren’s syndrome who had been followed for 8 years [69]. The transient appearance of these antibodies simultaneous to the silicone transplant rejection, and their disappearance with its speedy removal, makes a strong case for not considering such transplants in patients with preexisting autoimmune disease or diathesis.

In some reports there was evidence for regression of the autoimmune symptoms after taking the implants

off [65]. The authors discussed the connection between the autoimmune symptoms to the implants and found that following their removal, they found at least 21 months free of symptoms. So where there is smoke there is fire. The silicone breast implant controversy continues to flicker [70].

However, there is still a wide debate about this subject. On the basis of meta-analyses, there was no evidence of an association between breast implants in general, or silicone-gel-filled breast implants specifically, and any of the individual connective-tissue diseases, all definite connective-tissue diseases combined, or other autoimmune or rheumatic conditions [71]. From a public health perspective, breast implants appear to have a minimal effect on the number of women in whom connective-tissue diseases develop.

Occupational and other chemical exposures as trigger of autoimmunity

There is some evidence for occupational exposures associated with the development of autoimmune diseases and aromatic amines, hydrazines, hair dyes and tobacco smoke have been studied [72].

Some environmental factors associated with systemic sclerosis are Silica dust (Coal and gold miners, Stone masons, Scouring powder), Aromatic hydrocarbons (Toluenebans, Benzene, Xylene, Aromatic mixes, white spirit, dieselene) and Aliphatic chlorinated hydrocarbons (Vinyl chloride, Trichloroethylene, Perchloroethylene) [73]. Silica dust exposure has been associated with systemic sclerosis and has also been linked with the development of ANA and other autoantibodies, and renal disease [72,73].

Phthalates (i.e. *o*-benzene dicarboxylates) comprise one such group of chemicals that are widely used as plasticizers in flexible polyvinylchloride (PVC) polymers used in medical devices, children's toys, and as solvents for cosmetics. Another type of phthalate is widely used in making synthetic fibers [74]. Phthalate, induced serum anti-self DNA antibodies in BALB/c, NZB and autoimmune-prone NZB/W F1 mice. The latter group experiences a high mortality, and significantly higher anti-DNA antibody levels along with nephritis and other histopathologic changes in kidney. Phthalate exposure leads to an activation of a significant number of autoreactive B-cells, with the consequence of a significant pathogenic progression in susceptible NZB/W F1 mice but not in non-autoimmune-prone BALB/c. A phthalate-specific BALB/c monoclonal antibody (mAb), 2C3-Ig (c1,j), showed considerable affinity for DNA and had extensive sequence homology with the heavy and light chain variable regions of a known anti-DNA immunoglobulin, BV04-01, from lupus-prone NZB/W F1 mice.

The splenocytes of autoimmune-prone and resistant mice have been stimulated *in vitro* with synthetic

peptides corresponding to the heavy- and light-chain variable regions (idiotype) of that mAb, 2C3-Ig. That antibody was secreted by an anti-phthalate hybridoma clone, and had extensive homology with BV04-01, an anti-DNA immunoglobulin identified in autoimmune susceptible, lupus-prone NZB/W F1 mice [75]. 2C3-Ig exhibits considerable binding affinity for DNA, and has extensive sequence homology with a well-characterized anti-DNA immunoglobulin, BV04-01. Hyperimmunization with phthalate-KLH induces active CD8 + T cells that regulate the anti-DNA response in BALB/c mice [75]. CD8 + T-cell-induced response to expression of the Vj 1 germline gene that has been implicated in autoimmunity [74]. These CD8 + CTLs are generated not only during exposure *in vitro* to the idiopeptides (VL1) corresponding to the first CDR of Vj1 gene, but also *in vivo* when the immunogen is a protein conjugate of phthalate, an environmental factor. Interestingly, these CTLs recognize VL1-peptide-loaded target cells, in the context of the Kd allele, and exert inhibitory effects *in vitro* on the growth and antibody secretion of a prototype autoreactive B-cell hybridoma, 2C3 [75].

Sexual dimorphism in autoimmunity—and the role of its factors as trigger of autoimmunity

The clinical and epidemiologic observations of autoimmune diseases is more common in women, is most frequent during female reproductive years, and is modulated by physiological and pharmacological hormonal changes [76].

The unassociated factors include: early menarche, early natural menopause, number of pregnancies of live births, and current or chronic use of oral contraceptive or of hormonal replacement therapy. A history of breast-feeding was associated with a decreased risk of developing SLE, while a history of pre-eclipse was associated with an increased risk of developing SLE [77].

Autoimmune disease such as SLE, Sjogren's syndrome, RA, Hashimoto's thyroiditis, and MS affect women predominantly [78].

The potential role of estrogen in SLE has been extensively investigated. The male female ratio in USA patients is 1:10. It has been shown by Lahita that there is an increased frequency of SLE in males bearing XXY chromosomes. Furthermore, abnormal estradiol metabolism in females with SLE as well as alleviation of SLE symptoms (in some) using hormonal therapy has been shown.

Estradiol increases phosphatase and free phosphatase activity in T cells from SLE patients in comparison to a non-SLE control group. Calcineurin is a final end product of T-cell activation by antibodies, via the CD40 ligand which is expressed on T cells. *In vitro* studies have shown an increased expression of

calcineurin mRNA when T cells from SLE patients were exposed to estrogen. Estrogen increases the expression of CD40 ligand in T cells from SLE female patients in a dose dependent fashion, an effect which is not seen in male patients and controls without SLE. Females with SLE seem to have an over sensitivity to estrogen, compared to healthy females or male lupus patients [26,28].

Suspicion for the difference in incidence between the sexes understandably falls on hormones, especially estrogen. Differences in estrogenic potencies and actions of their metabolites exist and may be important in the modulation of immunity or autoimmunity [78]. Estrogen and prolactin have multiple effects on lymphohematopoietic cells. Estrogen has been shown to modulate lymphoid cell growth and differentiation, proliferation, antigen presentation, cytokine production, antibody production, cell survival, and apoptosis, and estrogen deviates the immune response from a cell-mediated to a humoral response [78]. RA or MS is a predominantly cell-mediated disease (monocyte/macrophage/T cell), they improve due to the estrogen mediated suppression of cellular function, followed by exacerbation post-partum due to the removal of estrogenic suppression, with moderate stimulatory role for prolactin. In comparison, as an autoantibody/immune complex manifest disease, SLE worsens due to estrogenic and prolactin induced potentiation of the humoral response, and this is continued in the post-partum period by elevated prolactin concentrations [78]. These concepts have experimental support in autoimmune animal models [76].

SLE and systemic sclerosis are autoimmune diseases thought to have an exogenous trigger. Estrogen replacement therapy in postmenopausal women increases the risk of developing lupus, systemic sclerosis and Raynaud's disease, although the increase in risk is relatively modest. Oral contraceptives may also play a role in disease susceptibility in lupus but not apparently in systemic sclerosis [28,79].

Attempts to elucidate the role of estrogen in human autoimmune disease have typically turned up weak effects or conflicting results [79].

Suggested mechanisms

Potential mechanisms of induction of autoimmunity

Potential mechanisms of induction of autoimmunity for these diverse environmental agents can be classified into three broad categories: (a) a change in the hormonal milieu to favor estrogenic stimulation of the immune system; (b) suppression of one of the immune system (such as complement levels), which disrupts normal immune surveillance and (c) chemical binding to a self antigen forming a neoantigen, thus breaking tolerance by inducing

immunity to the unmodified native molecule as well as to the modified antigen [28].

Pathogen-induced inflammation

Pathogen-induced inflammation results in the enhanced presentation of self antigens, which causes the expansion of the activated autoreactive T cells that are required for disease onset [80]. The most appealing hypothetic mechanism for the triggering of autoimmune diseases by infection is molecular mimicry [27]. The host immune systems recognize determinants of the infectious factor as being similar to its own antigenic determinants. Thus not only trying to eliminate the infectious agent, but also attack hosts tissue [1,27]. In many cases, however, it remains an open question whether cross-reactivity represents an epiphenomenon or whether autoimmunity arises from a breakdown in the ability of T-cells to distinguish self from non-self antigens through the mechanism of epitope spreading [81].

An example for molecular mimicry regards studies on experimental APS and synthetic peptides which share common epitopes with bacteria, viruses or tetanus toxoid, and the β 2GPI molecule [34,35]. This proves the existence of molecular mimicry between pathogens and autoantigens in experimental APS. We speculate that the mimicking antigen, similar in only one epitope, may initiate a primary cross-reactive response to that epitope that subsequently results in recognition of numerous epitopes in the mimicked host β 2GPI. Mimicry may be one of the mechanisms for ending the tolerance and triggering the autoimmune response, but the mere presence of self determinants in a virus or bacteria need not result in pathogenesis [33,34]. We hypothesized that molecular mimicry mechanism between pathogen and β 2GPI molecule may be the cause for APS, based on (1) a correlation between APS clinical manifestations and infectious agents in human and (2) strong homology between β 2GPI-related peptides (target epitopes for anti- β 2GPI Abs) and different common pathogens, detailed in the protein database [11,33,34].

Toll like receptors (TLRs) are pattern recognition receptors that trigger innate immunity, providing both immediate protective responses against pathogens and instructing the adoptive immune response. The role of pathogens mimicking the β 2GPI in B cell TLR triggering, may promote the humoral response leading to the development of APS. The importance of TLRs in the procoagulative state of endothelial cells in APS was proposed recently by Raschi *et al.* [82], showing the role of MyD88 transduction signaling pathway in endothelial cell activation by anti- β 2GPI. The Abs reacted with β 2GPI in association with TLR/IL-1 receptor family on the endothelial cells surface [82].

Table III. Hypothesis proposed to explain the role of enterobacteria in B27-associated diseases (modified from Ref. [43]).

Hypothesis	References
Molecular mimicry of HLA-B27 with enterobacteria	[83,84]
Presentation of arthritogenic peptides from environmental antigens by HLA-B27 to CD8 ⁺ T cells	[85]
Presentation of HLA-B27-derived peptides by class II molecules	[86]
Polymorphisms of genes of molecules involved in antigen processing and presentation (Tap-1/Tap-2, proteosomes)	[87–89]

Some suggested mechanisms for the bacterial induction of seronegative arthritides are listed in Table III.

Parasitic antigens may induce autoimmune activity and immune-mediated damage to self antigens by several mechanisms including: molecular mimicry between host and parasites, induction of pathogenic autoantibodies, polyclonal activation of B cells, and manipulation of the idiotypic network [45–47].

Some possible mechanisms have been offered for explaining vaccine induced autoimmunity [56]. The 1st is possible persistence of the viruses in the target tissue, the 2nd is the potential of induction of autoantibodies production. Abnormal cytokine production induced by vaccination may be the 3rd mechanism. There is an option that the vaccines work as the infections do, by molecular mimicry, so this is the 4th proposal [56]. It is plausible that in a patient with a “suitable” genetic background the immune stimulation caused by the vaccine contributed to the final clinical manifestation and flare of the disease [52]. So in the context of an autoimmunity-high-risk individual elective vaccination may, perhaps, be reconsidered.

Conclusions

The majority of the autoimmune connective tissue diseases have no known etiological agents. Nevertheless, certain drugs and environmental or occupational factors have undoubtedly been shown to either exacerbate a known autoimmune disease or to trigger the onset of a syndrome that closely resembles one of the established diseases. So by diagnosing a new patient with autoimmune disease a wide anamnesis work should be done.

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