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Trends Mol Med. Author manuscript; available in PMC 2013 February 1.

Published in final edited form as:
Trends Mol Med. 2012 February ; 18(2): 101–108. doi:10.1016/j.molmed.2011.10.005.

Immunodeficiency and autoimmunity: lessons from systemic lupus erythematosus

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Abstract

Recent evidence suggests that systemic autoimmunity and immunodeficiency are not separate entities, but rather interconnected processes. Immunodeficiency results from distinct defects of the immune response and primarily presents as infections, but also frequently with autoimmune features. Systemic autoimmunity is the combined effect of multiple genetic variations, infectious and immunoregulatory factors that result in dominant autoimmune manifestations in addition to frequent and opportunistic infections. The overlap in disease manifestations and symptoms suggests that immunodeficiency should be considered in the presence of autoimmunity, and *vice versa*. In this review, we present the shared or similar aspects of immunodeficiency and autoimmunity using systemic lupus erythematosus as a paradigm and discuss the implications for clinical care.

The basis of systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an immune complex disease that predominantly affects women of reproductive age. Multiple autoantibodies are produced that bind diverse nuclear antigens, including double-stranded DNA, RNP (ribonucleoproteins) and Sm (Smith). These autoantibodies deposit on several organs, including kidneys, skin and joints, causing inflammation [1]. The etiology of SLE has still not been clearly elucidated, but a strong genetic contribution to disease development is postulated to exist. Gene polymorphisms, single nucleotide polymorphisms (SNPs), gene deficiencies, duplications and aberrant expression of splice variants have all been identified as contributing to the expression of SLE in certain individuals [2]. Genome-wide association studies (GWAS) performed in SLE patients have identified intriguing links between genetic diversity in major components of the immune system and susceptibility to SLE [3]. What is even more interesting is that genetic variations in genes previously associated with immunodeficiency are now also linked to SLE [4] [5]. The complete understanding of gene involvement in the expression of the disease may improve our understanding of the pathways used by pathogens and other environmental contributors to disease pathology [6, 7].

Several cases where monogenic defects in genes encoding immune system components lead to immunodeficiency and a phenotype associated with infections by specific microbial

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Conflicts of interest: The authors have no conflicts of interest.

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agents have recently been reported [6]. Examples are patients with late complement component deficiencies who are particularly prone to infection with *Neisseria meningitidis*, the causative agent of meningitis [8], Toll-like receptor 3 (TLR3)-deficient individuals, who are prone to herpes simplex virus (HSV) encephalitis [9], and MyD88-deficient patients, who are prone to invasive pneumococcal disease [10].

Immune defects in SLE

Primary immunodeficiency syndromes (PIDs) result from distinct defects of immune genes, whereas in SLE, besides rare cases such as *C1q* and *C4* deficiencies, widespread SNPs and gene variants appear to contribute subtly to aberrant immune system function [11]. Thus, weakly contributing genetic factors allow ample space for environmental influences (e.g. infections, diet or psychology) [12] and other factors to contribute to the manifestation of autoimmunity and related pathology (Figure 1).

SLE patients experience a high rate of infections, even from opportunistic pathogens normally observed in immunocompromised individuals, such as *Toxoplasma gondii*, *Pneumocystis carinii and Cryptococcus neoformans* [13]. There is increasing evidence that these infections, at both a clinical and a subclinical level, may represent the primary trigger for constant immune system activation and autoimmunity [14, 15] (Figure 1). Infection causes neutrophils to form web-like structures, the so-called neutrophil extracellular traps (NETs) [16]. Increased formation of NETs has been reported in SLE, although this formation has not been linked to a specific infection [17, 18]. Several pathways have been described that allow an immune response against a particular microbial agent to develop into generalized immune system activation and autoimmunity (Box 1).

Box 1

Spread of inflammation and development of systemic autoimmunity

The higher number of infections that affect patients with SLE could contribute to the development of systemic inflammation. Epitope spreading, superantigen activation, and bystander activation are some of the mechanisms through which the spread of inflammatory response can occur.

1. **Epitope spreading** Antigen presenting cells (APCs) that recognize a viral epitope internalize the whole protein and not just the specific epitope, allowing them to present many different types of antigenic determinants to T cells [78]. In this way, multiple T-cell specificities can be generated from a single epitope, allowing for the subsequent activation of multiple B cell clones [79]. Under physiological conditions, epitope spreading is beneficial in that it allows for a quick and robust immune response to be generated from a single antigenic determinant. However, it can also function in a harmful manner by leading to the generation of autoreactive cells. The fact that multiple antibody specificities accrue over time in SLE, so that the average number of autoantigens recognized gradually increases, suggests that epitope spreading might indeed occur early on in the course of this disease [80].
2. **Superantigen activation** Several bacterial pathogens, such as staphylococcus and mycoplasma, exhibit superantigen properties. Superantigens have the unique capacity to cross-link several T cell receptors, and thus activate many different antigenic specificities synchronously [81, 82]. Again, not only immune responses against pathogens are enhanced by this process but also self-reactive clones can be generated [83]. Evidence for the involvement of superantigens in the pathogenesis of two other autoimmune diseases, experimental autoimmune

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encephalomyelitis (EAE) and inflammatory bowel disease has been previously produced.

3. **Bystander activation**. Apart from engulfing microbial particles, APCs in the inflammatory microenvironment also take up apoptotic material from host cells that are present. Peptides from this material can then be presented to T cells and, in the context of inflammation, autoreactive T cell clones be generated [84, 85].

In a genetically predisposed individual, exposure to environmental factors may be chronic and begin long before disease development as can be concluded from the reports that autoantibodies appear several years prior to disease diagnosis [19]. Increased susceptibility to infection in patients with SLE [20] may very well exist prior to the development of clinical disease and during the long period of preexisting autoimmunity. Exposure to infections and other environmental factors occurs in a discontinuous fashion and may fuel the immune system, causing a disease flare [13, 21].

Infections implicated in the pathogenesis of SLE

One characteristic of SLE is the “interferon (IFN) signature”, a significant upregulation of type I IFN-inducible genes (IFN-α and IFN-β) in peripheral blood cells [22], which suggests the presence of high levels of IFN-α and IFN-β cytokines (Box 2). The IFN signature seems to strongly support the idea that a chronic viral infection is involved in the pathogenesis of SLE. An immune system defect that allows uncontrolled viral proliferation and reactive immune cell activation could underlie the high IFN production. Indeed, high numbers of infiltrating plasmacytoid dendritic cells (pDCs), one of the major producers of type I IFNs, are observed in skin and renal lesions from SLE patients [23, 24]. Furthermore, pathogen-associated nucleic acids seem to be able to exacerbate SLE pathology [21]. Cultured mesangial cells that are exposed to synthetic polyinosinic-cytidylic acid (pI:C) RNA *in vitro* produce CCL2 as well as IL-6, and *in vivo* injection of pI:C RNA increases serum IL-12p70, IL-6, and IFN-α levels.

Box 2

Type I interferon (IFN) production pathways

Plasmacytoid dendritic cells (pDCs) represent one of the major sources of IFN-α (interferon- α). These cells carry pattern-recognition receptors (PRRs) that are able to recognize evolutionarily conserved structures on infectious microorganisms as ‘foreign’ and trigger an immune system reaction against them (Figure I). Two different types of PRRs are involved in this process, TLRs (Toll-like receptors) and CNARs (cytosolic nucleic acid receptors). Located in endosomal compartments, TLRs scan phagocytosed material for the presence of viral particles [86, 87]. Single-strand RNA and double-strand DNA from viral particles are recognized by TLR-7 and TLR-9 receptors, respectively[87]. CNARs, by contrast, are present in all nucleated cells and allow recognition of viral particles directly at their point of entry. Examples of such receptors include RIG-I (retinoic acid-inducible gene I), MDA-5 (melanoma differentiation-associated gene) and DAI (DNA-dependent activator of IFN-regulatory factors)[88]. When either of these two pathways is activated the end result is the production type I IFNs. The binding of IFNs on their respective receptors on infected cells allows the latter to activate intracellular pathways that limit pathogen replication and promote its clearance.

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One candidate viral pathogen implicated in SLE immunopathogenesis is the Epstein-Barr virus (EBV). Infectious mononucleosis caused by EBV exhibit similar epidemiologic characteristics as SLE, in that they both afflict young adults, are less common in areas where primary EBV infection is endemic, and follow the same geographic latitude gradient [25]. Once infected, SLE patients seroconvert to EBV faster than controls and the EBV load is found to be higher in SLE affected individuals [26]. In a study performed in young adult lupus patients, 99% of them were found to have antibodies against EBV antigens in peripheral blood, compared with only 70% of their matched controls [27]. It appears that SLE CD8+ T cells cannot effectively respond to EBV-infected B cells, as seen by the fact that very low proportions of EBV-specific CD8+ T cells are able to produce IFN-γ in SLE patients in comparison with controls [28].

An association between EBV infection and autoimmunity has already been established for X-linked lymphoproliferative syndrome (XLP). XLP, a disease due to deficiency of the SLAM-associated protein (SAP), is characterized by chronic inflammatory responses and a hemophagocytic lymphohistiocytosis picture (Table 1) [29]. SAP is known to be part of T cell and natural killer (NK) cell signaling pathways, and its absence seems to result in an inability to counteract acute EBV infection, which leads to the chronic inflammation observed in these patients [30].

An association between parvovirus B19 infection and SLE has also been reported. Parvovirus B19 DNA and IgM anti-B19 antibodies have been reported in a small groups of patients and an undefined molecular mimicry has been claimed to be the linking mechanism [31].

Despite the presence of several lines of evidence suggesting the involvement of infectious agents in SLE immunopathogenesis, there are a number of reasons why distinct infectious agents causing SLE may never be found: (i) it is difficult to track individuals that are predisposed to develop SLE and observe the events they experience before becoming ill; (ii) the pathogenesis of SLE is likely the result of different factors acting together over time or simultaneously; (iii) more than one infectious agents may be involved; and (iv) the responsible pathogen may be an as yet unidentified infectious agent.

Defective immune response and pathogen clearance in SLE

SLE patients have been found to exhibit several immune defects that involve both the innate and adaptive immune pathways. In many cases, these have been found to affect proper pathogen recognition and/or clearance.

T cells and natural killer cells

CD8+ T cells, one of the most important players in antiviral immune defense, exhibit defective cytolytic abilities in patients with SLE, a defect that has not been found in any other autoimmune disease [32]. Lack of perforin leads to not only defective pathogen clearance but also accelerated humoral autoimmunity and lupus-like disease in mice [33]. A similar situation has been reported in humans, where complete loss of perforin function presents as familial hemophagocytic lymphohistiocytosis (FHL), a fatal autoimmune disorder of early childhood [34]. CD8+ T cell responses against EBV, one of the potential candidates for SLE pathogenesis, are found to be decreased in patients with SLE [35] and these patients have fewer IFN-γ producing cells against influenza virus A/H1N1 strain compared with control subjects [36].

CD4+ T helper cells also seem to be dysfunctional in SLE patients and exhibit an aberrant helper activity [37]. IL-2 production from CD4+ T helper cells, required for the

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differentiation and survival of antigen-specific CD8+ T cells, is decreased in SLE patients [38]. Reduced CD4+ cell responses against varicella zoster virus and a higher incidence of herpes zoster infection are also observed [39]. Furthermore, T helper cell responses against recall antigens are decreased in SLE patients. Both CD4+ and CD8+ T cells display increased rates of spontaneous apoptosis in SLE patients [40], leading to decreased numbers and a decreased immune defense repertoire.

The decreased CD3ζ chain expression observed in SLE patients could explain some of the above findings [1, 2]. CD3ζ chain constitutes part of the T cell receptor (TCR) signaling machinery and is responsible for transmitting downstream signals upon antigen recognition. Lack of CD3ζ expression could contribute to the defective immune responses against infections that are seen in SLE. Consistent with this, defective TCR signaling has been shown to lead to the development of a lethal, multiorgan autoimmune disease in mice [41]. Mutations in the gene encoding for ZAP-70, a downstream signaling target of the CD3ζ complex, also lead to the development of autoimmunity in mice [42]. Infectious agents seem to play an important role because mice that are bred in a microbial-free environment do not develop autoimmunity [43].

Finally, NK cell numbers, another key player in the defense against viral infections, are also decreased in SLE patients [44]. Overall, these defects suggest inadequate antiviral immunity in SLE patients. This could be responsible for the spread of multiple viral infections, both at a clinical and a subclinical level.

Complement

Complement deficiencies, a distinct group of immunodeficiencies, provide a perfect background for the development of both autoimmunity and infections. Early complement component deficiency frequently leads to the development of autoimmunity and autoimmune-like manifestations (93% of individuals with C1q deficiency, 60–66% of individuals with C1s-r deficiency, 90% of individuals with C4 deficiency and 10% of individuals with C2 deficiency) [45]. Lack of C1 inhibitor, responsible for the development of angioedema, has been linked in some cases to lupus nephritis and other autoimmune manifestations [46]. Late complement factor deficiencies, by contrast, link preferentially to infections and not to autoimmunity [47].

Decreased expression of complement receptor 1 (CR1), the complement receptor for C3b, on erythrocytes, polymorphonuclear cells and B cells in SLE patients may account for the defective phagocytic capacity toward infectious microorganisms [48]. This is probably accentuated in certain patients who carry the R77H allele of *ITGAM* (which encodes Mac-1, also known as CR3). One of the Mac-1 ligands is C3bi, and therefore, complement-dependent opsonization and phagocytosis are compromised in these patients [49]

Decreased mannose binding lectin (MBL) is the most common immunodeficiency in humans, with 5% of the population affected. Although the phenotype of this deficiency is usually mild, an increased prevalence of SLE has been reported in these patients [50]. Similar to the case of early complement components of the classical pathway, both rheumatic manifestations and higher rates of infections are seen in patients suffering from MBL deficiency.

MHC-I and ribosomal genes

Microarray studies performed in SLE patients have revealed that major histocompatibility complex class I (MHC-I) and ribosomal-related genes are underexpressed, compared with controls [51]. Conversely, patients with MHC-I deficiency (bare lymphocyte syndrome) sometimes exhibit autoimmune phenomena reminiscent of granulomatosis with polyangiitis

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[52]. Lupus-prone mice with β2 microglobulin deficiency (a component of MHC-I) exhibit accelerated skin disease [53]. MHC class I is required for the detection of intracellular pathogens by CD8+ T cells, and its absence seems to lead to a failure to defend against such pathogens. A certain gene transcription signature in $CD8^+$ cells has been linked to SLE disease prognosis [54].

Similarly, patients with ribosomopathies commonly present features of immune deficiency [55]. Ribosomopathies are a diverse collection of bone marrow failure genetic disorders, typical examples of which are Diamond-Blackfan anemia (DBA) and Shwachman-Diamond syndrome (SDS). Several immune defects have been described in these patients, including low numbers and reduced function of both T cells and B cells. Low expression levels of ribosome-related genes in SLE patients could have similar effects on the immune system, making the clearance of pathogens less effective.

B cells

B cells from patients with SLE are characteristically polyclonally activated and produce autoantibodies against a large array of self-antigens [1]. Lower numbers of naïve B cells and higher numbers of antibody-producing plasma cells are routinely recorded [56].

Certain autoantibodies have been linked to pathology, yet IgM autoantibodies may have a protective role [57]. The fact that lupus-prone mice that lack soluble antibodies still develop lupus-like disease supports the idea that SLE pathology may occur independently of soluble autoantibodies [58]. Indeed, instead of hypergammaglobulinemia, decreased immunoglobulin levels or even typical combined variable immunodeficiency (CVID) [59, 60] is seen in some SLE patients. As many as 6% of SLE patients display concurrent IgA deficiency and the same drugs that have been associated with this, have also been associated to the development of SLE (e.g. phenytoin, d-penicillamine and sulphasalazine) [61].

Other cell types

Both monocytes and macrophages from SLE patients exhibit increased levels of apoptosis. Furthermore, monocytes exhibit decreased levels of FcRII and FcRIII receptors on the surface membrane in SLE patients, and both are necessary for the phagocytosis of foreign and apoptotic material [62]. Monocyte-derived DCs from patients with SLE also exhibit diminished phagocytic capacity associated with decreased expression of specific C-type lectin receptors on their surface [63].

Autoimmune manifestations in immunodeficiency diseases

Clinical and laboratory findings consistent with autoimmunity are common in immunodeficient patients (Table 1). The decreased ability of the immune system to clear infections in these patients can cause perpetual immune system activation and autoimmunity.

Familial hemophagocytic lymphohistiocytosis (FHL) is an autosomal recessive PID, where a defect in perforin excretion has been documented [34]. Lack of perforin deprives the immune system of one of its main effectors against viral infections. In response to multiple uncleared viral infections an overwhelming activation of T lymphocytes, macrophages, and persistent inflammatory responses are seen in these patients. As a consequence, multiple autoimmune phenomena develop, including pancytopenia, rashes, lymphadenopathy and hepatosplenomegaly.

In chronic granulomatous disease, where a decreased production of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase by neutrophils exists, recurrent bacterial and

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fungal infections develop, followed by chronic inflammation of the gut and lungs. Furthermore, asymptomatic carriers of the defective genes are reported to have an increased incidence of discoid lupus [64].

Defects in recombinase activation genes (*RAG)* have been associated with severe combined immunodeficiency syndromes (SCID), yet a recent study reported hypomorphic *RAG* mutations (resulting in 50% *RAG* activity) in patients suffering from midline granulomatous disease [65]. Midline granulomatous disease is an autoimmune disorder, commonly seen in patients with granulomatosis with polyangiitis and NK/T cell lymphomas. In this case also, although the complete absence of the gene product seems to be associated with profound immunodeficiency, autoimmune phenomena prevail in partial deletion [66].

Patients with Wiskott-Aldrich syndrome (WAS) lack the WAS protein (WASP), which is involved in regulation of the actin cytoskeleton. Affected individuals present with eczema, autoimmune manifestations, recurrent bacterial infections and lymphoma [67]. Both antibody production and cellular immune defects are seen in these patients and predispose individuals to chronic inflammation. Interestingly, malignancy develops primarily in patients with autoimmune manifestations [68]

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is another example in which autoimmunity and infections coexist. Although generally considered a disease of immune regulation dysfunction with organ-specific autoimmune manifestations (e.g. hypoparathyroidism and adrenocortical failure), chronic mucocutaneous candidiasis is also invariably present [69]. Although current concepts support the existence of regulatory pathway defects in this disease, a plausible explanation for the fact that infections are also commonly seen in these patients is still missing.

IgA deficiency is the most common type of primary immunodeficiency and although it can exist undiagnosed, it is associated with the development of autoimmune and atopic phenomena in a substantial number of patients. Unaffected relatives of IgA deficient patients also have a higher prevalence for autoimmune manifestations compared with the general population [70]. What is even more interesting is that IgA deficiency is frequently found in patients previously diagnosed with autoimmune diseases such as SLE (1–5.2%) and rheumatoid arthritis (2–4.7%) [71].

CVID patients display low IgG and IgM levels and decreased antibody responses to common infectious agents [73]. Autoimmune diseases such as inflammatory bowel disease (IBD), autoimmune thrombocytopenia and thyroid disease are frequently present [73], and lymphoproliferative diseases, including lymphoid interstitial pneumonia, sarcoid-like granulomas and even lymphoma, are frequently observed.

In X-linked agammaglobulinemia (XLA) patients, identified by low or absent B cells and low immunoglobulin levels, many autoimmune diseases are present including arthritis, autoimmune hemolytic anemia, scleroderma and type 1 diabetes, in addition to chronic and/or recurrent infections [74].

Concluding remarks

Emerging information on the genetic basis of various diseases has enabled a better appreciation for the diverse effects that genetic susceptibility defects can have on clinical disease phenotype. In particular, recent findings on SLE immunopathogenesis have allowed us to better appreciate the association between autoimmune manifestations and subtle immune system defects. Such immune defects, by virtue of not being critical enough to allow overwhelming infections to develop, seem to provide the perfect background for

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chronic inflammatory responses. Although no single pathogen has yet been associated with SLE immunopathogenesis, recent data seem to converge towards the fact that chronic inflammation in SLE could stem from the presence of chronic immune system activation towards an uncleared intruder.

Apart from SLE, it seems that this link may also apply to other autoimmune diseases such as type I diabetes mellitus (T1DM), multiple sclerosis (MS), rheumatoid arthritis (RA), IBD and Sjögren's syndrome. Genetic studies have confirmed that polymorphisms within an interferon inducible gene, IRF-5, are linked to a predisposition for not only SLE but also MS, RA, IBD and Sjögren's syndrome [72]. T1DM has also been linked to an IFN-signature, similar to the one seen in SLE, and *MDA-5* polymorphisms (a cytosolic nucleic acid receptor encoding gene) are associated with predisposition for T1DM in genome-wide association studies [75, 76]. Finally, high numbers of EBV-infected B cells are seen in the central nervous system tertiary lymphoid tissues of MS patients [77]. Thus, it seems that different autoimmune diseases might share common molecular defects and could share the same pattern of immunodeficiency that leads to the chronic infection and immune hyper-reactivity proposed above.

We have presented information that suggests overlapping features between systemic autoimmunity and immunodeficiency. Patients with SLE develop infections because of defects in elements of the immune response. Similarly, patients with immunodeficiency present with autoimmune manifestations. In states of immunodeficiency, defects in immune response genes lead to uncleared infections and autoimmunity, whereas in systemic autoimmunity subtle defects of immune response genes lead both directly to autoimmunity and indirectly by failure to clear pathogens, whose presence amplifies the autoimmune process (Figure 2). Although autoimmunity and immunodeficiency occupy distinct chapters in textbooks, it appears that they are inextricably interconnected and one should be always considered in the presence of the other.

Glossary

adrenocortical failure	Insufficiency of the cortical part of the adrenal gland, which is responsible for the production of corticosteroids, aldosterone and androgenic steroids. This insufficiency can be caused by many factors, including infections, emboli, and tumors
agammaglobulinemia (or hypogammaglobulinemia)	The absence or very low levels of immunoglobulins (antibodies), resulting in the development of multiple infections
atopy	Inherited predisposition that causes a tendency to suffer from one or more allergic diseases, such as asthma, rhino-conjunctivitis and dermatitis
autoimmune thrombocytopenia	a disorder of low blood platelet counts in which platelets are destroyed by antibodies produced by the immune system
CD4+ T helper cells	are responsible for orchestrating the immune response and providing signals for the activation of other immune cells, such as B and cytotoxic T lymphocytes

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chronic mucocutaneous candidiasis	a group of disorders characterized by recurrent or persistent infections of the skin, mucous membranes, and nails with Candida organisms
granuloma	a mass or nodule of inflamed tissue characterized histologically by transformed macrophages (epithelioid cells) surrounded by lymphocytes
granulomatosis with polyangiitis (Wegener's)	a vasculitic disorder characterized by small- and medium-sized blood vessel inflammation (vasculitis) and the presence of granulomas, mainly in sinuses, lungs and kidneys
hemophagocytic lymphohistiocytosis (HLH)	a syndrome characterized by fever, hepatosplenomegaly and lymphadenopathy due to uncontrolled cytotoxic T cell activation and tissue infiltration with histiocytes (macrophages)
hepatosplenomegaly	simultaneous enlargement of both the liver and the spleen
hypergammaglobulinemia	presence of elevated levels of immunoglobulins (belonging to the gamma globulin fraction in serum electrophoresis in the blood serum. Can be polyclonal (multi-epitope specific, as seen in chronic inflammatory conditions) or monoclonal (i.e. a specificity for a single epitope)
hypoparathyroidism	Disease characterized by decreased function of the parathyroid glands, responsible for the production of parathyroid hormone and body calcium homeostasis
lymphadenopathy	enlargement of lymph nodes
lymphoid interstitial pneumonia	a syndrome of fever, cough, and dyspnea, due to dense accumulations of lymphocytes at the alveolar interstitium
midline granulomatous disease	A disease characterized by necrotizing granulomas of the head and neck. It is most commonly caused by granulomatosis with polyangiitis disease, natural killer/ T-cell lymphomas, cocaine abuse, or infections
molecular mimicry	sequence similarities between foreign and self-peptides that allow for the development of cross-reactive T or B cells and autoimmunity
pancytopenia	reduction in the number of all blood cell subpopulations: red blood cells, white blood cells and platelets
plasmacytoid dendritic cells	one of the two principal subsets of human dendritic cells (DCs) with a plasma cell-like morphology
polyangiitis	inflammation involving multiple blood or lymph vessels
ribosomopathies	collection of disorders in which genetic abnormalities cause impaired ribosome biogenesis and function, e.g. Diamond-Blackfan anemia Schwachman-Diamond

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	syndrome, X-linked dyskeratosis congenita, cartilage hair hypoplasia, and Treacher Collins syndrome
sarcoid-like granulomas	granulomas that do not display necrosis and are surrounded by concentric scar tissue (fibrosis)

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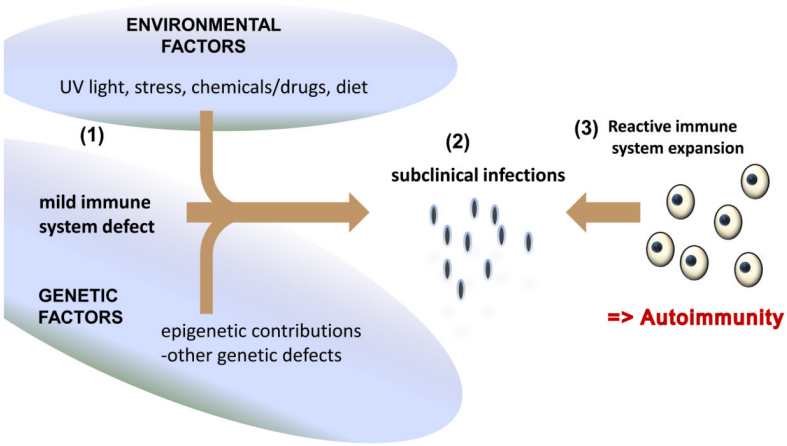

Fig. 1. Immune system defects and autoimmunity

The development of multiple subclinical infections may represent the triggering event in autoimmune patients that leads to uncontrolled immune system activation and chronic inflammation. A decline in immunity triggered by environmental factors (e.g. diet or psychological effectors) in combination with the presence of mild immune system defects may allow for these infections to develop.

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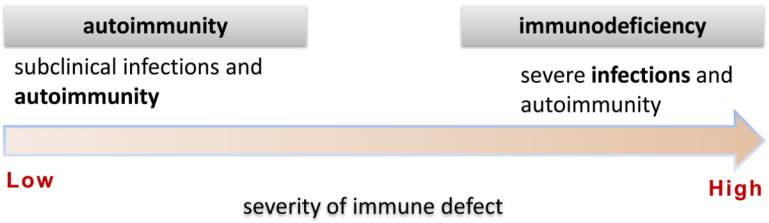

Fig. 2. Scale of severity of immune system-related genetic defects

Milder genetic defects may result in the culmination of multiple subclinical infections and the development of an autoimmunity-based phenotype. More severe genetic defects may manifest by the presence of frequent and/or severe infections and a more immunodeficiency-oriented phenotype.

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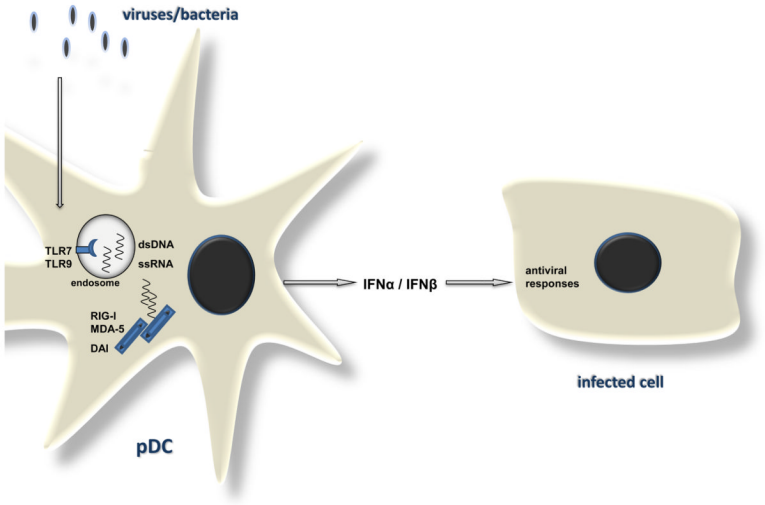

Fig. I. Type I interferon production

Toll-like receptors (TLRs) in endosomal compartments and cytosolic nucleic acid receptors (CNARs) scan phagocytosed material for the presence of viral particles. Upon recognition of their respective ligands, type I interferons responsible for activating intracellular pathways that promote pathogen clearance are produced (IFNα and IFNβ).

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Table 1

Immunodeficiency and associated autoimmune diseases

Disease	Defective molecule (involved in)	Infectious phenomena	Autoimmune/lymphoproliferative manifestations	Refs
FHL	Perforin gene (T/NK cell cytotoxicity)	Increased viral infections	HLH (inflammation and tissue destruction)	[34]
XLP	SLAM associated protein (SAP) (CD8+ T/NK cell signaling pathways)	Uncontrolled EBV infection	HLH (inflammation and tissue destruction), lymphoma	[29, 30]
WAS	WAS protein (WASP) (actin cytoskeleton)	Recurrent bacterial infections	ITP, AHA, vasculitis, eczema, lymphoma	[67]
CGD	NADPH oxidase (Neutrophil bactericidal mechanisms)	Recurrent bacterial/fungal infections	Chronic gut/lung inflammation	[64]
MGD	*RAG1*, *RAG2* (somatic rearrangement of Ig, TCR genes)	Systemic viral infections (CMV, EBV, VZV)	caseating granulomas of the nose, sinuses, palate, and upper airways	[65, 66]
APECED	AIRE gene (deletion of autoreactive lymphocyte clones)	Candidiasis	Organ-specific autoimmunity, (parathyroid, adrenals)	[69]
CVID	*TACI*, *ICOS*, *BAFF-R*, *CD19*, *MSH-5* genes (antibody production)	Recurrent sinopulmonary, GIT infections	IBD, ITP, AHA, LIP, lymphoma	[72, 73]
IgAD	IgA antibody production	Recurrent infections	SLE, rheumatoid arthritis, ITP, allergy, asthma	[71, 70]
XLA	Btk (B cell development/signaling)	Recurrent infections	Arthritis, AHA, scleroderma, type 1 diabetes	[74]

Abbreviations: FHL, familial hemophagocytic lymphohistiocytosis; HLH, hemophagocytic lymphohistiocytosis; XLP, X-linked lymphoproliferative syndrome; SLAM, signaling lymphocyte-activation molecule; EBV, Epstein-Barr virus; WAS, Wiskott-Aldrich syndrome; ITP, immune thrombocytopenia, CGD, chronic granulomatous disease, NADPH, nicotinamide adenine dinucleotide phosphate, MGD, midline granulomatous disease; RAG, recombination activating genes; Ig, immunoglobulin; TCR, T cell receptor; CMV, cytomegalovirus; VZV, varicella-zoster virus; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AIRE, autoimmune regulator; CVID, common variable immunodeficiency; TACI, transmembrane activator and calcium-modulator and cyclophilin ligand interactor; ICOS, inducible T-cell costimulator; BAFF-R, B cell-activating factor receptor; MSH-5, MutS protein homolog 5; GIT, gastrointestinal tract; IBD, inflammatory bowel disease; AHA, autoimmune hemolytic anemia; LIP, lymphoid interstitial pneumonia; IgAD, IgA deficiency; XLA, X-linked agammaglobulinemia; Btk, Bruton's tyrosine kinase