

# Primary Immunodeficiency and Autoimmunity: Lessons From Human Diseases

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## Abstract

Primary immunodeficiency diseases (PID) are a genetically heterogeneous group of >150 disorders that affect distinct components of the innate and adaptive immune system and are often associated with autoimmune diseases. We describe PID affecting T-regulatory cells, complement and B cells or their products and discuss the possibility of a cause–effect relationship. The high concordance of T-regulatory cell defects to organ-specific autoimmune disease implies an obligatory role of these cells in maintaining tolerance to epithelial and endocrine tissues; the absence of central nervous system involvement may reflect immunological privilege. Congenital defects in C1q, C1r/s and C4 are strongly associated with systemic lupus erythematosus (SLE), and this pattern along with laboratory evidence suggests a major importance of classical pathway activity in safe elimination of immune complexes and prevention of immune complex disease (ICD). It is debatable whether this ICD is to be regarded as an autoimmune disease (resulting from a breakdown of immunological ignorance to antigens that are normally hidden), as autoantibodies may be absent, and tissue damage because of deposition of immune complexes could account for all of the pathology observed. Evidence for a causative link between primary antibody deficiencies and autoimmune disease is much less compelling and may in fact involve a common genetic background. However, arguments have also been made in favour of the notion that an intense antigen load as a result of recurrent or persistent infections may affect either tolerance or ignorance, e.g. by molecular mimicry or the presence of superantigens. Similar immunological mechanisms might account for the vast majority of autoimmune diseases.

## Introduction

A primary immunodeficiency (PID) is a genetically determined disorder resulting in enhanced susceptibility to infectious diseases [1]. PID are a genetically heterogeneous group of disorders that affect distinct components of the innate and adaptive immune system. Unlike secondary immunodeficiency states, they are neither transient nor caused by events or circumstances. PID were not recognized as a group until 1952, when Ogden C Bruton [2] first described a failure of a male child to produce antibodies. Today, more than 150 different forms of PID are recognized [3], and the overall birth prevalence of significant PID in Europe, USA and Australia is estimated as 1:10,000 [4].

Many PID are monogenic, i.e. they can be explained by a simple Mendelian inheritance of one defective gene. For instance, Bruton's disease affects only men and was

thus traced to the X chromosome [X-linked agammaglobulinaemia (XLA)] [5]. X-linked PID affect all men with the gene, and autosomal dominant or co-dominant PID affect all the progeny. However, the majority of PID are autosomal recessive and thus have a much lower penetrance. Of the 47 or so monogenic PID, defects in T cells or the classical pathway of complement are particularly valuable to our understanding of autoimmune mechanisms. Mutations affecting B-cell activity provide a less clear-cut picture as most of them affect other cellular subsets as well. In contrast to monogenic PID, most polygenic PID are not well characterized, and in most cases, only some of the genetic defects are known. These PID are more heterogeneous clinically than monogenic PID, and the immunological dysfunction is much more complex and miscellaneous. Therefore, as a group they do not provide as definite answers to questions regarding a possible cause–effect relationship with autoimmune

diseases. For this reason, only a few polygenic PID will be dealt with in this treatise; for a more comprehensive review, the reader is referred to [3].

Primary immunodeficiencies usually manifest as frequent, recurrent or persistent infections. However, they are also very often associated with autoimmunity and/or formation of autoantibodies [6]. This has raised compelling questions about a possible cause–effect relationship, i.e. whether the congenital primary immune deficiency can be the cause of an autoimmune disease that later develops in the same individual. As outlined in the current review, this contention clearly holds true in certain cases, particularly in deficiencies involving T-regulatory cells, components of the classical pathway of complement and defects in lymphocyte apoptosis. Furthermore, it is also important to acknowledge the great impact that certain infections and environmental factors clearly have upon the immunopathogenesis of autoimmunity. This has led to speculations that the gap between the estimated population burden of PID (0.2%)<sup>2</sup> and autoimmune disease (3–5%) [7, 8] may be explained to a large extent by an underlying complete or incomplete primary or secondary immunodeficiency. This view is favoured by findings demonstrating a strong correlation (possibly through epigenetic factors) of various autoimmune diseases with familial predisposition [9, 10].

Overview: PID with autoimmune predisposition.

- (1) Monogenic immunodeficiencies.
  - (a) Defects in T cells and/or thymic or extrathymic tolerance induction.  
IPEX, APECED
  - (b) Complement defects.  
Deficiency in C1q, C1r/s, C4, C2.  
Deficiency in MBL and ficolins.  
Partial deficiency of C4A and/or C4B.
  - (c) Defects in B cells and immunoglobulins.  
Mutations in (i) CD40, (ii) CD40L, (iii) AID.
  - (d) Defects in genes which affect multiple cellular subsets.  
WAS, XLA, NEMO, PNP.
- (2) Polygenic immunodeficiencies.
  - (a) Defects in T cells and/or thymic or extrathymic tolerance induction.  
Omenn syndrome, ALPS.
  - (b) Primary hypogammaglobulinemia.  
Selective IgAD, selective IgG subclass deficiency, CVID.

<sup>2</sup>See text for the prevalence of individual PID. The estimated population prevalence (1:600–20,000) does not include MBL deficiency (prevalence 5%) as it is not universally recognized as a PID. IgA deficiency (1:600) is the most common universally recognized PID, followed by C2-deficiency (1:20,000) and CVID (1:10–100,000). For abbreviations see text.

## Monogenic immunodeficiencies

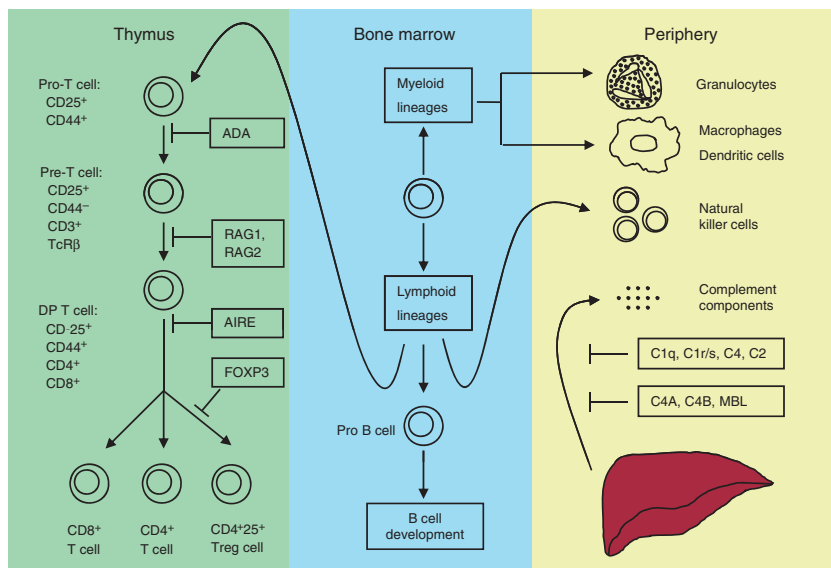
Monogenic immunodeficiencies represent a particularly valuable lesson in the study of aetiological links between primary immunodeficiencies and autoimmunity, because the defects operate from birth and associations with autoimmunity are less likely to be confounded by environmental triggers than in diseases with a polygenic multifactorial background. Observations on the associations of complete monogenic immunodeficiencies with autoimmunity demonstrate a central importance for immunological tolerance in preventing organ-specific autoimmune disease, whereas safe elimination of immune complexes appears to be one of the main pre-requirements for preventing systemic autoimmune disease.

### Defects in T cells and/or thymic or extrathymic tolerance induction

Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX) usually presents with the basic clinical triad of enteropathy, endocrinopathy (diabetes or thyroid disease) and dermatitis [11, 12]. This syndrome is owing to mutations in the gene forkhead X protein 3 (FOXP3) on the short arm of the X chromosome, which encodes a transcriptional repressor of T cells that is 'necessary and sufficient' for the normal development of CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells in the periphery (Fig. 1) [13]. IPEX is usually lethal in infancy unless treated with immunosuppression or bone marrow transplantation. An autoimmune disease is invariably associated with the syndrome (Table 1) accompanied by a variety of autoantibodies to multiple targets [14, 15]. In addition, almost all patients present concomitant allergic manifestations with eosinophilia and increased serum IgE [6]. IPEX is the earliest and most severe manifestation of autoimmunity, together with Omenn syndrome [6], and along with the FOXP3<sup>-/-</sup> *scurfy* mouse model, it provides a dramatic demonstration of the critical importance of T-regulatory cells in preventing autoimmunity [12, 15]. Furthermore, the autoimmune phenotypic presentation usually develops in early childhood, arguing against a role of unknown environmental triggers in its pathogenesis.

Autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED) is a rare disease, with higher frequency noted in Iranian Jews, Sardinians, Finns and Norwegians [11]. Chronic mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure are the classic triad of findings that characterize this syndrome. This syndrome has turned out to be because of a deficit of T-regulatory cells, and it is invariably associated with autoimmune disease (Table 1); strikingly, and similar to IPEX, these are organ specific and not systemic [16, 17]. APECED is a monogenic autosomal recessive disease associated with a defect in the AI regulator (AIRE) gene,

**Figure 1** Examples of gene defects in T-cell development or in the complement system that may lead to autoimmunity. Mutations in the genes coding for adenosine deaminase (ADA), the autoimmune regulator (AIRE) or forkhead X protein 3 (FOXP3) lead to severe combined immunodeficiency (SCID), autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED) or immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX), respectively, and mutations in recombination-activating gene 1 and 2 lead to Omenn syndrome (OS). Complete genetical deficiency of complement components in the classical pathway (C1q, C1r/s or C4) leads to systemic lupus erythematosus (SLE).



encoding a transcription factor which promotes ectopic expression of 'tissue-specific' genes in thymic medullary epithelial cells (Fig. 1). The AIRE protein regulates 'promiscuous gene expression' of non-thymic self-antigens, allowing clonal deletion of self-reactive thymocytes, with the end result being the development of self-tolerance of those proteins expressed. Original findings implicating AIRE in central tolerance are now complemented by evidence of AIRE expression in a unique subset of cells in the lymph nodes and the spleen (extrathymic AIRE-expressing cells, eTACs) [11]. AIRE in these cells is associated with organ-specific peripheral tissue antigens (PTA) that differ from those expressed in the thymus [11], suggesting that AIRE-induced PTA serve as a 'safety net' to delete autoreactive T cells that have escaped negative selection in the thymus. Evidence suggests that other 'AIRE-like' factors probably exist and remain to be identified [12]. APECED is a relatively benign condition compared to IPEX, supporting that T-regulatory cells may be generated by mechanisms other than AIRE-dependent antigen expression.

Monogenic defects in T-regulatory cells invariably lead to autoimmune disease (Table 1), and it can be safely assumed that this is primarily because of a breakdown in central (APECED) and peripheral (APECED and IPEX) tolerance. The strong association with organ-specific autoimmunity implies an absolute requirement for T-regulatory cells and a less absolute requirement for AIRE in tolerance to tissue-specific antigens, and the pattern (Table 1) suggests that this applies especially to epithelial and endocrine tissue. It is not clear why certain other tissues [e.g. the central nervous system (CNS)] are spared but this may relate to the immunological privilege of such sites (immunological ignorance). The link between IPEX and APECED on

one hand and autoimmune diseases on the other hand is strengthened by observations, suggesting that the level of protection against type I diabetes (T1D) and myasthenia gravis may be dictated by the expression level of the relevant peripheral tissue antigens [11].

### Complement defects

A complete genetical deficiency in C1q, C1r/s or C4 is strongly associated with immune complex disease (ICD) (93% for C1q, 60–66% for C1s/r, 90% for C4) (Table 1) [18–20]. It is less strong for C2 (32–33%) (perhaps owing to the ability of Bf to substitute for C2 in such cases [21]) but still compelling [18–20]. These findings indicate a central role of the classical pathway in prevention of ICD [22] and have been linked to laboratory studies demonstrating that classical pathway activity is required for safe elimination of immune complexes [23, 24] and apoptotic bodies [18].

A homozygous defect in exon 1 of the gene coding for MBL (mannan-binding lectin) represents the most common primary immunodeficiency of mankind, with 5% of Caucasians affected [25]. However, many compilers of the literature do not recognize this deficiency as a PID. This may relate to the benign nature of the defect, which is associated with moderately increased susceptibility to infections and systemic lupus erythematosus (SLE) (Table 1) [25, 26]. However, the same applies to many other PID (e.g. defects in the lytic system of complement), and it seems appropriate to add MBL deficiency to the list of currently recognized PID. MBL-associated serine protease (MASP) 2 deficiency has been described in one individual with chronic inflammation and recurrent infections [27], and ficolin-3 (normally expressed in the lungs and the liver) was found to be absent in one indi-

Table 1 The prevalence of autoimmune diseases in selected primary immunodeficiency diseases<sup>a</sup>.

Autoimmune disease		T-cell		Complement										B-cell			Complex <sup>b</sup>					
		IPEX	APECED	Omenn syndrome	C1q def.	C1r/s def.	C4 def.	C2 def.	C3 def.	MBL def.	C3a*Q1 def. to AIHb.1	C3a*Q1 - exon 29 mutation	C3b*Q1	ALPS	X-linked CD40L def.	AID def.	CVID	IgAD	WAS	NEMO def.	XLA	
Systemic	ICD	SLE			93	57	75	32-33	10	sp.	sp.	sp.	sp.		sp.		1-3	0-1				
		Vasculitis	2-3					sp.	sp.								1-2		20-29			
Systemic	Other	Henoeh-Scölein Purpura					8						sp.									
		Sjögren's/Sicca syndrome	12				4										1-10	0-1				
Organ-specific	Blood	Autoimmune haemolytic anaemia	30	2										29-39	2-3	3	2-3	2-3	15-36	1	sp.	
		Autoimmune thrombocytopenia	14											23-34	sp.	3	3-8	0.5	d			
		Autoimmune neutropenia	sp.											18-19	>60 <sup>c</sup>		1		25		sp.	
	Endocrine	Type 1 DM	73	2-20													3	sp.	sp.			sp.
		Autoimmune thyroid disease	16-28	2-11													2	1-3	3-7			
		Autoimmune hypoparathyroid disease		76-93																		
		Addison's disease		70-100																		
	Other	Glomerulonephritis				9	4	sp.	sp.						3-14				1	4		sp.
		Autoimmune hepatitis		20											sp.	6-20	7	1	1			
		Inflammatory bowel disease														2		6-10	0-1	9	21	sp.
		Coeliac disease																	0-1	1-4		
		Autoimmune enteropathy	97%	10													3					
Peniculous anaemia			13-15															1-9	1-2			
Alopecia			32-37															2-4			sp.	
Vitiligo			8-15															0-13	1-4			
Other autoimmune skin disease		62	100																			
Guillain-Barre syndrome													1-3									
Total	Autoimmune prevalence (%)	100	~100	100	93	60-66	90	32-33	>10	Rare	Rare	Rare	Rare	>80	20	21-25	20-26	7-36	30-72	23-25	11-20	
Ref.		11,12,14,15	11,12,16,17	12	18	18,20	18,20	18,20	18,20	25	30-32	79	34	12,51,53	37,40	39	74,81,82	63,64,67,74	12,43	47	80	

<sup>a</sup>All percentages in the table are rounded up to whole numbers. The focus is on monogenic PIDs, however Omenn syndrome, ALPS, CVID and IgAD are considered as polygenic. Sp. = sporadic (i.e. has been described in some references and may represent a weak association or simply case reports). For other abbreviations, see main text.

<sup>b</sup>Defects that involve multiple factors or cell types.

<sup>c</sup>Neutropenia is present at diagnosis in almost half of these patients but the autoimmune aetiology is controversial and circulating anti-neutrophil antibodies are quite uncommon.

<sup>d</sup>All WAS patients have thrombocytopenia that is likely to be of autoimmune origin.

vidual with a history of recurrent respiratory infections [28].

C3 deficiency is never complete, but even so, there is some association with autoimmune disease (Table 1). Genetical defects in other factors in the alternative pathway are very rare [19, 20]. Factor B deficiency is not known to exist, indicating that a complete lack of factor B is incompatible with survival. Factor D deficiency has not been associated with autoimmune disease. The severity of alternative pathway defects underscores its central importance in pathogen elimination.

Deficiencies in regulatory components are similarly rare [19, 20]. C1-inhibitor deficiency leads to uncontrolled classical pathway activation and hereditary angioedema [19]. Interestingly, it has been correlated with some rheumatologic conditions, but its underlying immunological mechanism is unclear. Deficiencies of other regulatory components are quite rare and lead to pyrogenic bacterial infections.

Deficiencies in components of the lytic pathway appear to be quite benign [19], no doubt because of the high redundancy in pathways of microbial elimination.

Association of this condition with autoimmune diseases is weak.

In summary, associations between regulatory components or factors belonging to the lectin pathway, the alternative pathway or the lytic pathway with autoimmune disease are weak and may be because of chance alone. In marked contrast to this, a complete genetical deficiency in components of the classical pathway leads to an autoimmune disease with a penetrance that may approach 100%; non-affected individuals are revealed by family studies of index cases, and this may lead to the identification of individuals too young for penetrance of the autoimmune condition. The pattern (Table 1) suggests that the association is caused by a breakdown in the mechanism responsible for safe elimination of immune complexes and apoptotic cells. Accumulation of apoptotic cells is predicted to result in increased release of intranuclear antigens from apoptotic cells and thus the formation of antinuclear antibodies. It has also been argued that antinuclear antibodies may be secondary to tissue damage as a result of widespread deposition of immune complexes. Both theories assume a breakdown in immu-

nological ignorance, leading to formation of antinuclear antibodies, but they differ in the emphasis of the role played by antinuclear antibodies in the aetiology of the disease. The latter theory is favoured by the absence of antinuclear antibodies in most SLE patients with a total deficiency in C1q, as well as the fact that antinuclear antibodies are formed in severe tissue trauma (e.g. burns) without an overt disease.

In this context, lessons from C4 may be particularly illuminating. Complement C4 exists as two distinct isotypes, C4A and C4B, coded for by adjacent genes within the major histocompatibility complex-III (MHC-III) region [29]. Each gene is inherited in a co-dominant fashion.<sup>3</sup> Complete absence of C4 involves mutations at both loci in both chromosomes and is thus extremely rare. Partial deficiency of C4A or C4B, on the other hand, is quite common, affecting 31.6% of the population [30]. This, along with the strong association of SLE with partial deficiency of C4, particularly C4A (C4A\*Q0) [31, 32], has led to the theory that transient or permanent deficiency in classical pathway activity may be a common denominator in ICD [22]. This widely accepted theory assumes that a breakdown in the mechanism responsible for the removal of immune complexes can lead to ICD and experimental evidence favours this notion [23, 24]. Defective prevention of immune precipitation was, however, not shown to be a common denominator for all patients, suggesting that the remaining cases are caused either by transient defects in classical pathway activity or by defects in other, yet unknown mechanisms [24, 33]. Current evidence also suggests another way in which a defect in classical pathway activity could lead to SLE, i.e. a defect in the elimination of apoptotic bodies [18]. This could lead to an increased production of antibodies to commonly encountered antigens (cf. serum sickness and the Arthus reaction) and, thus, a breakdown in ignorance. A new twist has been added to this tale by recent studies indicating an association between C4B\*Q0 and the prototype IgA ICD Henoch-Schönlein Purpura [34], suggesting that C4B\*Q0 may play a role in elimination of immune complexes containing IgA. This notion is in keeping with the known preferential binding of C4B to carbohydrates [35]<sup>4</sup> and the fact that IgA is highly glycosylated. The recent identification of C4B\*Q0 as a risk

factor for SLE in the Thai population is consistent with this contention [36], and the general conclusion may be that the two isotypes of C4 function in safe elimination of potentially inflammatory immune complexes of varying carbohydrate content, with C4A being more important for IgG complexes and other complexes with a high number of -NH derivatives and C4B being more important with IgA complexes and other complexes rich in carbohydrates. In summary, the association of ICD with defects in classical pathway activity may be attributed to either an increased load of autoantibodies and immune complexes or defective immune complex handling or both. However, alternative theories not based on defective classical pathway activity may hold true, at least for some patients or patient groups.

### Defects in B cells and immunoglobulins

Humoral immunodeficiencies include a heterogeneous group of immunoglobulin deficiencies. The spectrum of antibody deficiencies is broad, ranging from antibody deficiency syndromes (e.g. XLA), the most severe type of antibody deficiency with total absence of B cells and serum immunoglobulin, to less severe antibody deficiencies [common variable immunodeficiency (CVID), selective IgA deficiency (IgAD) and selective IgG subclass deficiencies]. The latter deficiencies are polygenic and are dealt with later, but some of the more severe hypogammaglobulinemias are monogenic.

### CSR defects

Defects of class-switch recombination (CSR) result in low levels of immunoglobulins other than IgM. A variety of molecules operate in class switching. Some of these are known, such as activation-induced cytidine deaminase (AID) and CD40/CD40L; defects in these genes lead to a group of PID commonly known as hyper IgM (HIGM) syndromes. They are characterized by normal or elevated serum IgM levels together with an absence of IgG, IgA and IgE (Fig. 2) [37, 38].

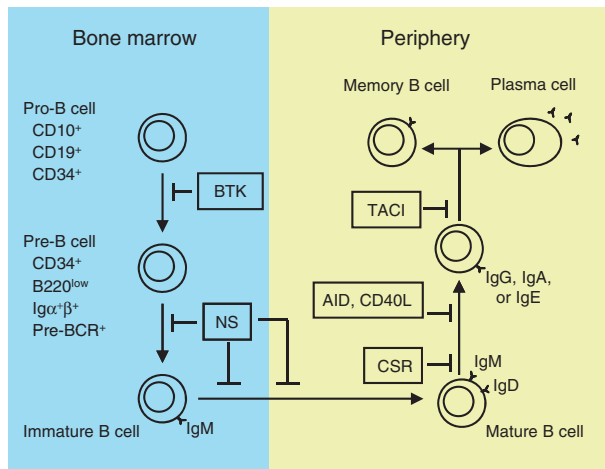
Defective CSR caused by mutations in AID is an autosomal recessive disease, associated with autoimmune disease in 25% of patients (Table 1), who show autoantibodies to multiple targets and suffer from various T cell-mediated inflammatory conditions [39]. This, and their inability to hypermutate their antibodies, suggests that 'germ line' antibodies can be autoreactive, in contrast to the previous view of a strict requirement of affinity maturation in the pathogenicity of antibodies [6]. The known AID mutations do not directly affect T cells, implying that in this case, the T cell-mediated inflammation may result from B-cell networking [6].

CSR-defect caused by CD40L-deficiency is an X-linked form of CSR. CD40 and CD40 ligand (CD40L)

<sup>3</sup>Inheritance in which two alleles of a gene pair are given full expression in a heterozygote, as in the alleles for the AB blood group antigens and the human leucocyte antigens (HLA).

<sup>4</sup>It should be noted, that the original studies suggesting preferential binding of C4A to immune complexes were based on immune complexes composed of the non-glycosylated antigen BSA, and antibodies of the IgG isotype, which are much less glycosylated than IgA. Although noted by the authors, this has been missed by most compilers of the literature. The fact that C4B binds more strongly to -OH derivatives than C4A strongly suggests a role for this isotype in binding carbohydrate-containing immune complexes.





**Figure 2** Examples of gene defects in B-cell development that may lead to autoimmunity. Mutations in the gene coding for Bruton's tyrosine kinase (BTK) lead to X-linked agammaglobulinemia (XLA). As discussed in the text, defects in apoptosis may lead to insufficient negative selection (NS) of B cells either centrally or peripherally, resulting in autoimmune lymphoproliferative syndrome (ALPS). Defects in activation-induced cytidine deaminase (AID) or CD40 ligand (CD40L) lead to defective switch recombination (CSR), known as HIGM syndromes. Other unknown and possibly polygenic defects in CSR may lead to selective IgA deficiency or selective IgG subclass deficiency. Defects in transmembrane activator (TACI) are shown as one example of defects leading to common variable immunodeficiency (CVID); other examples are discussed in the text.

are expressed on B cells and activated T cells, respectively, and an interaction between these molecules has traditionally been thought to involve only these cells. Deficiency of CD40 leads to a disease that is indistinguishable from CD40L deficiency, indicating that CD40L and CD40 interact exclusively with each other. Neutropenia is present at the time of diagnosis in almost half of these patients (Table 1) but its underlying aetiology is controversial and circulating antineutrophil antibodies are quite uncommon [37, 40]. Apart from neutropenia, the condition is mainly linked with autoimmune hepatitis and seronegative arthritis (Table 1) but overall, the paucity of autoimmune disease in the patients is interesting, given the importance of CD40/CD40L interactions in T-cell development, activation and effector function. This suggests that CD40/CD40L may not be strictly necessary for the generation and operation of T-regulatory cells. Thus, the inclusion of CD40L and CD40 deficiency in the section 'defects in B cells and immunoglobulins' may no longer be valid as these molecules have been found on other cellular subsets [41].

Other primary immunodeficiencies associated with defective B-cell differentiation and function with lack of immunoglobulins either result from defects affecting multiple cellular subsets, or represent polygenic immunodeficiency, and will be briefly discussed later.

Monogenic defects in B cells and their products are associated with autoimmune disease in a substantially lower proportion of patients than monogenic defects in T cells or the classical pathway of complement. Arguments for a cause-effect relationship are thus less evident for this group of PID. However, the data should be interpreted with caution, given the fact that today patients with severe immunoglobulin deficiencies are given prophylactic immunoglobulins, thus, possibly maintaining a crucial immunological homeostatic state.

#### Defects in genes which affect multiple cellular subsets

Wiskott-Aldrich syndrome (WAS) results from mutations of the WAS gene on the X chromosome. The defect affects expression of the WAS protein (WASP) which is involved in cellular signalling to the actin cytoskeleton. It is diagnosed on account of the triad of eczema, chronic thrombocytopenia and infections [12, 42]. A strong association with autoimmunity (30–72%) has been observed (Table 1), associated with high autoantibody titres [12, 43]. Autoimmune manifestations are also linked to worse prognosis. SLE and endocrinopathies have not been associated with WAS [43] despite of high antibody titres, possibly indicating a normal suppressive capacity of T-regulatory cells [12]. The effect of the defect on multiple cellular subsets precludes a definite explanation of the observed association of WAS with autoimmunity, but it is pertinent that a defect in the uptake of apoptotic bodies is a hallmark of the disease, inviting a comparison to autoimmune lymphoproliferative syndrome (ALPS), in which persistence of B cells reactive to antigens found in bone marrow or circulation leads to autoimmune cytopenia. The additional association of WAS (but not ALPS) with vasculitis and arthritis likely reflects the multicellular function of WASP.

X-linked agammaglobulinaemia in humans and X-linked immunodeficiency (Xid) in mice results from a mutation in Bruton's tyrosine kinase (Btk), which leads to a defect in B-cell development, differentiation and signalling [44–46]. Btk is expressed in other cells of bone marrow origin, and XLA is characterized by a general defect in myeloid dendritic cells. The defect leads to the arrest of B-cell maturation at the pre-B cell stage with resulting B-cell lymphopenia. Affected boys have undetectable or very low serum levels of IgM, IgD, IgE and IgA, with IgG usually being between 40–100 mg/dl; they remain relatively healthy while protected by maternal Ig but usually then start to suffer from frequent upper respiratory infections progressing to pneumonia. Manifestations of arthritis (15%), T1D, autoimmune hemolytic anaemia (AIHA), scleroderma and alopecia have repeatedly been observed (Table 1) [44–46].

NF- $\kappa$ B essential modulator (NEMO) defects, associated with X-linked anhydrotic or hypohydrotic ectoder-

mal dysplasia, have been described only recently [47]. NEMO (also known as IKK $\gamma$ ) is one of two modulators of the nuclear factor kappa B (NF- $\kappa$ B) family of transcription factors, which is central to the induction of both innate and adaptive immune responses to pathogens. The defect leads to impairment of dendritic cell IL-12 secretion and toll-like receptor signalling, profound T-cell lymphopenia and deficits in B cell response to specific immunization. NEMO defects are strongly associated with autoimmune disease, in particular inflammatory bowel disease (IBD) (Table 1). The reason for this association is not clear; NF- $\kappa$ B activity plays a role in T- and B-cell function but also in the generation of natural killer (NK) T cells, CD4<sup>+</sup>CD25<sup>+</sup> T-regulatory cells and memory T cells [6, 47]. Thus, given the complex immunological dysfunction observed, it is not surprising that mechanisms involving central and peripheral tolerance are impaired.

Purine nucleoside phosphorylase (PNP) deficiency is caused by a rare recessive defect in the gene for PNP on human chromosome 14 [1]. This causes a block in lymphocyte DNA synthesis and a partial deficiency in T-cell function, leading to severe infections after the first year of life, mainly by herpes viruses. AIHA has developed in some cases, but the link between this congenital immunodeficiency and autoimmunity is unclear, and the defect affects other organ systems, particularly the CNS.

Monogenic defects in genes affecting multiple cellular subsets present a heterogeneous class of PID, and the association with autoimmune disease may be variable. The pattern may differ according to which cellular subsets are affected and to what extent (Table 1). The deficiency of B cells in XLA and of T-cell function in PNP deficiency is only partial, and the penetrance of autoimmune disease is not high. The penetrance of autoimmunity in WAS is convincing and may indicate a role of cytolytic T cells in preventing autoimmunity.

## Polygenic immunodeficiencies

### Defects in T cells and/or thymic or extrathymic tolerance induction

Severe combined immunodeficiency (SCID) is a rare and heterogeneous group of genetic disorders that affect both T and B cells, resulting in early-onset severe infections. In 20–25% of cases, it is owing to a defect affecting the adenosine deaminase (ADA) gene on chromosome 20. Several other forms of SCID exist (reviewed in [48]). In the context of the present review, Omenn syndrome (OS) is the most informative as it differentiates from classical SCID by the additional features of autoimmunity.

Omenn syndrome may manifest itself in the first week of life and is characterized by erythrodermia (often with

desquamation), severe gastroenteropathy, enlargement of spleen and lymph nodes and susceptibility to infections [6, 12]. OS is characterized by the presence of activated T cells that infiltrate target organs such as the skin and the gut [12]. Association with autoimmune disease can be considered to be 100% as a result of the involvement of autoreactive T cells [6, 12]. The autoimmune disease is invariably organ specific and usually involves both the skin and the intestine (Table 1). It is most commonly caused by defects in RAG-1 and RAG-2 but defects in other genes affecting somatic V-(D)-J recombination and thymocyte development (e.g. ARTEMIS, ligase-4, IL-7R $\alpha$ ) also cause OS, and in almost 50% of patients, the genetic underlying defect has not been identified [48, 49]. Two animal models of OS were recently described, with specific mutations in RAG-1 and RAG-2, respectively. Data from the RAG-2 deficient model indicate that the defect leads to reduced thymic expression of AIRE and this is consistent with observations of reduced thymic AIRE expression in patients with OS [12]. Although polygenic in nature, the pathogenesis may be explained by a very low probability to generate T-regulatory cells, and this interpretation would allow OS to be compared more directly to APECED and especially IPEX; in fact, it might be considered to represent IPEX with no effector cells to organs other than skin and intestine [6, 12].

Autoimmune lymphoproliferative syndrome (ALPS) or Canale–Smith syndrome manifests as autoimmune cytopenia, lymphadenopathy and splenomegaly and is usually diagnosed in early childhood. It is characterized as a defect of lymphocyte apoptosis; most cases are caused by mutations of FAS, while mutations of FASL or of downstream mediators of the apoptosis pathway (caspases 10 and 8) have also been described [12, 50]. In ALPS, auto-antibody-induced autoimmune manifestations occur in >80% of cases and the targets are essentially limited to circulating cellular elements [12] (Table 1) [51–53]. This suggests an importance of apoptosis in the induction of tolerance to haematopoietic cells and is most likely explained by a defect in B-cell tolerance. The encounter of B cells with self-antigens during maturation in the bone marrow and under circumstances where T cell help is not available in the periphery leads to apoptosis. A failure in this mechanism would result in persistence of B cells with reactivity to antigens that are commonly encountered in the bone marrow and circulation, and an increased probability of developing autoimmune cytopenia.

The association of polygenic T-cell defects with autoimmune disease is strong when the defect affects T-regulatory cells (OS 100%) or lymphocyte apoptosis (ALPS > 80%). The high prevalence of autoimmune cytopenia in ALPS, in which T-regulatory cell activity is normal, suggests a role for B-cell tolerance in protection against autoimmune cytopenia.

### Polygenic antibody deficiencies

The main polygenic antibody deficiencies are selective antibody deficiency (selective IgG subclass deficiencies, selective IgA deficiency) and CVID.

Selective IgA deficiency (IgAD) is the most common deficiency of the adaptive immune system, with a prevalence of approximately 1:600 in the Western world. However, there is a marked variability in the prevalence in different ethnic groups, with a much lower frequency in the Japanese (1/18,000) and the Chinese (1/4000), suggesting a genetic basis for the disorder [54]. Individuals with IgAD have serum IgA < 0.07 g/L, but normal levels of serum IgG and IgM [55]. The disorder seems to be caused by a defect at the stem cell level, as indicated by studies on bone marrow transplantation between individuals with IgAD and normal IgA [56, 57]. The molecular basis of IgAD is not well known, but the underlying defect is probably regulatory in nature, at the level of switching, transcription or post-transcription [58, 59]. Interestingly, IgA-deficient individuals have been shown to have circulating B cells with cell surface IgA; however, these are immature cells which also express surface IgM and IgD and fail to develop into IgA-secreting plasma cells [60, 61]. The clinical manifestation of IgAD is variable and depends upon age and more importantly the cohort studied. Although a relatively benign PID, a significant proportion of affected individuals suffer from recurrent infections, asthma, allergic diseases and autoimmunity [62–66]. Autoimmunity is an important clinical manifestation of IgAD (Table 1), and the prevalence varies from 7–36% [67]. In a 20-year follow-up of 159 IgAD subjects, identified from a group of initially healthy blood donors, 36 (23%) later developed an autoimmune disease [64]. Although IgAD is usually thought to have stronger association with systemic autoimmune diseases, as demonstrated by high prevalence of IgAD in cohorts of patients with SLE (1–5.2%) and patients with RA (2–4.7%), the association with organ-specific diseases has been coming more evident [63, 67, 68].

Selective deficiencies of IgG subclasses are most probably caused by defects in factors that regulate immunoglobulin isotype switching in antigen-triggered B cells. This condition causes susceptibility to infections but does not appear to be associated with autoimmune diseases, unless co-occurring with IgAD [69, 70].

Common variable immunodeficiency disorders designate a heterogeneous group of diseases in which failure to produce immunoglobulins and protective antibodies usually results in recurrent respiratory and gastrointestinal infections, autoimmunity and cancer predisposition [71]. The patients display a marked reduction in serum levels of both IgG and IgA. In half of the patients, IgM is also reduced. The common feature is failure of antibody pro-

duction following known exposure to pathogens or immunization. The prevalence of this disorder is 1:10–100,000 so the order of magnitude is several degrees lower than the prevalence for selective IgA deficiency. Autoimmune diseases have been observed in 20–26% of patients with CVID, demonstrating a limited 'target range', directed primarily against haematopoietic cells, resulting in cytopaenias [idiopathic thrombocytopenic purpura (ITP) or AIHA] but solid organ-specific autoimmune diseases such as pernicious anaemia, thyroid diseases and vitiligo are also present (Table 1). The association with systemic diseases such as SLE, RA/juvenile RA (JRA) and psoriasis has been suggested but with lower penetration [71, 72].

In contrast to most of the primary immunodeficiency disorders, the genetic defects underlying IgAD, and most cases of CVID, are still unknown. Despite no conclusive evidence, there are several hypotheses that might explain how defects in immunoglobulin production could give rise to autoimmune diseases. The clustering and co-occurrence of IgAD and CVID within families suggests that genetic factors play an important role in the pathogenesis. The high prevalence of autoimmune diseases within IgAD (and CVID) cohorts (Table 1) together with a recent report on increased prevalence of autoimmunity (10%) in their normoglobulinemic first-degree relatives indicates a role for a common genetic denominator in the induction of these diseases [63]. Genetic linkage and HLA studies have demonstrated that IgAD and CVID share a major susceptibility locus in the DQ-DR haplotype on chromosome 6. This association is particularly strong and consistent with the ancestral haplotype (AH) HLA-A1, B8, DR3, DQ2 (AH8.1), an association common to several autoimmune diseases such as SLE, T1D and coeliac disease [71]. Furthermore, five genes have been identified which harbour CVID-associated mutations (TACI, ICOS, BAFF-R, CD19 and *MSH5*, a gene encoded in the MHC class III region) [54, 58, 71–73]; these genes all involve different elements of B-cell biology. Interestingly, the TACI mutations significantly predispose patients with CVID to autoimmunity. Together, these defects account for 10–15% of CVID, but for the vast majority of patients, the underlying defect is not known. It seems paradoxical that autoantibodies are produced against self-antigens in patients with CVID, whereas at the same time, they are low in IgG and do not produce specific antibodies after vaccinations. Moreover, CVID seems to be associated with defects (e.g. BAFF-R) that diminish, rather than augment, immune response, as expected if natural tolerance is indeed dominant. Lack of secretory IgA is common to both IgAD patients and CVID patients. IgA is known to be involved in the processing and clearing of external antigens from mucosal surfaces. Defective antigen clearance might result in end-organ deposition of immune complexes, chronic



inflammation, tissue damage and perhaps formation of anti-tissues antibodies. Furthermore, lack of IgA could lead to mucosal absorption of antigens present in diet or of microbial contents, some of which could cross-react with normal tissues [74]. Alternatively, the increased infections in cohorts of IgAD/CVID subjects might be the link to increased autoimmunity. Theories for this assume a breakdown of tolerance as a result of exposure of hidden or sequestered antigens, molecular mimicry, presence of superantigens or antigen drift because of a cytokine environment favouring bystander activation of B cells [71, 75]. Additional mechanisms that might permit autoimmune T- and B-cell reactive clones to persist are failure of apoptosis of self-reactive clones, cytokine dysregulation or failure of T-cell regulation.

### Immunodeficiencies with mild (<10%) or no association with autoimmune disease

As previously stated, deficiencies of C3 and C5–9 have rarely (<10%) been associated with autoimmune disease. The same holds true for chronic granulomatous disease (CGD), suggesting that at least in these cases, susceptibility to infections is not a major determinant in autoimmunity. This is supported also by the lack of association of asplenia with autoimmune disease, in spite of low resistance to capsulated bacteria. DiGeorge syndrome (deletion of chromosome 22q11.2) is associated with autoimmune disease in 5–10% of patients, mainly ITP and JRA [76]. This is probably because of defective T-cell selection in an abnormal thymus, possibly resulting in defective positive selection of natural T-regulatory cells or defective negative selection of autoreactive T cells. The association of DiGeorge syndrome with autoimmunity is only a mild one, and this is consistent with the observation that T-cell functions are only minimally impaired in the majority of affected individuals (only <1% manifest profound T-cell functional impairment) [76]. A few other PID have been associated with autoimmune diseases in rare cases (<10%). The association is not convincing, and the pathophysiology is poorly defined. Deficiencies of Fc $\gamma$ RIIIb, MHC class I and II and TAP1-2 (transporter associated with antigen processing 1 and 2) are relatively recently described; these PID affect several cellular subsets, and the association with autoimmune disease is not clear [6]. There have been no descriptions of associations with autoimmune diseases in factor D deficiency, IRAK-4 deficiency or the warts, hypogammaglobulinemia, infections, myelokathexis syndrome; this may be a result of incomplete clinical description as these disorders are rare and/or recently characterized [1]. The lack of associations with autoimmune disease in the few hundred patients with deficits in the IL-12/IL-23-IFN $\gamma$  axis is interesting, as these defects would have been expected to induce autoantibodies because of Th1/Th2 imbalance [6].

### Familial associations between primary immunodeficiencies and autoimmune disease

Although a strong case can be made for a cause–effect relationship between certain PID and autoimmune disease, this contention is much less clear in other cases, and the possibility remains that many of the associations are because of linkage between the PID gene and a gene affecting autoimmunity. Family studies may give valuable information on which genes are involved. An association within families is commonly observed between PID and autoimmune disease [63, 77]. A particularly strong example is provided by diseases associated with the MHC genetic region. SLE, T1D, Graves' disease (GD) and coeliac disease have all been linked with genes within the MHC region of human chromosome 6, and many studies have indicated a link between this region and familial CVID and/or IgAD. The relationship is particularly strong in the case of ancestral haplotype (AH) 8.1, a very conserved haplotype consisting of MHC A1, B8, BfS, C2C, C4AQ0, C4B1 and DR3. The C4 genes of this haplotype escaped the duplication event that led to the evolution of C4A and thus do not include a C4A gene.<sup>5</sup> In addition to a non-duplicated C4 (along with other genes of the RCCX module), this haplotype harbours many irregularities including gene deletions and duplications [29], and the high level of conservation (with e.g. no known recombinations within the MHC-III region) has been a strong obstacle for the search of the culprit gene, and the possibility remains that each of the above-mentioned diseases map to different genes within the haplotype [9]. For instance, T1D and GD appear to be associated with DQ-genes in the region [78], while strong evidence exists for a cause–effect relationship between C4A\*Q0 and SLE, as this relationship exists not only in AH8.1 but also in patients with C4A\*Q0 as a result of the 2bp insertion in exon 29 [79]. These observations suggest that the genetic basis for SLE may differ from that of T1D and GD and the observed clustering in families may result from linkage disequilibrium between the responsible genes. Further studies are warranted to reveal which of these genes are responsible to the linkage to IgAD and CVID, and indeed, the possibility of an epigenetic influence for all of these diseases cannot be excluded [10].

Taken together, observations on the MHC associations between IgAD/CVID and autoimmune diseases suggest that ICD are most likely related to low levels of C4A or C4B, while for T1D and GD, the risk factor appears to be a gene mapping to the DQ region, suggesting a role of antigen presentation in the induction of the disease. This is consistent with the organ-specific nature of these

<sup>5</sup>The description of C4A\*Q0 of this haplotype as C4A-gene deletion is a common misconception.

diseases, and when considered along with observations on monogenic diseases in T-regulatory cells, it reinforces the notion that antigen presentation to T cells and regulation of T cells is critical in induction of tolerance to organ-specific antigens. The familial association of CVID and IgAD with autoimmune diseases, such as SLE, T1D, GD and coeliac disease, favours the notion that the underlying cause may be the common genetic background rather than the PID itself but the possibility of an epigenetic and post-infectious immunopathogenetic influence remains.

## Conclusions

Primary immunodeficiency diseases that affect T-regulatory cells (IPEX, APECED, OS) lead to autoimmune disease with 100% penetrance. The pattern is interesting, as manifestations are almost invariably organ specific and affect mainly the endocrine glands and other epithelial tissue. Complete deficiencies of components in the classical pathway result in various ICD with a very high penetrance. This pattern is again quite interesting as manifestations are almost invariably systemic (SLE or similar condition). Incomplete deficiencies in complement C4 may lead to SLE in the case of C4A\*Q0 and Henoch-Schönlein Purpura in the case of C4B\*Q0. These findings have provided evidence for the theory that ICD are linked to a defective clearance of immune complexes from the circulation and tissue sites. Congenital defects affecting B cells and immunoglobulins are much less commonly associated with autoimmunity, but the association of ALPS with autoimmune cytopenia supports a role of B cells in establishing tolerance to circulating cells. In summary, lessons from the associations of PID with autoimmune diseases indicate that tolerance to epithelial and endocrine tissue is accomplished largely by the activity of T-regulatory cells, while full tolerance to haematopoietic tissues may depend on clonal deletion of autoreactive B cells.

## References

- 1 Kumar A, Teuber SS, Gershwin ME. Current perspectives on primary immunodeficiency diseases. *Clin Dev Immunol* 2006;13:223–59.
- 2 Bruton OC. Agammaglobulinemia. *Pediatrics* 1952;9:722–8.
- 3 Geha RS, Notarangelo LD, Casanova JL et al. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol* 2007;120:776–94.
- 4 Eades-Perner AM, Gathmann B, Knerr V et al. The European internet-based patient and research database for primary immunodeficiencies: results 2004–06. *Clin Exp Immunol* 2007;147:306–12.
- 5 Valiaho J, Smith CI, Vihinen M. BTKbase: the mutation database for X-linked agammaglobulinemia. *Hum Mutat* 2006;27:1209–17.
- 6 Carneiro-Sampaio M, Coutinho A. Tolerance and autoimmunity: lessons at the bedside of primary immunodeficiencies. *Adv Immunol* 2007;95:51–82.
- 7 Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007;29:1–9.
- 8 Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* 1997;84:223–43.
- 9 Candore G, Lio D, Colonna Romano G, Caruso C. Pathogenesis of autoimmune diseases associated with 8.1 ancestral haplotype: effect of multiple gene interactions. *Autoimmun Rev* 2002;1:29–35.
- 10 Hewagama A, Richardson B. The genetics and epigenetics of autoimmune diseases. *J Autoimmun* 2009;33:3–11.
- 11 Su MA, Anderson MS. Monogenic autoimmune diseases: insights into self-tolerance. *Pediatr Res* 2009;65:20R–5R.
- 12 Westerberg LS, Klein C, Snapper SB. Breakdown of T cell tolerance and autoimmunity in primary immunodeficiency – lessons learned from monogenic disorders in mice and men. *Curr Opin Immunol* 2008;20:646–54.
- 13 Lehman HK, Ballou M. Immune deficiency disorders with autoimmunity and abnormalities in immune regulation-monogenic autoimmune diseases. *Clin Rev Allergy Immunol* 2008;34:141–5.
- 14 Moraes-Vasconcelos D, Costa-Carvalho BT, Torgerson TR, Ochs HD. Primary immune deficiency disorders presenting as autoimmune diseases: IPEX and APECED. *J Clin Immunol* 2008;28 (Suppl. 1):S11–9.
- 15 Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *J Med Genet* 2002;39:537–45.
- 16 Betterle C, Greggio NA, Volpato M. Clinical review 93: Autoimmune polyglandular syndrome type 1. *J Clin Endocrinol Metab* 1998;83:1049–55.
- 17 Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med* 1990;322:1829–36.
- 18 Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ. Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol* 2000;76:227–324.
- 19 Rother K. Complement deficiencies in humans. In: Rother K, Till GO, Hänsch GM, eds. *The Complement System*, 2nd revised edn. Berlin: Springer, 1998:351–3, ISBN 978 354 0618942.
- 20 Sullivan KE. Complement deficiency and autoimmunity. *Curr Opin Pediatr* 1998;10:600–6.
- 21 Traustadottir KH, Rafnar BO, Steinsson K, Valdimarsson H, Erlendsson K. Participation of factor B in residual immune complex red cell binding activity observed in serum from a C2-deficient systemic lupus erythematosus patient may delay the appearance of clinical symptoms. *Arthritis Rheum* 1998;41:427–34.
- 22 Lachmann PJ, Walport MJ. Deficiency of the effector mechanisms of the immune response and autoimmunity. *Ciba Found Symp* 1987;129:149–71.
- 23 Arason GJ, Geirsson AJ, Kolka R, Vikingsdottir T, Valdimarsson H. Deficiency of complement-dependent prevention of immune precipitation in systemic sclerosis. *Ann Rheum Dis* 2002;61:257–60.
- 24 Arason GJ, Steinsson K, Kolka R, Vikingsdottir T, D'Ambrogio MS, Valdimarsson H. Patients with systemic lupus erythematosus are deficient in complement-dependent prevention of immune precipitation. *Rheumatology (Oxford)* 2004;43:783–9.
- 25 Dommett RM, Klein N, Turner MW. Mannose-binding lectin in innate immunity: past, present and future. *Tissue Antigens* 2006;68:193–209.
- 26 Saevarsdottir S, Vikingsdottir T, Valdimarsson H. The potential role of mannan-binding lectin in the clearance of self-components including immune complexes. *Scand J Immunol* 2004;60:23–9.
- 27 Stengaard-Pedersen K, Thiel S, Gadjeva M et al. Inherited deficiency of mannan-binding lectin-associated serine protease 2. *N Engl J Med* 2003;349:554–60.

- 28 Munthe-Fog L, Hummelshoj T, Honore C, Madsen HO, Permin H, Garred P. Immunodeficiency associated with FCN3 mutation and ficolin-3 deficiency. *N Engl J Med* 2009;360:2637–44.
- 29 Blanchong CA, Chung EK, Rupert KL *et al.* Genetic, structural and functional diversities of human complement components C4A and C4B and their mouse homologues, Slp and C4. *Int Immunopharmacol* 2001;1:365–92.
- 30 Blanchong CA, Zhou B, Rupert KL *et al.* Deficiencies of human complement component C4A and C4B and heterozygosity in length variants of RP-C4-CYP21-TNX (RCCX) modules in caucasians. The load of RCCX genetic diversity on major histocompatibility complex-associated disease. *J Exp Med* 2000;191:2183–96.
- 31 Yang Y, Chung EK, Wu YL *et al.* Gene copy-number variation and associated polymorphisms of complement component C4 in human systemic lupus erythematosus (SLE): low copy number is a risk factor for and high copy number is a protective factor against SLE susceptibility in European Americans. *Am J Hum Genet* 2007;80:1037–54.
- 32 Yang Y, Chung EK, Zhou B *et al.* The intricate role of complement component C4 in human systemic lupus erythematosus. *Curr Dir Autoimmun* 2004;7:98–132.
- 33 Arason GJ, Kolka R, Hreidarsson AB *et al.* Defective prevention of immune precipitation in autoimmune diseases is independent of C4A\*Q0. *Clin Exp Immunol* 2005;140:572–9.
- 34 Stefansson Thors V, Kolka R, Sigurdardottir SL, Edvardsson VO, Arason G, Haraldsson A. Increased frequency of C4B\*Q0 alleles in patients with Henoch-Schonlein purpura. *Scand J Immunol* 2005;61:274–8.
- 35 Law SK, Dodds AW, Porter RR. A comparison of the properties of two classes, C4A and C4B, of the human complement component C4. *EMBO J* 1984;3:1819–23.
- 36 Ittiprasert W, Kantachuesiri S, Pavasuthipaisit K *et al.* Complete deficiencies of complement C4A and C4B including 2-bp insertion in codon 1213 are genetic risk factors of systemic lupus erythematosus in Thai populations. *J Autoimmun* 2005;25:77–84.
- 37 Levy J, Espanol-Boren T, Thomas C *et al.* Clinical spectrum of X-linked hyper-IgM syndrome. *J Pediatr* 1997;131:47–54.
- 38 Notarangelo LD, Lanzi G, Peron S, Durandy A. Defects of class-switch recombination. *J Allergy Clin Immunol* 2006;117:855–64.
- 39 Quartier P, Bustamante J, Sanal O *et al.* Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. *Clin Immunol* 2004;110:22–9.
- 40 Winkelstein JA, Marino MC, Ochs H *et al.* The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. *Medicine (Baltimore)* 2003;82:373–84.
- 41 Wagner DH Jr. The co-evolution of our understanding of CD40 and inflammation. *Diabetologia* 2009;52:997–9.
- 42 Imai K, Nonoyama S, Ochs HD. WASP (Wiskott-Aldrich syndrome protein) gene mutations and phenotype. *Curr Opin Allergy Clin Immunol* 2003;3:427–36.
- 43 Dupuis-Girod S, Medioni J, Haddad E *et al.* Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. *Pediatrics* 2003;111:e622–7.
- 44 Ochs HD, Notarangelo LD. X-linked immunodeficiencies. *Curr Allergy Asthma Rep* 2004;4:339–48.
- 45 Winkelstein JA, Marino MC, Lederman HM *et al.* X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine (Baltimore)* 2006;85:193–202.
- 46 Howard V, Greene JM, Pahwa S *et al.* The health status and quality of life of adults with X-linked agammaglobulinemia. *Clin Immunol* 2006;118:201–8.
- 47 Hanson EP, Monaco-Shawver L, Solt LA *et al.* Hypomorphic nuclear factor-kappaB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. *J Allergy Clin Immunol* 2008;122 (6):1169–77.
- 48 Cunningham-Rundles C, Ponda PP. Molecular defects in T- and B-cell primary immunodeficiency diseases. *Nat Rev Immunol* 2005;5:880–92.
- 49 Milner JD, Fasth A, Etzioni A. Autoimmunity in severe combined immunodeficiency (SCID): lessons from patients and experimental models. *J Clin Immunol* 2008;28 (Suppl. 1):S29–33.
- 50 Oliveira JB, Gupta S. Disorders of apoptosis: mechanisms for autoimmunity in primary immunodeficiency diseases. *J Clin Immunol* 2008;28 (Suppl. 1):S20–8.
- 51 Rieux-Laucat F, Le Deist F, Fischer A. Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways. *Cell Death Differ* 2003;10:124–33.
- 52 Kwon SW, Procter J, Dale JK, Straus SE, Stroncek DF. Neutrophil and platelet antibodies in autoimmune lymphoproliferative syndrome. *Vox Sang* 2003;85:307–12.
- 53 Sneller MC, Dale JK, Straus SE. Autoimmune lymphoproliferative syndrome. *Curr Opin Rheumatol* 2003;15:417–21.
- 54 Hammarstrom L, Smith CIE. Genetic approach to common variable immunodeficiency. In: Ochs HD, Smith CIE, Puck JM, eds. *Primary Immunodeficiency Diseases: A Molecular and Genetic Approach*, 2nd edn. New York: Oxford Univ Press, 2007:313–25, ISBN 978 0 19 514774 2.
- 55 Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol* 1999;93:190–7.
- 56 Hammarstrom L, Lonnqvist B, Ringden O, Smith CI, Wiebe T. Transfer of IgA deficiency to a bone-marrow-grafted patient with aplastic anaemia. *Lancet* 1985;1:778–81.
- 57 Kurobane I, Riches PG, Sheldon J, Jones S, Hobbs JR. Incidental correction of severe IgA deficiency by displacement bone marrow transplantation. *Bone Marrow Transplant* 1991;7:494–5.
- 58 Hammarstrom L, Vorechovsky I, Webster D. Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). *Clin Exp Immunol* 2000;120:225–31.
- 59 Islam KB, Baskin B, Nilsson L, Hammarstrom L, Sideras P, Smith CI. Molecular analysis of IgA deficiency. Evidence for impaired switching to IgA. *J Immunol* 1994;152:1442–52.
- 60 Conley ME, Cooper MD. Immature IgA B cells in IgA-deficient patients. *N Engl J Med* 1981;305:495–7.
- 61 Conley ME, Kearney JF, Lawton AR III, Cooper MD. Differentiation of human B cells expressing the IgA subclasses as demonstrated by monoclonal hybridoma antibodies. *J Immunol* 1980;125:2311–6.
- 62 Janzi M, Kull I, Sjoberg R *et al.* Selective IgA deficiency in early life: association to infections and allergic diseases during childhood. *Clin Immunol* 2009;133:78–85.
- 63 Jorgensen GH, Thorsteinsdottir I, Gudmundsson S, Hammarstrom L, Ludviksson BR. Familial aggregation of IgAD and autoimmunity. *Clin Immunol* 2009;131:233–9.
- 64 Koskinen S. Long-term follow-up of health in blood donors with primary selective IgA deficiency. *J Clin Immunol* 1996;16:165–70.
- 65 Liblau RS, Bach JF. Selective IgA deficiency and autoimmunity. *Int Arch Allergy Immunol* 1992;99:16–27.
- 66 Jorgensen GH, Arnlaugsson S, Theodors A, Ludviksson BR. Immunoglobulin A deficiency and oral health status: a case-control study. *J Clin Periodontol* 2010;37:1–8.
- 67 Jacob CM, Pastorino AC, Fahl K, Carneiro-Sampaio M, Monteiro RC. Autoimmunity in IgA deficiency: revisiting the role of IgA as a silent housekeeper. *J Clin Immunol* 2008;28 (Suppl. 1):S56–61.
- 68 Cassidy JT, Kitson RK, Selby CL. Selective IgA deficiency in children and adults with systemic lupus erythematosus. *Lupus* 2007;16:647–50.

- 69 Pan Q, Hammarstrom L. Molecular basis of IgG subclass deficiency. *Immunol Rev* 2000;178:99–110.
- 70 Herrod HG. Clinical significance of IgG subclasses. *Curr Opin Pediatr* 1993;5:696–9.
- 71 Lopes-da-Silva S, Rizzo LV. Autoimmunity in common variable immunodeficiency. *J Clin Immunol* 2008;28 (Suppl. 1):S46–55.
- 72 Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. *Br J Haematol* 2009;145:709–27.
- 73 Yong PF, Tarzi M, Chua I, Grimbacher B, Chee R. Common variable immunodeficiency: an update on etiology and management. *Immunol Allergy Clin North Am* 2008;28:367–86. ix–x.
- 74 Cunningham-Rundles C. Hematologic complications of primary immune deficiencies. *Blood Rev* 2002;16:61–4.
- 75 Samarkos M, Vaiopoulos G. The role of infections in the pathogenesis of autoimmune diseases. *Curr Drug Targets Inflamm Allergy* 2005;4:99–103.
- 76 Sullivan KE. The clinical, immunological, and molecular spectrum of chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. *Curr Opin Allergy Clin Immunol* 2004;4:505–12.
- 77 Steinsson K, Jonsdottir S, Arason GJ *et al.* A study of the association of HLA DR, DQ, and complement C4 alleles with systemic lupus erythematosus in Iceland. *Ann Rheum Dis* 1998;57:503–5.
- 78 Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. *J Clin Endocrinol Metab* 2006;91:1210–7.
- 79 Sullivan KE, Kim NA, Goldman D, Petri MA. C4A deficiency due to a 2 bp insertion is increased in patients with systemic lupus erythematosus. *J Rheumatol* 1999;26:2144–7.
- 80 Ochs HD, Stiehm ER, Winkelstein JA. Antibody deficiencies. In: Stiehm ER, Ochs HD, Winkelstein JA, eds. *Immunologic Disorders in Infants and Children*, 5th edn. Philadelphia: Elsevier Saunders, 2004:356–426, ISBN 0 7216 8964 7 .
- 81 Agarwal S, Cunningham-Rundles C. Autoimmunity in common variable immunodeficiency. *Curr Allergy Asthma Rep* 2009;9:347–52.
- 82 Quinti I, Soresina A, Spadaro G *et al.* Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol* 2007;27:308–16.