The goal of prediction of autoimmune diseases is prevention and/or early intervention to avert morbidity and mortality. In most diseases with an autoimmune pathology, a long prodrome is associated with the production of disease specific autoantibodies and may provide a window of opportunity to reverse the autoimmune process. However, large prospective studies are necessary to evaluate the risk of disease development in autoantibody positive persons. In type 1 diabetes, autoantibody assays make it possible to accurately identify people at risk of future disease. A similar development can be promised for rheumatoid arthritis. Therefore, both diseases may serve as models for prevention and novel treatment strategies. A prerequisite for prevention and curative therapy is the very early or even predictive diagnosis employing by biomarker analyses. The improvement, optimization and standardization of autoantibody determinations combined with evaluation studies play an important role in this process. This current volume will focus on different aspects of the pathogenesis, the prediction, novel treatment regimes and prevention of systemic and organ specific autoimmune diseases as well as autoimmune graft rejections. Rare autoimmunopathies such as autoimmune forms of thrombotic microangiopathies, nephropathies, myopathies and cardiomyopathies are also included.

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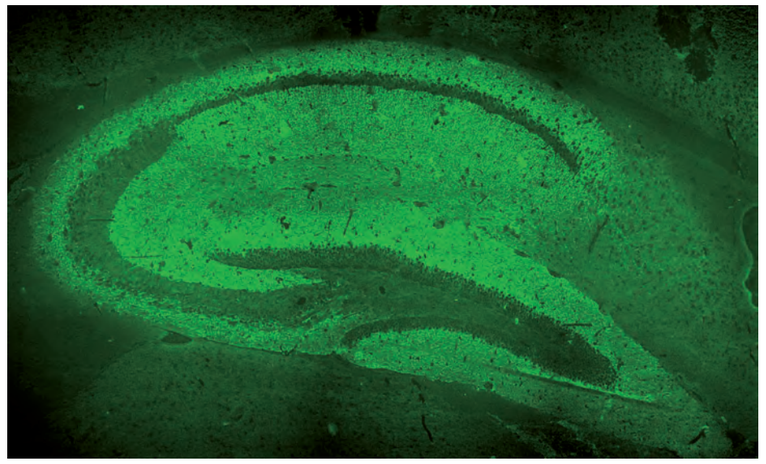

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Contents

1.1 Diabetes Mellitus Type 1

1.2 Rheumatoid Arthritis

1.3 Connective Tissue Diseases, Systemic Vasculitides and Antiphospholipid Syndrome

1.4 Neurological Diseases

1.5 Gastrointestinal and Liver Diseases

1.6 Autoimmune Heart Diseases

1.7 Autoimmune Thrombotic Microangiopathies

1.8 Autoimmune graft rejection

Chapter 2 Perspectives in the Treatment of Autoimmune Diseases

3.2 Role of Immunofluorescence in Autoantibody Detection

3.3 Novel Assays for Autoimmune Diagnostics

3.4 Multiplex Immunoassays – Autoantibody Profiling

Preface

The goal of prediction of autoimmune diseases is prevention and/or early intervention to avert morbidity and mortality. In most diseases with an autoimmune pathology, a long prodrome is associated with the production of disease specific autoantibodies and this may provide a window of opportunity to reverse the autoimmune process. However, large prospective studies are necessary to evaluate the risk of disease development in autoantibody positive persons. In type 1 diabetes, autoantibody assays make it possible to accurately identify people at risk of future disease. A similar development can be promised for rheumatoid arthritis. Therefore, both diseases may serve as models for prevention and novel treatment strategies. A prerequisite for prevention and curative therapy is the very early or even predictive diagnosis employing biomarker analyses as well as the better understanding of the etiopathogenesis of autoimmune diseases including the interplay between genetic and environmental factors in initiating and maintaining pathogenic autoimmune responses. This current volume will focus on different aspects of the pathogenesis, the prediction, novel treatment regimes and prevention of diabetes mellitus type 1, rheumatoid arthritis and other systemic rheumatic diseases, autoimmune neurological, gastrointestinal, and liver diseases as well as autoimmune graft rejections. Rare autoimmunopathies such as autoimmune forms of thrombotic microangiopathies, nephropathies, myopathies and cardiomyopathies are also included. Novel therapeutic concepts such as plasma cell targeting, peptide and aptamer based immunotherapy and new vaccination techniques will be presented.

In the future, autoantibodies may be used for a more accurate prediction of diseases development with the hope that early and effective intervention will be able to terminate ongoing pathologic processes. The major challenge for the improvement of predictive diagnosics is the optimization and standardization of autoantibody determinations combined with standardized evaluation studies as well as the search for novel clinical relevant autoantibody specificities. Ideally, cost effective multiparametric assays including novel autoantibodies will be developed. Therefore, the second focus of this volume deals with historical and perspective aspects of autoantibody determinations, the role of immunofluorescence in autoantibody detection, novel assays for autoimmune diagnostics and multiplex immunoassays.

Hopefully, the data and information described and discussed in this volume will stimulate novel concepts that will further the search for better prediction, prevention and treatment of autoimmune diseases.

The editors

From prediction to prevention of autoimmune diseases – Role of autoantibodies

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Abtract

More and more autoantibodies (AAb) have become important biomarkers for the diagnosis, differential diagnosis, prognosis and in some circumstances monitoring of autoimmune diseases. Furthermore, it has been shown that disease specific AAb may be detectable in preclinical stages. However, their potential role in the very early diagnosis or risk assessment of disease development has to be further evaluated. Hopefully, the more accurate prediction of diseases by AAb — perhaps in combination with other biomarkers — will lead to early and effective interventions that are able to terminate ongoing pathologic processes.

1 Introduction

Up to now more than 100 clinically distinct diseases have been identified in which autoimmune responses participate significantly as the initial cause or as a contributor (Table 1). With the exception of rheumatoid arthritis and autoimmune thyroid diseases most of these entities are rare or very rare but considered together autoimmune diseases (AID) affect approximately 5 percent of the population in industrialized countries (1). As major contributors to morbidity and mortality, the cumulative economic and social impact of AID approaches that of cardiovascular disease and cancer. The initiation and development of most AID are very complex processes. There are manifold pathogenic processes and disease accelerating factors that are thought to lead to the development and manifestations of an AID. Accordingly, we speak about autoimmune pathogenesis as a "mosaic" that involves definite genetic and environmental factors with individually different expression and effectiveness (2). Although the past decades of research on the immune system

have yielded a wealth of new information and extraordinary growth in conceptual understanding many of the factors involved in autoimmune pathogenesis have not been identified yet. Another problem regarding medical care and research is that AID often shows long preclinical phases, which can hardly be studied as clinical signs and symptoms are (still) absent. Interestingly, disease specific AAb can be detected prior to diagnosis and before symptoms draw an individual to medical attention. Thus, such AAb may serve as markers of early diagnosis or prediction of the development of a disease. If we identify factors and mechanisms involved in these early stages of disease development, strategies can be established to prevent disease manifestation or to alleviate or cure AID even before eventually identifying their original cause (3).

2 Autoimmune diseases – Definition and classification

Unfortunately, there is no generally valid and practicable definition to categorize a disease as autoimmune. The revised Witebsky-Rose criteria (4) are the most scientific one to classify autoimmune diseases (AID), but the spectrum of relevant criteria is hardly to identify in diseases assumed to be autoimmune in nature. A more practicable, but not perfect, definition was formulated by Feltcamp (5). According to his definition, an AID is "*a disease characterized by a significantly increased frequency of autoantibodies in significantly increased titres if compared to healthy local controls, matched for sex and age*." This is true for the majority of known AID, but also for some non-autoimmune diseases (e.g. tumors). Furthermore, T cell mediated AID with no (or not yet identified) specific AAb responses can not be classified as autoimmune by this definition. In conclusion, all diseases in which autoimmune mechanisms play a major role in disease development, should be regarded as AID compared to diseases with no or a secondary autoimmune response. However, a secondary autoimmune response may also be involved in the pathogenesis and therefore of diagnostic or predictive relevance. From the etiopathological point of view, AID are diseases in which adaptive immune responses play the predominant role whereas autoinflammatory diseases are characterized by self-directed inflammation that are independent of adaptive immunity. Because many noninfectious inflammatory diseases can not clearly defined as primary autoimmune or primary autoinflammatory, an autoinflammatory-autoimmune continuum has been postulated that offers an comprehensive classification of immunological disease and a better understanding of the pathogenesis and treatment of self-directed inflammation (6). In particular cases (e.g., Crohn's disease) it has to be clarified if autoimmune responses are only secondary to autoinflammation or are signs of a potential autoimmune disease subset. So far, more than 100 different diseases may be classified as classic AID or as probable AID within the autoinflammatory-autoimmune continuum (see Table 1).

Table 1. Autoimmune diseases and their characteristic autoantibodies. Autoantibodies shown in red have been demonstrated to be predictive or potentially predictive markers in retrospective and/or prospective studies (see (9–24)).

Autoimmune disease	Autoantibodies against
Blood diseases	
Aplastic anemia	moesin, kinectin, PMS1, DRS-1
Autoimmune hemolytic anemia (AIHA)	erythrocyte surface antigens
Autoimmune hemophilia	factor VIII, factor IX
Autoimmune lymphoproliferative syndrome (ALPS)	thrombocyte and neutrophil surface antigens (among others)
Autoimmune neutropenia	neutrophil surface antigens
Autoimmune thrombocytopenia (AITP, ITP)	thrombocyte surface antigens
Evans syndrome	thrombocyte, erythrocyte and neutrophil surface antigens
Heparin induced thrombocytopenia (HIT) type II	platelet factor 4/heparin complex
Pernicious anemia	H^+/K^+-ATPase, intrinsic factor
Endocrine diseases	
Autoimmune adrenalitis (Addison's disease)	21-hydroxylase
Autoimmune hyperparathyroidism	calcium sensitive receptor (CaSR) (stimulating AAb)
Autoimmune hypoparthyroidism	calcium sensitive receptor (CaSR) (inhibiting AAb)
Autoimmune hypophysitis	pituitary gland antigens
Autoimmune hyperthyroidism (Graves' disease)	TSH receptor

Autoimmune polyglandular syndromes type 1	P450scc, 17α- and 21-hydroxylase, enzymes of neurotransmitter synthesis (among others)
Autoimmune polyglandular syndromes type 2	21-hydroxylase, TSH receptor, thyreoperoxidase, GAD (among others)
Autoimmune thyreoiditis (Hashimoto's thyreoiditis)	thyreoperoxidase (TPO), thyroglobulin (Tg)
Diabetes insipidus centralis	vasopressin producing cell antigens
Diabetes mellitus type 1	GAD, IA2, Insulin, ZnT8
Diabetes mellitus type 3G	insulin receptor
Insulin autoimmune syndrome (IAS)	insulin
Insulin resistance type B	insulin receptor
IPEX syndrome	enterocyte antigens (among others)
Ovarian insufficiency	P450scc, 17α-hydroxylase, pituitary gland antigens
Ear diseases	
Autoimmune inner ear diseases	heat shock protein 70
Eye diseases	
Autoimmune uveitis	
Autoimmune retinopathy, incl. paraneoplastic forms (CAR, MAR)	retinal antigens (e.g. recoverin, carbonic anhydrase II)
Sympathetic ophthalmia	

Gastrointestinal diseases	
Autoimmune enteropathy	enterocyte and goblet cell antigens
Autoimmune gastritis	H^+/K^+-ATPase, intrinsic factor
Celiac disease	tTG
Crohn's disease	ASCA, pancreatic acinus cells/GP2
Ulcerative colitis	ANCA, goblet cell antigens
Heart diseases	
Chagas cardiomyopathy	beta 1 adrenergic and/or muscarinergic type 2 acetylcholine receptor
Congenital heart block	Ro/SS-A, La/SS-B
Dilated cardiomyopathy	beta 1 adrenergic and/or muscarinergic type 2 acetylcholine receptor
Kidney diseases	
Goodpasture syndrome/anti-GBM nephritis	collagen type IV (NC1 domain) of GBM
IgA nephropathy (Berger disease)	aberrantly glycosylated IgA1
Membranous glomerulonephritis (MN)	phospholipase A2 receptor
Membranoproliferative glomerulonephritis (MPGN)	complement factors C1q, B and H, C3 convertase C3bBb (C3NeF)
Pauci-immune glomerulonephritis	myeloperoxidase, proteinase 3, LAMP-2

Liver diseases	
Autoimmune hepatitis	cytochrome P450 2D6 (LKM1), formiminotransferase cyclodeaminase (LC1), F-actin, UGA-suppressor serine tRNA associated protein (SLA/LP), nuclear antigens, ASGPR
Primary biliary cirrhosis	PDH-E2 (AMA-M2), sp100, gp210
Primary sclerosis cholangitis	neutrophil antigen(s)
Neurological diseases	
Autoimmune autonomic gangliopathies (AAG)	ganglionic nAChR
Autoimmune encephalitides (more than 5 different forms, e.g., paraneoplastic limbic encephalitis, Anti-NMDA receptor encephalitis)	glutamate (NMDA, AMPA) receptors, onconeuronal antigens, Lgi1
Autoimmune (poly)neuropathies (more than 10 different entities, e.g., Guillain-Barré syndrome, multi-focal motor neuropathy)	gangliosides (e.g., GM1, GQ1b), sulfatides
Cerebral folate deficiency syndrome (CFDS)	folate receptor
Multiple sclerosis	(myelin oligodendrocyte glycoprotein)
Narcolepsy	Tribbles homolog 2 protein (Trib2)
Neuromyelitis optica (NMO)	aquaporin 4
Paraneoplastic neurological syndromes (e.g. cerebellar degeneration)	onconeuronal antigens

Neuromuscular diseases	
Arthrogryposis multiplex congenital (AMC)	γ subunit of fetal nAChR
Lambert-Eaton myasthenic syndrome (LEMS)	P/Q type voltage-gated calcium channels
Myasthenia gravis (MG)	α1 subunit of nAChR, MuSK, titin, ryanodine
Morvan's syndrome	Caspr2, Lgi1
Neuromyotonia (Isaac's syndrome)	Caspr2
Stiff person syndrome	GAD
Skin diseases	
Alopecia areata	hair-follicle specific proteins
Autoimmune blistering diseases (more than 10 different entities, e.g., dermatitis herpetiformis, pemphigus vulgaris)	tTG, desmosomal (e.g. desmoglein 1 and 3) and hemidesmosomal antigens, collagen VII
Acquired angioedema type II	C1 inhibitor
Autoimmune urticaria	Fcε receptor of type I (FcεRI)
Hypocomplementemic urticaria-vasculitis syndrome (HUVS)	C1q
Vitiligo	melanocyte specific tyrosinase, melanin metabolism influencing antigens

Systemic AID	
Rheumatoid arthritis	RF, ACPA, RA33
Connective tissue diseases	
Systemic lupus erythematosus	dsDNA, Sm, U1-RNP, ribosomal P-protein, Ro/SS-A, La/SS-B
Systemic sclerosis	CENP-A,-B, Scl70
Sjögren's syndrome	Ro/SS-A, La/SS-B
Mixed connective tissue syndrome	U1-RNP
Autoimmune myositides	tRNA synthetases, Mi-2, signal recognition particle
Overlap syndromes	exosomal antigens, Ku
Antiphospholipid syndrome	phospholipids (PL) and PL associated proteins
ANCA associated vasculitides (AAV)	proteinase 3 (PR3), myeloperoxidase (MPO)
IgG4-associated sclerosing disease	carboanhydrase II
Thrombotic microangiopathies	
Hemolytic uremic syndrome (HUS)	complement factor H, B
Thrombotic thrombocytopenic purpura (TTP)	ADAMTS13

3 Autoantibodies in the prediction of disease development

Autoantibodies with high disease specificity are important markers for the differential diagnosis of autoimmune diseases (AID) and they are often a key element in the classification or diagnostic criteria for these diseases (reviewed in (7, 8)). In many cases, an AID can be virtually ruled out if the AAb or a combination of certain AAb are negative. For example, only rare or unusual cases of systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD) have a negative AAb test and the vast majority of type 1 diabetes mellitus (T1DM) have AAb directed against islet cells, glutamic acid decarboxylase, insulin, IA2 and/or ZnT8. The diagnosis can be often confirmed by detection of AAb if there are typical clinical symptoms, even if the classification or diagnostic criteria of the disease are not completely fulfilled (9). As early adequate therapy is necessary for optimal control of disease progression, the diagnosis should be secured at the earliest possible phase of the disease. For this, the determination of AAb that have high disease specificity and high predictive value becomes more and more important.

Both retrospective and prospective studies have clearly shown that disease specific AAb can be detected months to several years before clinical manifestations of the corresponding disease (reviewed in (10–20)). One of the challenges for retrospective studies is that sera from patients are ideally required before the onset of clinical manifestations. Thus, with the exception of anecdotes and case studies, retrospective cohort studies are difficult and seldom done. Extensive studies have been performed regarding AAb in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and chronic inflammatory bowel diseases (9, 21–24). In these studies, the investigators had access to serum banks that were created for other purposes. The aim of retrospective studies is to show how often and how long the disease specific AAb are detectable before clinical manifestations. On the other hand, the aim of prospective studies consists of determining the risk that AAb-positive individuals will have in developing the corresponding disease. Prospective studies are — with the exception on studies of type 1 diabetes development — mainly done with cohorts of individuals that have an increased risk to develop an AID. Middle to high titred disease specific AAb in persons of tested cohorts may indicate an underlying autoimmune pathological process. Indeed, a high predictive value regarding disease development has been shown in prospective studies for islet cell, insulin, GAD and IA2 antibodies (diabetes mellitus type 1), adrenal cortex/21-hydroxylase antibodies antibodies (Addison's disease), thyreoperoxidase antibodies (Hashimoto thyreoiditis), type 2 antimitochondrial antibodies (primary biliary cirrhosis), tissue transglutaminase antibodies (celiac disease), rheumatoid factors (RF) and CCP antibodies (rheumatoid arthritis) as well as for Ro/SS-A and La/SS-B antibodies (autoimmune rheumatic diseases) (reviewed in (19)). However, the potential role of AAb in the very early diagnosis or risk assessment of disease development has to be further evaluated as a major prerequisite for prevention studies.

It is important to mention, that AAb may not only indicate the probable development of an appropriate AID (see Table 1) but also the course of the disease and therefore may influence disease management. Furthermore, heterogeneous conditions such as the spectrum of autoimmune myositides can be differentiated in distinct clinicoserological phenotypes that may help to predict complications of disease, prognosis, and responses to treatment (25).

4 Prevention of autoimmune diseases

To prevent the development of AID, the following prerequisites have to be fulfilled: (i) A high relevance of AAb (perhaps in combination with other biomarkers) for risk assessment of disease development has to be demonstrated by large prospective studies. For example, highly credible studies indicate that the risk for the development of type 1 diabetes in children and adults can be predicted with a high sensitivity and specificity by the determination of diabetes specific AAb (26–28). (ii) Knowledge of factors critically involved in pathogenic or repair processes. The elimination of environmental risk factors such as smoking or the application of potential protective factors such as vitamin D may help to prevent disease development in AAb positive persons, for instance to prevent manifestation of rheumatoid arthritis in RF or CCP antibody positive persons (29, 39). (iii) Knowledge of major pathomechanisms leading to disease manifestation to find optimal strategies to influence these mechanisms. The genetic predisposition, which determines the possible immune reactivities and regulatory mechanisms, is an important but not a sufficient component of autoimmune pathogenesis. Exogenic factors (e.g. viral or bacterial infections, xenobiotics, ultraviolet light) are necessary for the initiation and expression of the autoimmune condition as well as the chronicity and progression of the immunopathogenesis. The knowledge of the specific interplay between genetic and environmental factors will show possibilities for preventive interventions.

The development of an AID may be divided into different stages (Figure 1): I. The induction phase is characterized by the generation of disease specific autoimmune phenomena (autoreactive T cells and/or AAb). II. In the preclinical phase the autoimmune phenomena exert pathogenetic effects that are influenced by various triggering or accelerating as well as regulating factors (e.g., regulatory T cells). III. The progressive effectiveness of autoimmune mechanisms leads in the clinical phase to corresponding symptoms as well as to diagnostic relevant paraclinical alterations. For example, the clinical manifestation of type 1 diabetes only occurs after 80–90 % of the insulin producing β cells of the pancreas being immunologically destroyed. The course of disease development may be influenced at different stages by influencing triggering and effector as well as regulating mechanisms of the particular immunopathogenesis. The better the knowledge of these

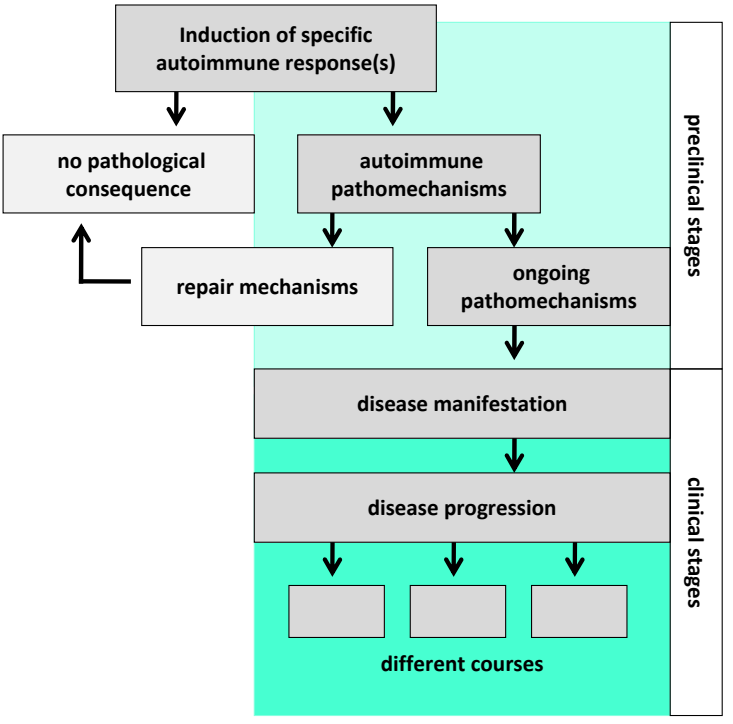

Figure 1. Simplified scheme of the stages of the development of autoimmune diseases (AID). The development of a classic AID starts with the induction of a more or less disease specific autoimmune response. Depending on additional factors, autoimmune mechanisms lead to chronic inflammation of the appropriate tissue (e.g., pancreatic islet cells in type 1 diabetes, adrenal cortex cells in Addison's disease) or to chronic interference with biological structures (e.g., stimulation or blocking of receptors or regulatory proteins). If regulatory processes and/or repair mechanisms are effective, the pathomechanism may be stopped and no disease develops. Otherwise the process is ongoing up to the clinical manifestation of the disease (e.g. type 1 diabetes becomes manifest, if 80–90 % of the insulin producing cells are destroyed). The course of disease development may be influenced at different stages by endogeneous and environmental factors that act as trigger, effector or regulator of the particular immunopathogenesis. Because disease specific autoantibodies (AAb) are detectable not only in AAb mediated but also in most T cell mediated AID (e.g., type 1 diabetes) at early stages, they are good indicators for disease development and their positivity may serve as a criterion for predictive intervention studies. Furthermore, clinically heterogeneous AID (e.g., systemic sclerosis, autoimmune myositis) can be differentiated in distinct clinicoserological phenotypes that may help to predict complications of disease, prognosis, and responses to treatment.

mechanisms and the earlier the intervention the better should be the possibility to prevent disease manifestation.

5 Perspectives

As already mentioned, a key characteristic of many AID is the presymptomatic production of disease specific autoantibodies. Therefore, the presence of disease specific AAb may indicate preclinical autoimmune mechanisms. Because the risk of disease development depends on further factors, AAb determinations alone may not be sufficient enough for risk assessment of most AID. Persons may be AAb positive without development of the appropriate disease. Therefore, the search for better prediction of disease development is a major challenge to establish predictive intervention studies. Besides AAb characteristics (epitope spreading, isotype, titer, affinity, AAb profiles) the combination of different biomarkers may be helpful. On the other hand, studies on involved genetic (31, 32), hormonal (33) and environmental factors (34, 35) as well as on pathological autoimmune processes may offer new intervention strategies at early stage of disease development (3, 36). Hopefully, the better understanding of autoimmune pathogenesis of certain AID along with novel options for early intervention may help to prevent disease development in risk persons positive for disease specific AAb.

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Abbreviations

ACPA, anticitrullinated protein antibody; **ADAMTS13**, a disintegrin and metalloprotease with thrombospondin-1 like domains 13; **AMA-M2**, antimitochondrial antibody type 2; **AMPA**, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; **ANCA**, anti-neutrophil cytoplasmic antibodies; **ASCA**, anti-Saccharomyces cerevisiae antibodies; **ASGPR**, asialoglycoprotein receptor; **C3NeF**, C3 nephritis factor; **CAR**, cancer associated retinopathy; **Caspr2**, contactin-associated protein-like 2; **CCP**, cyclic citrullinated peptide; **GAD**, glutamic acid decarboxylase; **DRS-1**, diazepam-binding inhibitor related protein-1; **GBM**, glomerular basement membrane; **GP2**, glucoprotein 2; **ITP**, idiopathic thrombocytopenic purpura; **IPEX**, immune dysregulation, polyendocrinopathy and enteropathy, X chromosome inherited syndrome; **LAMP-2**, lysosomal-associated membrane protein 2; **LC1**, liver cytosolic 1; **Lgi1**, leucine-rich glioma inactivated 1; **LKM1**, liver-kidney microsomal; **MAR**, melanoma associated retinopathy; **MuSK**, muscle-specific receptor tyrosine kinase; **nAChR**, nicotinergic acetylcholine receptor; **NMDA**, N-methyl-D-aspartate; **P450ssc**, cytochrome P450 side chain cleavage enzyme; **PDH-E2**, Pyruvate dehydrogenase, subunit E2; **PMS1**, post-meiotic segregation increased 1; **RNP**, ribonucleoprotein; **SLA/LP**, soluble liver antigen/liver-pancreas antigen; **TSH**, thyroid stimulating hormone; **tTG**, tissue transglutaminase.