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Preclinical and Predictive Algorithms in Monitoring Patients with Autoimmune Diseases and Their Relatives-at-Risks

Sergey Suchkov[1,2], Dmitry Kostyushev[1], Dmitry Gnatenko[1],
Sevindzh Gadzhieva[1] and Mikhail Paltsev[3]
[1]I.M. Sechenov First Moscow State Medical University
[2]Moscow State Medical Dentistry University, National
[3]Research Center "Kurchatov Institute"
Russia

1. Introduction

Millions of people all round the world suffer from various autoimmune disorders. T1D, MS, SLE, autoimmune diseases of the heart, liver, intestine and other internal organs, etc., all represent severe manifestations, which deteriorate the quality of life and cause physical disability and even death in patients with chronic illnesses. Every year, the largest world economies incur megabuck losses associated with medical services, insurance and drug procurement, not to mention the ever decreasing size of the able-bodied population. The development of preclinical diagnostic algorithms for autoimmune diseases, their implementation and introduction into routine clinical practice will help detect tissue or organ pathologies at the stages where their reversal is still possible. Early implementation of causal therapy allows the physician to compensate for the lack of one or another organ and ensures complete recovery or significant improvement of the patient's health status. However, in developing updated preventive protocols, the investigator is faced with a necessity to solve fundamental problems in order to understand:

- Who should be selected for examination?
- What exactly needs to be checked?
- When should the examination be performed?
- And, last but not least, what are the analytical procedures for mass-scale monitoring?

While constructing preclinical monitoring algorithms, one should also take into consideration the diseases suffered by patients' relatives. One of the cornerstones in preventive and predictive medicine is screening for genetic abnormalities or hereditary predisposition. All-encompassing analysis of gene units and construction of individual genetic maps not only facilitate the assessment of individual risks for each concrete patient, but also allows prediction of disease development in first-degree-relatives. Therefore, today's objective demands include not only large-scale monitoring of definite cohorts of the general population, but, rather, identification of high risk cohorts coupled with genetic abnormalities and/or shifts and social factors (residence, place of employment, occupation, living conditions, etc.). However, even a comprehensive analysis is inadequate without a set

of criteria providing high accuracy and reliability of state-of-health data. By illustration, it has long been believed that the same gene loci are specific for definite diseases including integer disease-related clusters. T1D, celiac disease, rheumatoid arthritis, multiple sclerosis, etc., they exist in close linkage with one another and often form polyglandular syndromes. Being a positively provisional discipline, genetics provides a fairly accurate prognosis for an individual; however, genetic tributes cannot always be adequately understood by reason of their ability to provoke extremely severe diseases. It should be taken into consideration that deleterious environmental (exogenous or endogenous) factors may strongly destabilize the physiological status of the organism by triggering pathological processes even in the presence of protective genes, and *vice versa*.

Therefore, screening of patients for the presence and evolution of biomarkers should be included into all preventive medicine protocols alongside with the patient's individual genetic map.

Even an unambiguous allocation of patients into risk groups, selection of basic state-of-art (additional, individual, etc.) screening criteria and personalized approaches to every new patient will hardly be successful without selection of optimal conditions and methods for obtaining reliable and reproducible clinical data on a mass scale.

The practical realization of these principles will enable the physician to diagnose abnormalities and/or disorders at the very earliest stages and to predict their outcome. However, suspension or blockade of pathological processes presents a formidable challenge to the medical community. In designing therapeutic strategies for autoimmune diseases, two important issues, namely, targets for autoimmune attacks and depth of morphofunctional deficiency of an organ or a tissue, should be taken into consideration. The first issue is more or less clear, since immunosuppressors with specific or nonspecific activities have long been used in the clinical practice, while the second one is not so apparent. Restoration of the structure and function of affected tissues can successfully be achieved through practical realization of the following strategies:

- allogeneic or xenogeneic transplantation. The main challenges include high risk of so-called "graft-versus-host" responses and rejection of transplanted tissues (graft rejection);
- medical products with regenerative resources. This technology seems to hold especially great promise in modern medicine. Some medicinal drugs (e.g., IgM for MS) are widely employed in the clinical practice, while others (e.g., peptide-based drugs for MS, rheumatoid arthritis, T1D) are under intensive development. The main obstacles on the way to large-scale application of such drugs are low efficiency, particularly due to organism's addiction to their active substances (reduced number of receptors, downregulation, etc.), and hyperactivation of the excretory system (augmented synthesis of liver microsomal enzymes, hyperexcretion with urine, faeces or sweat, etc.);
- stem cell technology. This trend is especially actively debated by the medical community because of its high relevance to ethic problems and legal prohibitions, on the one hand, and inability to maintain "stemness" for sufficiently long periods of time and differentiation of stem cells into "undesirable" pools, on the other. Similar problems arise at virtually every stage, viz.: search for and isolation of stem cells from the organism; enhanced accumulation of biological material, which may be critical under conditions of fulminant progression of the disease and pronounced deficit of time; necessity to maintain the pluripotent state of cells for sufficiently long periods of time without malignization *in vitro*; delivery of SC; provisional differentiation and

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acquisition of high-quality material *in vitro* and control over differentiation into desired cellular pools *in vivo*.

Taking into consideration the foregoing and being guided by the Major Preventive and Preventive Medicine Principle, we developed an original protocol for screening and postscreening management of patients, which includes:

Comprehensive genetic analysis for estimating potential risks for patient's (or his/her relatives') individuality and design of protocols for diagnostic assessment and preventive treatment;

Proteomic analysis and detection of metabolic shifts including identification of biomarkers (e.g., autoAbs in case of autoimmune disorders); monitoring of evolutional and spectral characteristics of biomarkers; control over emergence of new biomarkers for updating prophylactic and preventive treatment protocols and maintenance of high curability standards;

Persistent control over predisposing factors including identification of factors potentiating specific pathologies (analysis of bacterial and virus-borne infections, monitoring compliance with regimen and other preventive measures, etc.);

Psychologic doctor-patient cooperation, strict compliance with doctor's recommendations and requirements through elucidation of disease severity (including the preclinical stage).

The use of advanced screening strategies and early implementation of specific therapy ensure substantial reduction of morbidity and mortality from autoimmune disorders and, as a consequence, significant improvement of life quality and minimization of economic losses. The same principles are embodied in the guidelines of preventive and predictive medicine. Their practical realization may culminate in the establishment of an international research network, development of novel criteria for preclinical diagnosis and treatment and validation of uniform specifications and standards for laboratory diagnostics.

2. The preclinical diagnosis algorithm and a new conceptual model of T1D etiology

T1D is an autoimmune disease induced by a vast variety of triggering factors. In individuals with genetic predisposition to T1D, these factors initiate autoimmune processes culminating in the appearance of autoAbs and infiltration of the pancreas with self-reactive T cells. In its turn, progressive deterioration of pancreatic functional activity leads to systemic metabolic and immune failures. These processes show a tendency for self-acceleration, aggravation by associated diseases or numerous adverse factors and formation of new linkages between immunoregulatory and immunoeffector compartments within the immune system. T1D is also distinguished for alterations at the cellular level including pathological changes in cell to-cell interactions, incompatibility of packages of secreted humoral factors, and so on. Intracellular events provoked by specific uncongenial conditions in the cell environment also play a role. Therefore, humoral factors secreted at any (cellular, tissue or organic) level and pathological changes in any link of the metabolic cascade can be regarded as highly specific *biopredictors* and valuable tools for *preclinical diagnosis* of T1D.

In the course of the autoimmune process, T1D goes through a number of sequential stages, which differ from one another by the degree of severity of the underlying pathology, functional peculiarities of affected organs and clinical manifestations of the disease. A *personalized* therapeutic approach must be based on a detailed analysis of the immune status with special reference to the patient's genetic map and is prerequisite to the construction of

any early diagnosis protocol designed to indicate the pathology, to identify the stage of the autoimmune process and the functional status of the target organ and to develop, on their basis, a strictly individual treatment schedule. In addition, this approach entails early implementation of pharmacocorrective therapy and prediction of scenarios for disease progression. (Suchkov et al., 2010)

In order to follow the dynamics of T1D on the time scale and to estimate efficiency and sensitivity of innovative approaches to *preclinical diagnosis,* we developed a fundamentally new strategy of pathogenesis. Its major goal is crucial features of the disease with special emphasis on its diagnosis allowing the physician to implement adequate *preventive therapy*, to prolong the *preclinical* stage and to delay clinical manifestations of the disease.

Stage I is often defined as the "*genetic predisposition*" step. Its most salient feature is a repertoire of predisposition genes (predominantly, MHC class II) responsible for susceptibility to autoimmune diseases and direct initiation, gradation and exacerbation of immune pathologies.

Stage II is often referred to as the "intervention" step. At this stage, provoking exogenous or endogenous factors interfere with the normal functioning of immune mechanisms and deplete the functional reserves of the affected organs providing the formation of the autoimmune status (e.g., postinfective autoimmune syndrome).

Stage III represents an "ignoring" step where progressive disturbances in immune homeostasis are unaccompanied by direct attacks at target organs. Clinical manifestations of T1D and visible lesions in the pancreas architectonics are absent in this step, while the functional activity of the pancreatic gland is unimpaired. AutoAbs are either not produced or their titers are negligibly small.

Stage IV is characterized by termination of the ignoring step and initiation of autoimmune processes. The main participants at this stage are molecular factors (e.g., addressins) triggering autoimmune reactions specifically directed against islet cells. At this particular level, clonal ignoring collapses and organ infiltration occur.

Stage V is closely associated with the development of immunological disorders. Its central event is generation of autoAbs to insulin, GAD, β-cells, heat shock protein 60 (hsp60), zinc transporter and fogrin. AutoAbs can be specific against a single antigen (Ag) or several Ags.

Stage VI is defined as a "transition from uncontrolled violence to chaos". Here, minor systemic failures related to immunological disregulation progress to the extent of profound disorders. Clinical symptoms are still missing at this stage, but latent tolerance to glucose develops.

Stage VII. This "complete overall imbalance" step occurs when β-cell destruction reaches a certain critical level (80%). This stage is characterized by hyperglucosemia and insufficient production of insulin. Metabolic processes fluctuate slightly within normal limits due to residual secretion of the C-peptide.

Stage VIII, often referred to not as a T1D stage, but, rather, as emerging complications, is defined as "total or genuine diabetes", since beta cell destruction is fully complete in this step. It is distinguished for steadily decreasing titers or complete disappearance of autoAbs, functional failure of the pancreas, high glucosemia and glycosylation of proteins (including hemoglobin) against the background of systemic hypoxia and metabolic collapse. Other manifestations include disturbances in water-salt metabolism, osmotic diuresis, dehydration, activation and acceleration of gluconeogenesis and ketogenesis, enhanced breakdown of proteins and lipids, impaired lipid metabolism (low HDL levels and high LDL levels) and elevation of osmotic blood pressure resulting in microvascular and nerve

tissue injuries. These disturbances are usually concomitant with acute manifestations (coma) or form the basis for more distant pathologies (micro- and macroangiopathies, neuropathies, ophthalmopathies, nephropathies, etc.).
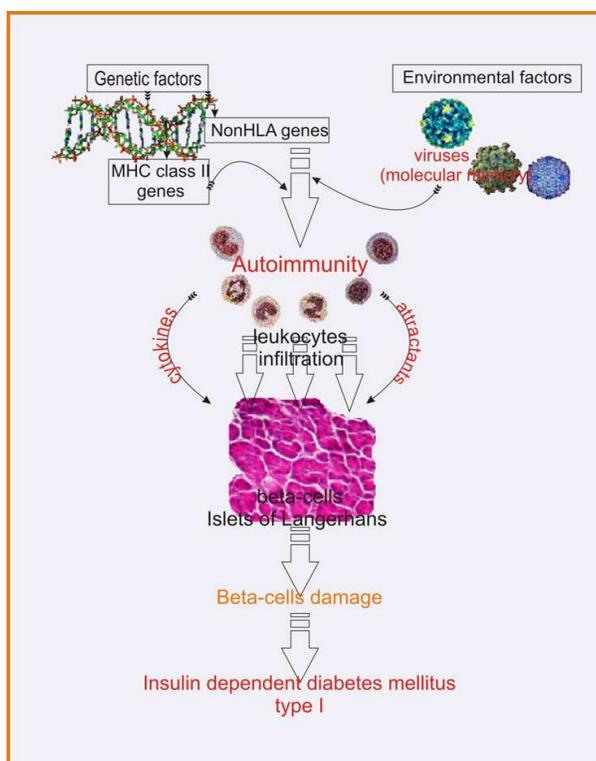

Fig. 1. The pathogenesis of T1D. Genetic and environmental factors are key elements in the susceptibility to **T1D**. Susceptible individuals develop autoimmune insulitis, which is mediated by CTL against autoAgs of *beta* cells and is characterized by enhanced production of a vast array of antiinflammatory cytokins and free radicals triggering the death (apoptosis) of *beta* cells as main targets in inflammation.

The first five stages are defined as preclinical pathology stages, while Stage VI is thought to represent a transient step. It is diagnosing T1D at stages I – V and the use of preventive treatment protocols that enable the physician to delay the progression of the underlying disease and to procure complete recovery. (Antonio Gonzalez at. al., 1996s; Matthias von Herrath at al., 2007)

3. The origin of genetic predisposition or "genomics: A base of preclinical medicine"

Our knowledge of pathological processes occurring in the human organism has progressed considerably in the past decades, but the mechanisms of many human diseases are still poorly understood. Recent developments in genomics made it possible to discover a wide variety of novel genes and genetic variations including clinically important ones. i.e., those triggering pathological processes in various body tissues and cells. Every year, the clinical diagnostic instrumentarium is supplemented with efficient analytical techniques for detecting single-nucleotide polymorphisms (SNP's) which determine the susceptibility of

the organism to diseases, drugs and/or environmental factors. A deeper insight into gene structure and regulatory mechanisms can significantly facilitate diagnosis and treatment of individuals at risk and, in a more distant future, provide the physician with potent tools for diagnosing diseases, preventing their progression and implementing effective therapy as early as the preclinical stage.

Rapid progress in science and technology created necessary prerequisites for high-throughput screening of several hundreds of thousands of SNP variants and enabled adequate involvement of all human DNA blocks in selection of the disease associated variant provided the latter is present in the genome. From theoretical standpoint, linking of genotyping data to epidemiological findings provides a way to identification and/or characterization of gene sequences and gene interactions with the environment determining the susceptibility of various body cells and tissues to normal genetic variations and/or the underlying disease.

Genomewide association studies represent an effective tool for detecting genetic associations between specific genetic variations and complex pathological conditions in large cohorts of the general population and provides a deeper insight into mechanisms underlying genetic predisposition to various diseases.

The contribution of SNP's to the pathogenesis of many common diseases is relatively small and does not exceed 5–10%, which significantly restricts their application as markers for predicting disease risks. However, today well-established associations number in hundreds and their panel grows with every passing week. Taking into account considerable investments in the search for hitherto unidentified sources of inherited risks, it may be expected that existing (both genomic and nongenomic) models for estimating potential risks will soon be improved and rationalized.

The current need for highly multiplexed tests increases with every passing day. Innovative gene chip- and sequencing-based technologies displace rapidly traditional methods for establishing variations and mutations in the human genome. In future, the advent of improved nanotechnological sequencing protocols may further increase the accuracy and reduce the cost of genetic analysis. The idea of complete sequencing of the human genome at the cost of $1000 is becoming more and more realistic. The project, which got the name "$1000 genome", is expected to improve existing protocols through direct sequencing of individual DNA molecules. This approach is potentially oriented at elimination of the amplification step, further reduction of chemical reagents expenditure and construction of a high-precision database of genetic sequences in the foreseeable future.

The feasibility of reliable and low-cost estimation of human genetic variations put forward the idea of personalized medicine as an indispensable element of modern-day public health care. The key principle of personalized medicine is in that the health status of any human individual is most effectively controlled through implementation of individual preventive and curative treatment schedules. Although unsolvable controversies between principles of personalized medicine and populational (probative) medicine really exist, they are not inconsistent. Novel decisions are being taken in the private and public sectors, and those would enable progressive studies to provide the linkage between personalized and probative medicine.

All-round cognition of gene structure and genetic regulatory mechanisms is extremely important not only from theoretical, but also from practical point of view, particularly, for

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the development of state-of-art diagnostic, prognostic, preventive and therapeutic strategies for treatment of rarely occurring and common diseases.

3.1 IDDM1 as an example of crucial role of genomics in clinical researches

The use of high-throughput technologies in human genome studies was a step forward towards getting a deeper insight into pathogenetic mechanisms of many human diseases including insulin-dependent type 1 diabetes mellitus (T1D). Recent developments in the field of genetic factors and their pathogenetic roles suggest their high utility in the design of novel predictive strategies, stratification of patients according to disease risk and a search for new therapeutic targets. Among the immense variety of T1D strategies, two approaches are used methods of choice, viz.: (I) linkage studies of pairs of affected relatives (typically, siblings) aimed at a search for rarely occurring risk factors having large effective sizes; (II) association studies into more common risk factors having small effective sizes.

3.2 MHC: Genes of instability

As can be seen, identical genes can simultaneously trigger a variety of body-related autoimmune disorders. The latter form a disease-based cluster, which further develops into a polyglandular autoimmune syndrome. (Fernando MM et al., 2008)
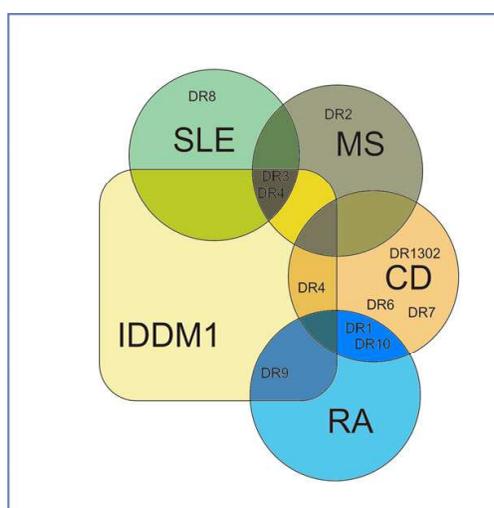

Fig. 2. The role of MHC genes in the development of diseases the key pathogenetic role in which is played by genetic predisposition. Some genes (DR7, DR8) determine the risk for only one disease (DR7, DR8), while others are responsible for two (DR1, DR10), three or even more (DR4) diseases. However, their presence is not prerequisite to the development of pathological processes, but, rather, significantly increases the likelihood of their early occurrence during the patient's lifetime.

MHC represents a large family of genes encoding molecules of three major HLA classes, viz., HLA class I, HLA class II and HLA class III. MHC plays an essential role in the functional activity of the immune system being directly involved in presentation of peptide antigens to APCs and formation of the so-called MHC restriction phenomenon. To-date, MHC is the most thoroughly investigated gene family in the human genome by virtue of its extremely close linkage to autoimmune diseases, hypersensitivity to infections and hyperbolic immune responsiveness. These genes are usually present in patients with severe autoimmune disorders and/or imbalances, e.g., rheumatoid arthritis (RA), multiple sclerosis

(MS), Crohn's disease, aneurisms of large vessels (ALV), ulcerative colitis (UC), systemic lupus erythematosus (SLE) and type 1 diabetes (T1D).
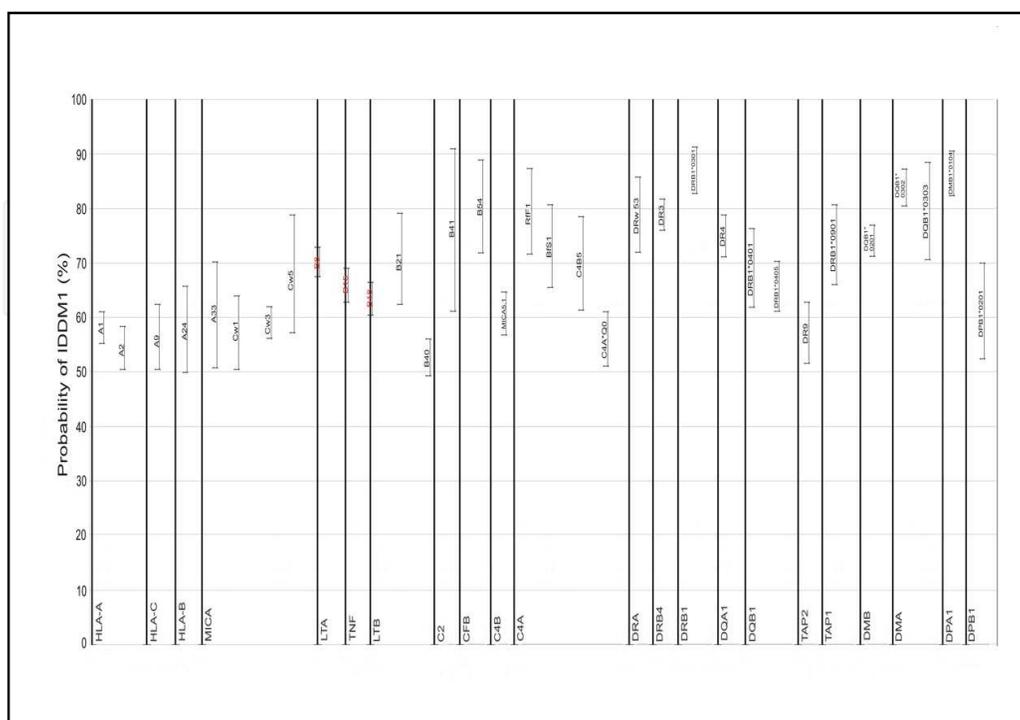
Fig. 3. The role of various MHC classes I, II and III alleles in the development of T1D. The x axis designates the continuous arrangement of some MHC 123 regions. The vertical graph segment indicates the association of an allele with a specific MHC region and the typical scatter of diabetogenicity probabilities for the given allele.

3.3 HLA class I: Role in T1D

Molecules of HLA class 1, jointly with HLA class II molecules and in closest association with one another afford effective protection against T1D and risks thereof. The HLA class I compartment contains both diabetoprotective genotypes (A*1101, A*3201, A*6601, B*0702, B*4403, B*3502, C*1601, C*0401) and highly associative genes (B*5701, B*3906). The diabetogenic alleles of MHC class I genes display age-related features. For example, HLA-E*0101 is predominant in patients in whom T1D developed during the first 10 years of life, while HLA-E*0103 is found in children under 10. (Hodgkinson AD et al. 2000) Apart from borderline (diabetogenic or diabetoprotective) genes, there exist several intermediate types (A*2402, A*0201, B*1801, C*0501). All of them increase the risk of diabetes, but their role in triggering autoimmune responses is insignificant. (Noble JA et al., 2010)

The increasing number of publications devoted to genes associated with T1D (Howson JM et al., 2009; Viken MK et al., 2009) and identification of reactions stimulating or potentiating beta cell destruction testify to the fact that HLA class I initiate and potentiate autoimmune destruction of beta cells and manifest close linkage to HLA class II. (Lipponen K et al., 2010) Systemic autotolerance of homogeneic CD8(+) T cells is one of the patterns subject to regulatory control of HLA class I. It is well known that T1D is concomitant with disturbances in coordinated interactions between HLA-E CD8(+) T cells and HSP60sp that are specific to them. This phenomenon is responsible for disturbances in so-called "friend or foe" identification during a switchover of normal immune processes to self-destruction. (Jiang H et al. 2010)

Some methods for early diagnosis of T1D e.g., *ex vivo* detection of GAD65 autoreactive T cell CD8(+) by HLA class I tetramers, are based on the use of HLA class 1 I antigens. (Giuliani L et al. 2009)

3.4 HLA class II: A wheelhorse or a time bomb?

HLA class II constitute a family of genes localized on the short arm of the 6th chromosome. These genes encode glycoproteins with an Ig-like structure and are predominantly localized on the APCs surface. Their functional role consists in presentation of Ags peptides to CD4(+) T helper cells type I. There exist several autoimmune diseases (including T1D) supported by promoting effects of HLA class II Ags.

Presumably, MHC glycoproteins modify positive and negative selection in the thymus allowing some immature autoAg-reactive T cells to escape from immune surveillance and thus avoid negative selection. However, presentation of morbid peptides to cytotoxic T lymphocytes (CTLs) or T helper cells by mature MHC seems to be more likely. Polymorphic variants (cytokin-related genes) residing in the vicinity of MHC classes I, II and III and non-MHC significantly increase the predisposition to autoimmune diseases and impart high (in comparison with healthy individuals) genomic instability. When the cells switch over their modality from Ag expression to MHC class II production, the molecules localized on the cell surface begin to form potentially autoreactive complexes and thus provoke self-reactive immune responses. Such nondiscriminating Ags were identified on the surface of beta cells of patients with T1D, on thyroid cells of patients with Grave's disease and on bile duct cells of patients with primary biliary cirrhosis. (Béatrice Faideau et al. 2005)
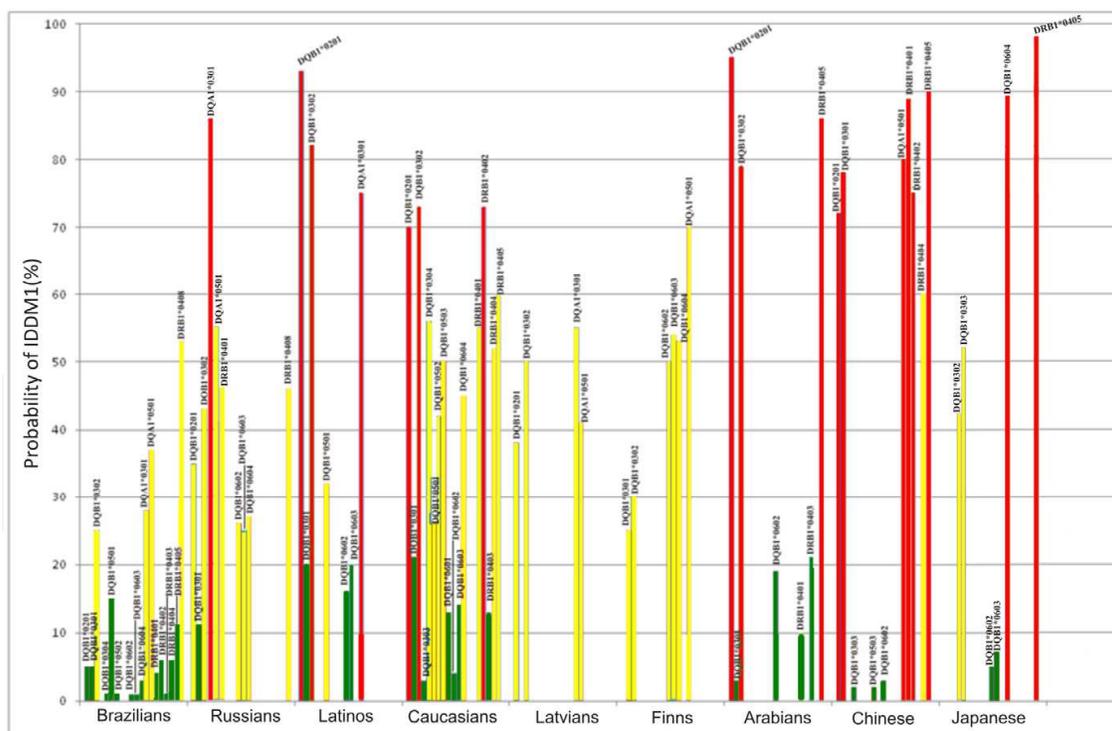
Fig. 4. The distribution of diabetogenic and protective potentials of HLA class II in different racial populations. Green columns: low risk (diabetoprotective); yellow columns: medium risk (moderately diabetogenic); red columns: highly diabetogenic. The diabetogenicity of the same alleles in different populations is either similar or radically different. It is not excluded that this parameter is controlled by environment factors.

This bar chart displays the most important T1D-predetermining haplotypes and their distribution in different populations. As can be seen, the presence of the same haplotype in two different populations contributes differentially to T1D-associated risks. For example, in Russians DQA1*0301 elicits a nearly 85% risk of T1D, whereas in Latinos the risk is less than 75%. Moreover, haplotypes spreading risks of diabetes in one population can be nonspecific for other populations. As regards DQA1*0301 its effect on acquisition of sensitivity to T1D is negligibly small in Brazilians, while in Chinese, Japanese, Arabians, Finns and Caucasians this haplotype is not associated with diabetes. These findings suggest that genetic features, haplotype frequency and contribution of specific haplotypes to susceptibility to T1D vary widely in different populations indicating different diabetogenic or protective orientation and high risk of T1D development.

Analysis of specific domains of the human genome made it possible to establish their roles in pathological processes and to get a deeper insight into molecular mechanisms responsible for instability of the human biome. The clue to the practical solution of problems in this area is to discover novel genetic markers, to secure low cost of the analysis and to ensure high accuracy of the methods employed. The totality of these factors may culminate in the construction of unique tools for subclinical diagnosis and preventive medicine.

3.5 HLA class III: Role in genetic predisposition

Far fewer (compared to HLA classes I and II) messages deal with contribution of HLA class III to background predisposition to T1D. In constructing a basic screening algorithm with special reference to early diagnosis potentials, one should take into consideration the crucial role of this region's genes in predisposition to T1D.

There exist about a dozen HLA class III genes manifesting a diagnostically significant association with T1D. These include NOTCH4 (rs2395106) responsible for susceptibility to rheumatoid arthritis and MSH5 (rs707915) associated with a high risk of T1D. As an overall trend, HLA classes II and III provoke diabetes at the highest levels of the odds ratio, while the effect of HLA class I on T1D is much less expressed (see Figure 3). (Valdes AM et al. 2006; Yamaji K et al.2006)

3.6 Non-MHC genes and their contribution to T1D

Any systemic approach to T1D diagnosis demands a large set of complementary and mutually specifying biomarkers. In addition to screening of circulating autoAbs and MHC Ags, systemic analysis of non-MHC genes is extremely important for validating the diagnosis. Though the odds ratios of the overwhelming majority of MHC genes are by one order of magnitude lower than that of MHC, identification of these gene clusters allows a qualitative description of risks for various autoimmune disorders including generation and progression of insulitis and, in a more distant perspective, objective prognosis of T1D outcomes.

In all probability (and not too surprisingly), each individual gene does not act specifically upon every component of the immune system or cell metabolism, but, rather, exerts a complex action by forming a kind of a pathological system. An immense variety of genes responsible for susceptibility to T1D are known, but their functional capabilities are either obscure or poorly investigated. Some SNPs whose role in etiology and pathogenesis of T1D leaves no doubt are described below. (Barret et. al., 2009)
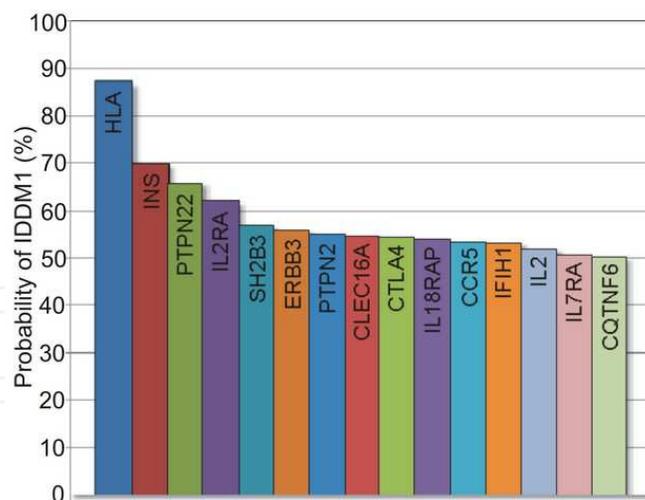
Fig. 5. A comparison of some diabetogenic non-HLA genes having mean values for HLA. The height of the column reflects the average probability of the clinical stage of type 1 diabetes (IDDM1) for the given allele. at the same time, MHC genes manifest a high degree of variation and, in some special cases, diabetoprotective activity.

TNFAIP3 (A20), tumor necrosis factor, alpha-induced protein 3. In the pancreas, this gene performs miscellaneous functions to include inactivation of NF-kappa B signals, prevention of inflammatory lesions of pancreatic cells, deceleration or delayed recruitment of immunocompetent cells into target organs, retardation of intercellular matrix restructuring, and so on. Studies by Liuwantara D et al. established that expression of the A20 gene is an effective mechanism of beta cell protection from TNF-induced apoptosis. Mutations in this gene and formation of SNPs initiate functional disturbances in NF-kappa B and represent the most common mechanism of disregulation and disorganization of immune reactions resulting in autoimmunity. Yet another salient feature of A20 is its ability to stimulate angiogenesis. Knockout of A20 shortens the tubule area and length in mice *in vitro.* (Grey ST et al., 2003)

A crucial role in specification of APCs and pathogenesis of T1D is played by the **ERBB3** gene known under the official name "v-erb-b2 erythroblastic leukemia viral oncogen homolog 3 (avian)". This gene encodes the family of specific receptors to the epidermal growth factor (EGFR).

Mutations in ERBB3 lead to immunoregulatory collapses coupled with continuous emergence of autoreactive cells. By virtue of its ability to provide linkage between genetic predisposition, infectious diseases and adaptive immune reactions, ERBB3 has every right to be regarded as a central molecular constituent element of the T1D-inducing complex. (Hongjie Wang et al., 2010)

PTPN22 (LYP), known under the official name "protein tyrosine phosphatase, non-receptor type 22 (lymphoid)", encodes lymphoid-specific intracellular phosphatase able to bind to the molecular adaptor protein CBL and thus controls its activity in the signaling pathway of the T cell receptor (TCR).

PTPN22 contains several SNPs disturbing normal operation of immune mechanisms. SNP rs2476601 is a valuable biomarker of susceptibility to autoimmune diseases, but its role in NK cell biology is not yet finally elucidated. The fact that SNP rs2476601 upsets the balance between T and NK cells *in vitro* points to the involvement of PTPN22 in immune regulation

of NK function. (Douroudis et al., 2010) The PTPN22 allele 1858T worsens the function of beta cells. 1858T is associated with IAA, an autoAb participating in pancreas destruction. The 1858TT and 1858CT genotypes exhibit a steadily increasing risk for the appearance of additional autoAbs and clinical manifestations of the disease.

The primary mechanism of PTPN22 SNPs is launched upon triggering of insulin-specific autoimmune responses. SNPs produce multifarious effects: they disturb functional activity and suppress metabolic responses of beta cells to changing blood glucose levels, stimulate the transition from prediabetes to type 1 diabetes, and so on. (Fichna et al., 2010; Taniyama et al., 2010; Hermann et al., 2006)

The **IFIH1** gene (interferon induced by helicase C domain 1, also known as MDA5) encodes the DNA receptor associated with viral infections with a concomitant formation of autoreactive T cells and induction of autoimmune diabetes. Moreover, IFIH1 fulfils a protective function in hypomorphic expression of IFIH1. (Downes K et al., 2010) IFIH1 is directly involved in the destruction of Langerhans islets due to pooling and mobilization of autoreactive cells in response to viral invasion. This circumstance aggravates immune dissonance and promotes self-restructuring of targeted organs by provoking persistent deficiency of the pancreas and accelerating insulin failure. IFIH1 disturbs cell-mediated and humoral immunity by initiating selective deficiency of IgA. (Ferreira et al., 2010)

IL2RA (interleukin 2 receptor, alpha, also known as CD25, T1D0, TGGFR) represents, along with IL2RB and the γ-chain IL2RG, a fragment of the high-affinity receptor IL-2 (homodimerization of α-chains yields low-affinity receptors, while homodimerization of β-chains gives receptors with medium affinity). By virtue of its structural and functional peculiarities, IL2RA makes the greatest contribution to the progression of T1D. It regulates immune and inflammatory responses, exerts negative control over cell proliferation and favors differentiation of T cells. In addition, IL2RA controls apoptosis via a positive feedback mechanism. Mutations in the IL2RA gene point to IL2RA insufficiency. Genetic variations in IL2-IL21 and IL2RA/CD25 regions predetermine the susceptibility to T1D by interfering with the transcription and/or splicing of mRNA. In this way, IL2 and IL2RA exert genetic control over protein expression in different cell subpopulations. (Dendrou et al., 2008)

The **INS** (ILPR, IRDN, IDDM2, MODY) gene is a key participant in the synthesis of insulin molecules. In patients with T1D, the mutation frequency of this gene does not exceed 0.1%. (Rajasalu et al., 2007)

CD226 (rs763361) SNPs regulate the activity of certain cells involved in immune mechanisms mediating beta cell destruction. The susceptibility to T1D is associated with SNPs rs763361 (genotype TT, OR = 2.29) and allele T (OR = 1.48). (Douroudis et al., 2009; Hafler et al., 2009)

In conclusion, we can state with assurance that nearly the overall repertoire of genes whose mutations are known to increase the risk of T1D development has been identified and characterized in terms of functional activity, which includes:

- Protection of beta cells from apoptosis (TNFAIP3);
- Secretion and metabolism of insulin (INS);
- General immunity (ERBB3, IL2RA, PTPN22, PTPN2, SH2B3, CTLA4, SUMO, ICOS;, etc.);
- Undefined function (CTSH, CLEC16A, IL7RA, CIQTNF6);
- Generation of autoAbs to beta cells (mostly, in adults) (HLA-DR3);
- Generation of autoAbs to insulin and formation of the insulin resistance syndrome (mostly, in adolescents)(HLA-DR4);

- Supporting high risks of autoimmune processes (HLA-DQ-related T1D) (NB: HLA-DR3-DQ2 and HLA-DR4-DQ8 genes are among the most popular T1D inducers in young children);
- Diabetoprotective function (HLA-DR2, DR6, DR7) (**NB**: HLA-DR1, DR5, DR8 and DR9 genes are usually identified in individuals for whom T1D is uncommon).

From the foregoing it follows that the first step of preclinical diagnosis must include identification of classical genetic biomarkers for each concrete pathology and acquisition of information from three basic resources: (i) genealogic tree, (ii) anamnesis morbid and (iii) anamnesis vita.

This approach would enable identification of individuals predisposed to a concrete disease and their distribution into risk groups with further transition to the second stage where patients are subject to investigation, using target panels of genotypic and phenotypic biomarkers and continuous monitoring of potentially affected cohorts and those predisposed to the preclinical pathology stage. The primary testing approach demands validated procedures for detecting molecular and cellular shifts in one or another cell and/or tissue function in the paradigm of the most pathogenetically significant targets. The methods employed thereupon include high-performance genomic and metagenomic scanning as well as proteomic and metabolic analyses in the paradigm of microbial colony-forming populations. Moreover, biomonitoring is based on the use of a vast array of nanotools as well as visualization and biosensoric facilities allowing comprehensive examination of "suspected" individuals and elaboration of wide-range activity-oriented treatment schedules in a real-time mode.

4. Proteomics: A powerful tool for predictive medicine

The role of proteomic technologies in the study of autoimmune diseases can hardly be overestimated. Virtually all currently known autoimmune diseases including diabetes mellitus, multiple sclerosis, systemic lupus erythematosus and other severe autoimmune disorders have proteomic markers of their own. At the same time, the advent of efficient high-precision diagnostic technologies opened up new opportunities in the search for novel preclinical diagnostic markers. Identification of autoAbs to immunoglobulins GADA, IAA, ICA, IA-2A and ZnT8 has become a routine procedure in T1D diagnosis. In this chapter, the main emphasis will be laid on some characteristics of specific proteins for progressive T1D.

Clusterin (apolipoprotein J) holds considerable promise as a candidate biomarker; its main function is traditionally recognized as a tool to control apoptosis. It should be noted, however, that clusterin exhibits the behaviour of an antiapoptotic chaperone when used at low concentrations; at higher concentrations (~ 12% of control), it causes disruption of mitochondria and initiates cell apoptosis by a mitochondrial mechanism. Recent reports highlighted a high regenerative potential of Clusterin, particularly, with respect to beta cells. The functional activity of this protein demands further verification and analysis, but its elevation always points to apoptosis of pancreatic beta cells. (Lee et al., 2011)

Transcortin (Corticosteroid-binding globulin, CBG) and Lumican are capable to induce pronounced (1.5–2-fold against control) upregulation. Transcortin fulfils the function of a glucocorticoid transporter and is strongly inhibited by insulin; hence, insulin deficiency is always associated with hyperproduction of Transcortin. (Fernández-Real et al., 1999) However, this protein is hardly effective as a selective biomarker for T1D, since it emerges exclusively at the latest stages of autoimmune aggression and its role in T1D etiogenesis is

still unclear. Lumican, the key mediator in fibrosis-related processes, manifests an even higher degree of upregulation than Transcortin and is widely distributed in all body tissues. Its significant elevation may represent an acute response of renal tissues to high plasma levels of glucose and is also characteristic of nephropathies. However, being a convenient tool for predicting diabetic nephropathies, Lumican cannot predict associated diseases.

It may be concluded from the above-said that Clusterin is the only candidate for a selective protein biomarker for T1D, because it emerges at early stages of the disease and is more related to cause than effect.

5. Effects of autoAbs on the launch of autoimmune processes and pancreas deficiency: Dynamics of spectra and prognostic value in preclinical diagnosis of T1D

Today, autoantibodies (autoAbs) are the main biomarkers of diabetes mellitus. The presence of small concentrations of autoAbs in peripheral blood does not always indicate initiation of an autoimmune process, because the organism possesses a vast number of autoregulatory mechanisms. However, their collapse and significant elevation of Ab titers indicate a nearly 100% risk for diabetes in the foreseeable future. Many autoAb classes are currently known including GADA (65 and 67), IA-2Ab, INSab, HSPab, ZnT8ab, IAA, etc.

Each of these autoAbs has a prognostic value of its own and is associated with a definite type of diabetes (T1D, latent diabetes, fulminant diabetes, etc.). The factors initiating the appearance of autoAbs are also different. Among the immense diversity of causative factors, diabetogenic genes (classes I, II and III MHC) responding by activation to virus-induced inflammation (molecular mimicry) are of paramount importance. The results of in-depth studies on associativity between MHC II alleles and auto-Abs unequivocally suggest that in the present state of the problem generation of certain classes of auto-Abs and further progression of T1D can be predicted on the basis of genetic data even at the earliest stages of the disease.

5.1 GADA

Glutamate decarboxylase catalyzes the conversion of glutamic acid into γ-aminobutyric acid and CO_2 and plays a prominent role in the functional activity of the central nervous system (CNS). Its substrate (glutamic acid) is responsible for excitation, while its major metabolic product (γ-aminobutyric acid) is a key mediator of inhibition in brain neurons. The physiological role of this enzyme is confined to various aspects of insulin-dependent diabetes.

Two isoforms of GAD (GAD65 and GAD67) are encoded by two non-allelic genes localized on different chromosomes, more specifically, on the 2nd (GAD65) and 10th (GAD67) chromosomes. Both isoforms are actively expressed in CNS neurons. In human islet cells, GAD65 is a predominant isoform, while GAD67 is either present in negligibly small amounts or is not expressed at all. In contrast, in rat islet cells both GAD isoforms are expressed with a nearly equal efficiency, but the GAD67 isoform is predominant.

The prognostic significance of GADA is rather high. These autoAbs appear in circulating blood before other auto-Abs (~ 10 – 15 years before the appearance of first clinical manifestations of T1D) and are detected in 70 – 90% of cases.

Risks for T1D and Ab titers

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Autoantibody titer	10-year risk (% ± SE)	HR (95% CI)	P
I quartile	35 ± 9	1*	
II quartile	22 ± 9	0.8 (0.3–1.9)	0.55
III quartile	52 ± 9	1.7 (0.8–3.6)	0.18
IV quartile	43 ± 10	1.6 (0.7–3.6)	0.26

Likelihood of developing diabetes depending on the combination of epitope-specific GADA antibodies

GADA					
Epitope combination				n (T1D cases)	10-year risk
MID	COOH	NH2	67		
+	+	+	+	24 (8)	39%
+	+	+	–	12 (6)	26%
+	+	–	+	15 (5)	56%
+	+	–	–	62 (21)	45%
+	–	+	–	1 (0)	
+	–	–	–	13 (3)	27%
–	+	+	+	1 (0)	
–	+	–	–	5 (2)	48%
–	–	+	–	6 (1)	20%
–	–	–	–	10 (3)	33%

For GAD antibodies, MID refers to epitopes within GAD65 amino acids 235–442, COOH refers to epitopes within GAD65 amino acids 436–585, NH2 refers to epitopes within GAD65 amino acids 1–100, while GAD67 refers to epitopes present in GAD6 (combinations with no relatives are not shown). (Buzzetti et al., 2007; Mayr et al., 2007)

5.2 IA-2

IA-2 belongs to type 1 membrane-bound proteins containing extracellular NH_2-terminal glycosylated, membrane-bound and COOH-terminal cytoplasmic regions. The immune epitope of IA-2 is localized exclusively in the cytoplasmic region of IA-2 where its PTP (protein-tyrosine-phosphate)-like domain is the main recognition site for auto-Abs. The fact that the dominant T cell epitope of IA-2, also localized in the PTP-like region, is structurally similar to the VP7 region (VP7 is a major immunogenic protein of rotaviruses) provides additional evidence for the crucial role of the molecular mimicry mechanism in the pathogenesis of T1D.

IA-2β (also known as fogrin, PTP-NP, ICAAR and IAR) is structurally similar to IA-2. Its intracellular and extracellular domains are structurally identical (by 74 and 26%, respectively) to IA-2. IA-2β is predominantly localized in secretory vesicles of beta and some other neuroendocrine cells. Anti-IA-2β Abs are present in nearly 50% of patients with newly diagnosed T1D; their emergence is usually recorded several years before the appearance of the first clinical manifestations of the disease.

AutoAbs against the insulin antigen are detected in 70–90% of individuals as early as 10 – 12 years before the clinical stage of T1D.

Auto-Ab titer	10-year risk (% ± SE)	HR (95% CI)	P
I quartile	20 ± 14	1*	
II quartile	74 ± 15	6.0 (1.6–22.4)	0.008
III quartile	84 ± 10	5.9 (1.7–21.1)	0.006
IV quartile	71 ± 15	4.8 (1.3–17.9)	0.02

Likelihood of developing diabetes depending on combination of epitope-specific IA-2 antibodies

IA-2ab				
Epitope combination			n (T1D cases)	10-year risk
IA-2β	PTP	JM		
+	+	+	13 (8)	81%
+	+	−	12 (10)	100%
+	−	+	1 (1)	
+	−	−	4 (3)	
−	+	+	8 (3)	34%
−	+	−	10 (4)	44%
−	−	+	9 (2)	41%
−	−	−	4 (1)	

For IA-2 antibodies, IA-2β refers to epitopes found in the PTP region of IA-2β and IA-2, PTP refers to epitopes found in the PTP region of IA-2 (but not IA-2β), while JM refers to epitopes within the IA-2 juxtamembrane region in amino acids 601–682 (combinations with no relatives are not shown). (Kordonouri et al., 2010; Kawasaki E et al., 2003; Hanifi-Moghaddam et al., 2003)

5.3 ICA

The target antigen for pancreatic islet cell antibodies has not yet been finally identified. In all probability, it represents a heterogeneous cluster of antigens expressed in beta cells. In contrast to IA-2ab, ICA is a polyclonal antibody able to interact with all populations of islet cells (α, β, γ, δ, PP) and other auto-antigens (sialoglucoconjugate, GAD, IA-2A, etc.).

Antibodies to islet cells are found in 85-90% of patients with onset T1D (cf. 0.5% in unaffected individuals) during the very first week after clinical diagnosis. Four weeks thereafter, their incidence does not exceed 50%. In patients with one-year history of T1D, antibodies to beta cells are present in only 10-20% of cases.

Similar to other cell-related Abs, ICA does not play any crucial role in beta cell degradation, but is one of key markers of cell-mediated autoimmunity. Its detection in blood serum suggests latent autoimmune diabetes (LADA) and slow degradation of beta cells.The prognostic capacity of ICA is neither high, nor low and is usually manifested 12 years prior to T1D development. Its incidence at the clinical diagnosis stage varies from 60 to 80%. Correlation between antibody titers and risks for T1D over a period of 7 years. (Achenbach et al., 2004; Williams et al., 2002)

5.4 IAA - AutoAbs to insulin

Insulin is a peptide hormone produced by beta cells of pancreatic Langerhans islets. The main physiological role of insulin consists in reducing glucose levels in the blood; its absolute deficiency is the main cause of T1D.Anti-insulin Abs are indispensable constituent elements of blood sera of healthy individuals where their concentrations vary from 1 to 5 µg/ml. In patients with T1D, serum concentrations of anti-insulin autoAb IgG class can reach very high levels.

Insulin antibodies are associated with many autoimmune pathologies including Graves' disease (40%), Hashimoto's disease (autoimmune thyroiditis) (20%), Addison's disease (40%), chronic hepatitis (36%), systemic lupus erythematosus (29%), etc.

Insulin-binding Ab are always present in the blood sera of insulin-treated patients. In patients with T1D, the therapeutic effect of insulin diminishes gradually with emergence of anti-insulin antibodies, especially after prolonged insulin therapy or administration of high daily doses of the hormone. Other factors, e.g., dosage form or purity of the hormonal preparation, also play a role.

Seroconversion of insulin ABS is usually recorded as early as eight years before the onset and clinical diagnosis of T1D. However, after this period high antibody titers begin to decrease gradually up to the moment of their complete elimination and are detected in only 30–60% of patients.

Auto-Ab titers	10-year risk (% ± SE)	HR (95% CI)	P
I quartile	45 ± 16	1*	
II quartile	30 ± 13	0.7 (0.2–2.4)	0.55
III quartile	38 ± 17	0.8 (0.2–2.7)	0.68
IV quartile	77 ± 12	3.0 (1.1–8.1)	0.03

(Catherine Pihoker et al., 2005; Heli et al., 2009)

6. Metabolome as applicable to T1D management at subclinical stages to prevent or minimize the imbalance

In a recent study, a comparison of blood sera from children with type 1 diabetes (T1D), non diabetic children and children without autoimmune antibodies revealed metabolic disturbances (significant reduction of serum levels of succinate, phosphatidylcholine, phospholipin and ketoleucine, drastic elevation of glutamate, etc.) in the T1D group. , (Bougnères et al., 2008) The true reason for these disturbances is difficult to establish, since all these changes can be associated, with an equal degree of probability, with asymptomatic damage of liver and body musculature, T1D, metabolic imbalance caused by environmental factors, etc.

High lysophosphatidylcholine levels are detected in patients' blood as early as several years before the first clinical manifestations of T1D. It should be noted, however, that the aforecited studies were performed on children, but not on adults with T1D; therefore, their clinical significance is ambiguous.

Notable elevation of blood sera levels of glutamate potentiates the activity of GAD65, the major autoimmune antigen for autoAbs. The figure below shows the dynamics of the "glutamine–GABA–GADA" sequence. As can be seen, neither GADA and IAA, nor unlimited

elevation of glutamine and moderate elevation of GABA take place in the initial steps. However, in the course of time the concentration of glutamic acid begins to decrease, while that of GABA increases; however, autoAbs are not generated even under these conditions. Subsequent decreases of glutamic acid and GABA are noted only against the background of increasing titers of anti-GAD65 and anti-insulin autoAbs (seroconversion). After T1D passes to the clinical diagnosis stage, auto-Abs titers begin to decrease gradually to a nearly undetectable level (this widely occurring phenomenon usually lasts 10 to 20 years).
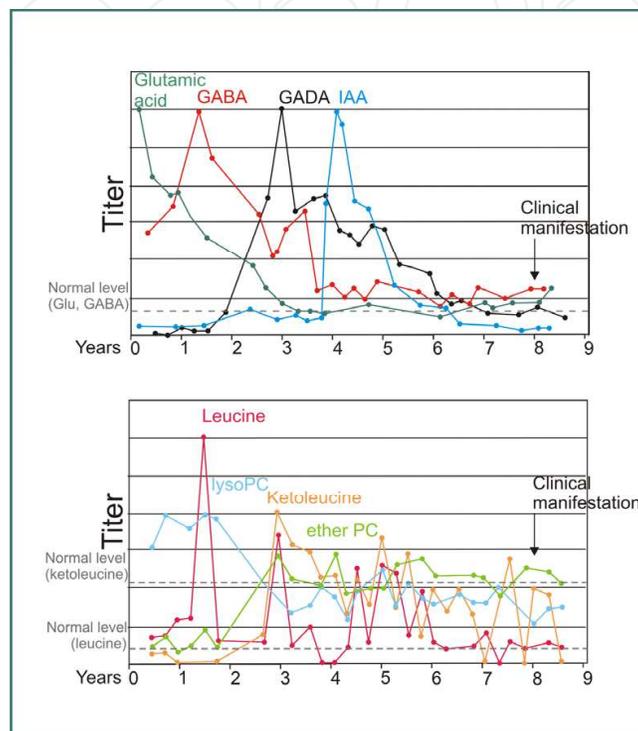
Fig. 6. The dynamics of changes in the concentrations of Glu / GABA / GADA and insulin Abs in the period between the commencement of the effect of the irreversible diabetes-inducing factor and first clinical manifestations of T1D. There is a clear seroconversion sequence Glu / GABA / GADA with a period of about 1 year. By the moment of appearance of first clinical manifestations, some antibodies detected several years theretofore, may be missing. (Noteworthy, each individual case may be different from the average).

There is evidence that in addition to the aforesaid metabolites T1D is characterized by fluctuations in the levels of succinic acid, phosphatidylcholine (even in newborns), triglycerides and phospholipids.

7. Environmental factors triggering T1D

Estimation of the role of environmental factors in triggering one or another pathology and development of adequate approaches to diagnosis within maximally short intervals of time is one of currently central problems in preclinical medicine. Here, it is necessary to draw a demarcation line between autoimmune disorders and background events in order to select optimal diagnostic procedures and reliable criteria, since clinical tests do not always provide unfailing results that are crucial for diagnosis. Therefore, development of strict elaborate protocols is of vital importance for identification and analysis of environmental factors.

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Continuous exposure to hazardous effects of environmental factors and large-scale application of chemical substances in food industry, pharmaceutics and other sectors of national economy are harmful for human immune system, since all of them trigger pathological reactions resulting in diabetes. Furthermore, uncontrolled intake of drugs and frequent viral and bacterial infections form predisposition to allergic reactions and provoke autoagression and development of various immune disorders.

8. Phase 2 characteristics

8.1 Viral infections as triggering factors in type 1 diabetes

The large body of evidence (serological, epidemiological, biological, etc.) obtained thus far testifies to the ability of certain viruses to provoke type 1 diabetes mellitus (T1D) in human beings. Among the immense diversity of other disease-provoking factors, enteroviruses, retroviruses, reoviruses, parotiditis viruses, cytomegalovirus, Epstein-Barr virus and a clinical variant of the diabetogenic encephalomyocarditis virus are the most likely candidates for T1D-triggering factors.

Viral infections provoke diabetes by operating at different regulatory levels, e.g., by disregulating immune mechanisms, by stimulating the activity of pathological systems or by interfering with the normal course of regulatory processes occurring in the organism.

The risks of viral infection and T1D development correlate with the functional stability of the organism and its genetic and immune backgrounds. It is well known that morbidity from seasonal (especially, in the winter period) virus-borne infections correlates with very high incidence of autoimmune diseases including T1D. The reason is in shorter (in comparison with summertime) duration of the daylight period and, as a consequence, low level of vitamin D synthesis and increased morbidity from viral infections and autoimmune disorders. Additional support in favor of this hypothesis can be derived from much greater incidence of T1D in North European countries in comparison with Southern Europe.

8.2 Bacterial infections as triggering factors of T1D

Recent advances in immunologic research and numerous animal and human model studies shed new light on the role of enteric bacteria in triggering autoimmune reactions. It was shown, in particular, that certain bacteria (e.g., *Bacteroides ovatus*) induce diabetes in young children predisposed to T1D. The mechanisms whereby bacterial agents interfere with immune homeostasis and provoke diabetes are still poorly understood; it is known, however, that intestinal bacteria trigger autoimmune responses that initiate destructive insulitis. The strongest argument in favor of this viewpoint is an ever increasing (by 20% in comparison with control) number of affected individuals infected with sporadic variants of these bacteria. The extent of bacterial infection is especially apparent in young children whose autoimmune microbiome is the least stable and diversified. Continuous sophistication and diversification of the microbiome with ageing point to the decreasing role of bacteria in initiating diabetes in adult individuals. (Giongo et al., 2010)

8.3 Nutritional factors

For quite a long period of time, viruses were considered to be the only etiogenic external factors in T1D. Today, there is evidence that nutritional factors also play a role in T1D development. Although the pathogenetic mechanisms of the disease are not yet completely

understood, the role of T1D as one of the most essential links in the human immune system leaves no doubt, particularly with regard to its tolerance to food antigens.

As a rule, tolerance to food antigens largely depends on peculiarities of local immune reactions whose functional role consists in suppression of immune responses formed under the influence of several factors, viz., (i) oral tolerance, (ii) controlled chronic inflammation (so-called "physiological inflammation") and (iii) local secretion of IgA.

Disturbances in the coordinated functioning of these mechanisms stimulate the appearance of characteristic manifestations of food allergy. Measurements of blood plasma levels of Abs against various food antigens in patients with clinically confirmed T1D revealed high titers of IgA and IgG against cow's milk Ags (bovine serum albumin, BSA), beta lactoglobulin, BLG) and some other food Ags, e.g., ovalbumin, OVA. It should be noted, however, that in this particular case we deal with the so-called abuse tolerance, which can hardly be compared to food allergies associated with high levels of circulating IgE. (Kohno et al., 2002; Luopajärvi et al., 2008)

8.3.1 Nitrosamines

There is a statistic association between nitrosamines and diabetes as can be judged from some biochemical data on destructive effects of nitrosamines on pancreatic Langerhans islet beta cells. In a statistical study, nitrosamine levels were determined in foods consumed by children under 14 at risk of diabetes. It was found that in children with low dietary nitrosamine levels the Odds Ratio (OR) was equal to 1.0 (cf. 1.7 OR and 2.6 OR in children with medium and high levels of dietary nitrosamine). (Dahlquist et al., 1990)

Statistic analysis established a correlation between the quality and quantity of consumed food, on the one hand, and susceptibility for diabetes, on the other hand. However, this correlation is purely statistical, since biological, biochemical and immunological mechanisms responsible for this phenomenon demand further investigation and analysis. (Essien & Akpan, 2006)

8.4 Age

The growing tendency in the past decades is towards higher incidence of T1D in young people and children. In the first place, this is due to negative influences of environmental factors. The first peak of T1D is normally observed between the 4th and 6th years of life; the second peak is associated with hormonal transformations in the pubertal period (10–12 years).

On the other hand, there exists a special form of diabetes termed as latent autoimmune diabetes in adults (above 30) (LADA). Its most characteristic features are moderate clinical manifestations and slow progression of the autoimmune process. The finding that 6% of patients with LADA carry protective haplotypes responsible for more slow progression and less severe (in comparison with IDDM1) manifestations of the disease indicates that LADA appears to be a more widespread form of diabetes than its classical form, viz., T1D. This and the aforementioned data emphasize the need for elaborating novel effective criteria and approaches to treatment of patients with diagnosed LADA. (Bermúdez et al., 2010)

8.5 Gender

Analysis of sex steroids revealed that clinical manifestations of many autoimmune diseases vary widely depending on the hormonal status of the organism, e.g., menstrual cycle, administration of oral contraceptives, etc. Pregnancy should also be included in this list. The

alternative hypothesis states that higher X-linked genetic predisposition of females to autoimmune diseases is a result of unbalanced X chromosome inactivation. The X-inactivation skew theory was recently corroborated for dermatosclerosis and autoimmune thyroiditis. Yet another possible mechanism is small-scale exchange of cells between mother and fetus pregnancy.

At the same time, the current views on the role of environmental factors in T1D are often diametrally opposite and many practitioners in medicine are inclined to think that the stably increasing incidence of this severe autoimmune disease is unrelated to external factors. For example, a mass-scale retrospective investigation was carried out in Saudi Arabia in the period between 1980–2009. In this study, 119 patients with T1D were divided into six groups depending on early clinical manifestations of the disease. There was no correlation between the impact of environmental factors and the incidence of T1D over a period of three decades.

9. Medicaments as potential T1D inducers

For many decades, it was believed that certain chemical substances including patented medicaments are harmful for the pancreas and provoke T1D. The mechanisms whereby chemical drugs exert their hazardous effects vary widely and are not clearly understood. Active drug components accumulated in body cells slow down the functional processes in different body tissues and organs and trigger pathological reactions, e.g., by providing tropism of certain pathogens or restructuring the systemic architectonics of body organs including the pancreas. The presence, in such active components, of sequestered or cryptic epitopes provokes negative phenomena, such as molecular mimicry. Not infrequently, medicinal drugs trigger a series of immunoregulatory and immunoeffector shifts, which culminate in immune disorders including autoimmune destruction of the pancreas.

10. T1D and vaccination: Is there a correlation between them? The role of passive immunization in T1D development

There exist quite a few hypotheses concerning the role of vaccination in triggering autoimmune diseases including T1D. This fact notwithstanding, only few instances proved to display a clearcut correlation between vaccination and development of autoimmune syndromes. (Ethan Rubinstein, 2004) In the meantime, heated discussions about association between autoimmune disorders and vaccination do not abate. Advocates of the "autoimmunization" hypothesis refer to recent flagrant global-scale spreading of autoimmune diseases with a particular on responsibility of children's vaccines manufacturers. (Classen JB & Classen DC, 1999)

There is evidence that T1D indeed develop in response to immunization. At the same time, in newborn infants vaccinated at the age of several months the incidence of T1D did not exceed the morbidity level in children immunized with a single vaccinating dose at the age of 2 years. (Karvonen et al., 1999) Mass-scale serial investigations carried out in the USA did not establish any associativity between these two events. Similarly, studies into the role of vaccination and vaccination timing as risk factors in childhood diabetes failed to establish a correlation between vaccination and the risk for autoimmune diseases. (DeStefano et al., 2001; Blom et al., 2001)

11. Associativity between T1D and autoimmune diseases. Polyglandular autoimmune syndromes

T1D is often concomitant with local or systemic autoimmune disturbances, which further progress to complex autoimmune diseases or polyglandular syndromes via the cross-reactivity mechanism. By illustration, in many patients T1D is associated with autoimmune thyroiditis (24.5%/autoAbs vs 47.5%), celiac disease (1.4%/autoAbs to gliadin and IgA to tissue transglutaminase vs 18.7%), MS (0.5-2%/autoAbs vs 7%), Addison's disease (1.4%/adrenal cortex autoAbs vs 0.7%), autoimmune gastritis (6.9-7.2%/parietal cell autoAbs vs 20.9%), etc. (Somers et al., 2009; Villano et al., 2009; De Block et al., 2006)

Secondary autoimmune disorders associated with later steps of T1D have a number of specific features. Thus, autoimmune thyroiditis (AIT) (autoimmune polyglandular syndrome 3A version (APS3Av)) is diagnosed in 12-15% of T1D patients; its clinical manifestations correlate positively with age, gender (AIT is more frequent in females (8.6%) than in males (3.4%)), duration of T1D (mean age of AIT patients varies between 5 and 15 years), serum levels of the thyroid-stimulating hormone (TSH), etc. Both diseases have a common familial hereditary background, but can also be present in a single individual suggesting a crucial role of genetic predisposition in the development of polyglandular syndromes. Furthermore, high incidence of AIT among first-degree relatives of T1D patients points to a significant contribution of genetic factors to immune system failures (see above). (Severinski et al., 2003; Hunger-Battefeld et al., 2009)

Noteworthy, the predominant form of AIT in patients of both sexes is hypothyroidism (8.1%), but in males with anti-thyroid Abs AIT is prevalent (85.7% vs 37.5% in females). the total incidence of hypothyroidism in T1D patients with anti-thyroid Abs is 52.2%. The interval between the onset of T1D and the appearance of first clinical manifestations of AIT varies from one year to 5–6 years, while the first thyroid autoAbs appear in the period between 6 months and 5–3 years before the onset of the disease. Blood sera of patients with APS3Av (AIT and T1D) (Hunger-Battefeld et al., 2009) contain circulating anti-thyroid peroxidase and anti-thyroglobulin Abs emerging soon after emergence of GADA (10% and 8% of cases, respectively); more than 6% of such patients contain both types of autoAbs. As mentioned earlier in this chapter, MS is also associated with T1D. In this case, morbidity from MS among male patients exceeds that in females nearly fourfold (2% vs. 0.5%). According to statistic reports, non-diabetic sisters run five times higher risks for MS than other cohorts of the general population. Consequently, adult females with T1D can be assigned to the highest risk group for associated autoimmune disorders (e.g., MS). (Bussone et al., 2009; Otto-Buczkowska et al., 2009)

The association between T1D and RA is not so apparent as in the case of T1D and MS. In depth studies established that about 13% of patients whose first-degree relatives suffer from T1D have clinical signs of RA. According to other authors, no such linkage does not exist. (Hakala et al., 1992)

Based on these findings, we can state with assurance that T1D increases the risk for autoimmune disorders through triggering the formation of autoimmune clusters and polyglandular autoimmune syndromes. As a rule, circulating autoAbs begin to appear in the blood serum as early as several years before the development of severe secondary disorders and absolute clinical manifestations of the disease. The genetic data provide the physician with a broad spectrum of autoimmune diseases that are likely to develop in patients with T1D. Time-lapse monitoring of patients' blood sera not only affords reliable

dynamic control over disease progression, but also enables the physician to estimate the efficiency of ongoing therapy, to search for early-stage biomarkers for diagnosing secondary autoimmune disorders and, last but not least, to implement adequate preventive and curative treatment.

12. Multiple Sclerosis (MS)

12.1 State-of-art models of multiple sclerosis

Multiple sclerosis (MS), a remitting and relapsing autoimmune disease of the central nervous system (CNS), represents a generalized degenerative inflammatory process. Its main causative factors are demyelination, degradation of oligodendrocytes and degeneration of axons.

The clinical course of MS includes three stages, viz., the preclinical stage, the autoimmune inflammation stage and the neurodegeneration stage. Some basically important targets (including gene-oriented ones) emerging in the course of MS evolution can be used in the design of novel preclinical diagnostic tools. Expression of gene products including functionally important transcripts is currently employed in the design of proteomes. The use of these constructs (commonly referred to as diagnostic microchips) as early as at the preclinical pathology stage allows multifarious manipulations with specific targets in the course of immune attacks. Impaired structure of the myelin sheath (demyelination) and degradation of axons take place at the very earliest stages of preclinical MS, i.e., long before the clinical onset of the disease. This generates a need for innovative preclinical diagnosis protocols and, in a more distant perspective, preventive treatment of MS. In this context, genetic tests acquire special importance as valuable analytical tools for predicting and estimating risks in MS. In terms of present-day classifications, the genes supporting predisposition to MS are divided into three main groups, viz., immune system genes (DRB1, OPN, CD44, CD24, CCR5-Δ32), myelin metabolism genes (MBP, CTLA4, ICAM1) and cytokins (TGFβ1, TNF). AutoAbs to the basic protein of myelin are amont the key autoaggression markers for demyelination-related pathologies. Some of these Abs have functional resources of their own, e.g., proteolytic activity towards the Ag substrate. The dynamics of Abs spectra in patients with MS reflect etiogenic peculiarities of MS evolution. It is now well established that pre-early stages of MS are accompanied by the appearance of specific Abs against two categories of determinants, viz., mimicking and myelin epitopes. After termination of the preclinical phase, serum titers of mimicking Abs show a tendency to decrease, while those of antimyelin and antineural autoAbs increase in contrast. This upward trend points to escalation of antitissue autoaggression and formation of a typical clinical picture of the disease including a complete set of clinical and serological criterial features of PIFAS. Early emergence and long persistence of antimyelin autoAbs in MS patients points to a correlation between serum positivity and duration of the disease. (Sepiashvili et al., 2010; Martynov et al., 2010)

13. Aortic aneurisms

Aortic aneurisms (AA) are related to the category of socially important diseases involving a high risk for lethality. Its main causal factors are degradation of elastin (e.g., by proteases), pronounced structural changes in medial smooth muscle cells (SMC), aortic vasculature atrophies and formation of the *preclinical* pathological syndrome. The main clinically

important causes of AA established thus far can be presented as follows: (i) genetic predisposition and hereditary diseases affecting the molecular architectonics of connective tissue (e. g. Marfan's syndrome); (ii) atherosclerosis and arterial hypertension. Very often, AA is associated with atherosclerosis, especially, in patients of senior age groups. Male gender, smoking, carriage of specific infectious pathogens (herpes simplex virus, cytomegalovirus, *Chl. pneumonia*, syphilis and tuberculosis pathogens) also play a role in the pathogenesis of AA.

Long duration of the *preclinical* stage (aortal dilation to the critical level) in patients with AA provides the physician with a unique opportunity to break the pathogenetic linkage and thus to arrest the further progression of the disease on going from the preclinical to the clinical stage.

It is more expedient to perform preclinical screening in three steps in full conformity with prenosological diagnostic protocols. *(i)* identification of blood serum levels of biomarkers in the form of so-called serodiagnostic packages (matrix metalloproteinases (MMP), cystatin *C*, osteoprotegerin (OPG), soluble fractions of elastin (SFE) and heavy chains of myosin (HCM), antibodies against *Ch. pneumonia*, CMV and HSV). These biomarkers are used as diagnostic package components and allow maximally accurate diagnosis and, which is no less important, estimation of lesion size even at the *preclinical* stage; *(ii)* MRT or contrasting CT scanning angiography for identifying exact location of dilated vessels, viz., *topological sites* in the vascular network responsible for hypersecretion of specific biomarkers; *(iii)* biopsy of the dilated portion of the aorta containing a suspected aneurism followed by morphological, immunogenetic and molecular-biological testing of bioptats. This procedure is highly invasive and its implementation is not recommended in the absence of positive results in the first two steps. If the dilated portion of the aorta cannot be visualized directly and the first-step tests give positive results, screening for biomarkers must be repeated after a period of several months. If positive results are obtained from serological doublet tests, MRT or CT angiography must be conducted to the required extent.

Early (*preclinical*) diagnosis holds especially great promise being the most efficient step in prophylactic and preventive treatment of AA. The uniqueness and high therapeutic potentials of *preclinical* diagnosis combined with low invasiveness of the nonsurgical approach and design, on its basis, of more advanced diagnostic protocols opens up fresh opportunities for the development of rationalized and practicable innovative technologies as a breakthrough in cardio- and angiosurgery. Prospective analysis of clinical utility of *targeted* therapy as a tool for *preventive* (preoperative) treatment and/or postsurgical angiorehabilitation will also make the subject of future investigations.

14. Rheumatic diseases

In considering the role of pathogenetic factors in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS), special emphasis should be laid on risk genes and the extent to which they overlap.

According to GWA data, the contribution of MHC to RA risk can approximately be estimated as 30%, HLA-DRB1 alleles (e.g., DRB1*0401 with OR of 3) being critical for RA. Additional loci essential for estimating RA risks were identified by high-density genotyping as HLA-DP in patients with anticyclic citrullinated peptide antibodies, (*HLA-DR2(DRB1*1501)*) and *DR3 (DRB1*0301)* alleles in the MHC class II region with Ors of 2, risk variants in the MHC class III cluster encoding the TNF gene and the C2 complement components C4A and C4B.

Other loci in the MHC class III region associated with SLE include: the SKIV2L gene encoding the superkiller viralicidic activity of a 2-like protein, the PTPN22 gene, TNFAIP3 and TRAF1-C5 loci (TNF-associated signalling pathway genes), Integrin-α-M (ITGAM), STAT4, IL23R and a number of other genes.

15. Conclusion

In-depth studies into pathogenesis and etiogenesis of autoimmune diseases and discovery of reliable biomarkers for diagnosing various pathological conditions provide a way for predicting, with a sufficiently high degree of probability, the risk of relapses and exacerbations and possible clinical manifestations of the disease. In its turn, considerable recent progress in medical science (in medical genetics, bionanomedicine and bioinformatics, in particular) provides a clue to the design of advanced protocols for preclinical screening of patients. The construction of individual genetic maps with special reference to familial predispositions and time-lapse monitoring of risk groups for pathomorphological markers have one common goal, viz., to collect information for early implementation of preventive and therapeutic intervention strategies. Moreover, dynamic control over functional activities of different body organs and tissues on the basis of well established and validated proteomic and metabolomic data enables early prediction of exacerbations and complications and implementation of preventive therapy. The latter is based on the use of state-of-art pharmacological protocols and, if surgical correction is required, of the most recent advances in transplantation and regenerative medicine.

Considerable improvement and wide-scale application of preclinical diagnosis algorithms and preventive treatment protocols for routine clinical application are among the most topical problems in today's medical practice. More urgent strategies are aimed at compensating structural and functional deficiencies of damaged organs and fragments thereof. In genetic studies combined with early detection of minor lesion foci and analysis of immune, proteomic and metabolomic disturbances open up new vistas for social welfare with the ultimate goal to improve current standards of public health care at large.

16. References

Achenbach, P.; Warncke, K.; Reiter, J.; Naserke, H.E.; Williams, A.J.; Bingley, P.J.; Bonifacio, E. & Ziegler, A.G. (2004) Stratification of type 1 diabetes risk on the basis of islet autoantibody characteristics. Diabetes, Vol.53, No.2 (February 2004) ISSN 384-92

Ahn, J.M.; Kim, B.G.; Yu, M.H.; Lee, I.K. & Cho, J.Y. (2010) Identification of diabetic nephropathy-selective proteins in human plasma by multi-lectin affinity chromatography and LC-MS/MS. Proteomics. Clinical applications, Vol.4, Nos.6-7 (July 2010) ISSN 644-53

Andre, I.; Gonzalez, A.; Wang, B.; Katz, J.; Benoist, C. & Mathis, D. (1996). Checkpoints in the progression of autoimmune disease: Lessons from diabetes models. Proceedings of the National Academy of Sciences of the United States of America.; Vol. 93, (March 1996), pp. 2260–2263, ISSN 2260-3

Andre, I.; Gonzalez, A.; Wang, B.; Katz, J.; Benoist, C. & Mathis, D. (1996). Checkpoints in the progression of autoimmune disease: Lessons from diabetes models. Proceedings of the National Academy of Sciences of the United States of America.; Vol. 93, (March 1996), pp. 2260–2263, ISSN 2260-3

Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, Julier C, Morahan G, Nerup J, Nierras C, Plagnol V, Pociot F, Schuilenburg H, Smyth DJ, Stevens H, Todd JA, Walker NM, Rich SS; Type 1 Diabetes Genetics Consortium (2009). Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet. 2009 Jun;41(6):703-7. (Epub 2009) May 10.

Blom, L.; Nystron, L. & Dahlquist, G. (1991) The Swedish childhood diabetes study: vaccinations and infections as risk determinants for diabetes in childhood. Diabetologica, Vol.34, No.3 (March 1991) ISSN 176-81

Bougnères, P. & Valleron, A.J. (2008) Causes of early-onset type 1 diabetes: toward data-driven environmental approaches. The Journal of experimental medicine, Vol.205, No.13 (December 2008) ISSN 2953-7

Bussone, G. & Mouthon, L. (2009) Autoimmune manifestations in primary immune deficiencies. Autoimmunity reviews, Vol.8, No.4 (February 2009) ISSN 332-6

Buzzetti, R.; Di Pietro, S.; Giaccari, A.; Petrone, A.; Locatelli, M.; Suraci, C.; Capizzi, M.; Arpi, M.L.; Bazzigaluppi, E.; Dotta, F. & Bosi, E. (2007) Non Insulin Requiring Autoimmune Diabetes Study Group; High titers of auto-Abs to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. Diabetes Care, Vol.30, No.4 (April 2007) ISSN 932-8

Cantor, J. & Haskins, K. (2007) Recruitment and activation of macrophages by pathogenic CD4 T cells in type 1 diabetes: evidence for involvement of CCR8 and CCL1. Journal of immunology, Vol.179, No. 9 (November 2007) ISSN 5760-7

Catherine Pihoker, Lisa K. Gilliam, Christiane S. Hampe and Åke Lernmark; Auto-Abs in Diabetes. Diabetes. 2005 Dec;54 Suppl 2:S52-61.

Cherian, M.P.; Al-Kanani, K.A.; Al Qahtani, S.S.; Yesurathinam, H.; Mathew, A.A.; Thomas, V.S.; Mathew, A.M. & Abduljabbar, M.A. (2010) The rising incidence of type 1 Diabetes mellitus and the role of Environmental Factors - three Decade experience in a Primary health care center in Saudi Arabia. Journal of pediatric endocrinology and metabolism, Vol.23, No.7 (July 2010) ISSN 685-95

Chistiakov, D.A.; Voronova, N.V. & Chistiakov, P.A. (2008) The crucial role of IL-2/IL-2RA-mediated immune regulation in the pathogenesis of type 1 diabetes, an evidence coming from genetic and animal model studies. Immunology letters, Vol.118, No.1 (June 2008) ISSN 1-5

Classen, J.B. & Classen, D.C. (1999) Association between type 1 diabetes and Hib vaccine: causal relations is likely. BMJ (Clinical research ed.), Vol.319, No.7217 (October 1999) ISSN 1133

Concannon, C.; Rich, S.S. & Nepom, G.T. (2009) Mechanisms of Disease Genetics of Type 1A Diabetes. The new england journal o f medicine, (April 2009)

Dahlquist, G.G.; Blom, L.G.; Persson, L.A.; Sandström, A.I. & Wall, S.G. (1990) Dietary factors and the risk of developing insulin dependent diabetes in childhood. BMJ (Clinical research ed.), Vol.300, No.6735 (May 1990) ISSN 1302-6

Darrasse-Jèze, G.; Deroubaix, S.; Mouquet, H.; Victora, G.D.; Eisenreich, T.; Yao, K.H.; Masilamani, R.F.; Dustin, M.L.; Rudensky, A.; Liu, K. & Nussenzweig, M.C. (2009) Feedback control of regulatory T cell homeostasis by dendritic cells in vivo. The Journal of experimental medicine, Vol.206, No.9 (August 2009) ISSN 1853-62

Darrasse-Jèze, G.; Deroubaix, S.; Mouquet, H.; Victora, G.D.; Eisenreich, T.; Yao, K.H.; Masilamani, R.F.; Dustin, M.L.; Rudensky, A.; Liu, K. & Nussenzweig, M.C. (2009) Feedback control of regulatory T cell homeostasis by dendritic cells in vivo. The Journal of experimental medicine, Vol.206, No.9 (August 2009) ISSN 1853-62

De Block, C.E.; De Leeuw, I.H. & Van Gaal, L.F. (1999) High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. The Journal of clinical endocrinology and metabolism, Vol.84, No.11 (November 1999) ISSN 4062-7

Dendrou, C.A. & Wicker, L.S. (2008) The IL-2/CD25 pathway determines susceptibility to T1D in humans and NOD mice. Journal of clinical immunology, Vol.28, No.6 (November 2008) ISSN 685-96

Dendrou, C.A. & Wicker, L.S. (2008) The IL-2/CD25 pathway determines susceptibility to T1D in humans and NOD mice. Journal of clinical immunology, Vol.28, No.6 (November 2008) ISSN 685-96

DeStefano, F.; Mullooly, J.P. & Okoro, C.A. et al (2001) Childhood vaccinations, vaccination timing and risk of type 1 diabetes mellitus. Pediatrics, Vol.108, No.6 (December 2001) ISSN E112

Dorman, J.S.; Steenkiste, A.R.; Burke, J.P. & Songini, M. (2003) Type 1 diabetes and multiple sclerosis: together at last. Diabetes Care, Vol.26, No.11 (2003) ISSN 3192-3

Douroudis K, Shcherbakova A, Everaus H, Aints A.; PTPN22 gene regulates natural killer cell proliferation during *in vitro* expansion.; Tissue Antigens. 2010 May 30

Douroudis, K.; Nemvalts, V.; Rajasalu, T.; Kisand, K. & Uibo, R. (2009) The CD226 gene in susceptibility of type 1 diabetes. Tissue Antigens, Vol.74, No.5 (November 2009) ISSN 417-9

Douroudis, K.; Shcherbakova, A.; Everaus, H. & Aints, A. (2010) PTPN22 gene regulates natural killer cell proliferation during in vitro expansion. Tissue antigens, Vol.76, No.4 (May 2010) ISSN 315-8

Downes, K.; Pekalski, M.; Angus, K.L.; Hardy, M.; Nutland, S.; Smyth, D.J.; Walker, N.M.; Wallace, C. & Todd, J.A. (2010) Reduced expression of IFIH1 is protective for type 1 diabetes. Public Library of Science one, Vol.5, No.9 (September 2010) ISSN e12646

Essien, A.D. & Akpan, J.O. (2006) Diabetogenic property of charred meat on litters of pregnant albino rats. Nigerian journal of physiological sciences : official publication of the Physiological Society of Nigeria, Vol.21, No.1-2 (June 2006) ISSN 37-41

Ethan Rubinstein MD (2004) Vaccination and Autoimmune Diseases: the Argument Against. IMAJ Vol.6 (July 2004); 6:433-435

Faideau, B.; Larger, E.; Lepault, F.; Carel, J.C. & Boitard. C. (2005). Role of β-Cells in Type 1 Diabetes Pathogenesis. Diabetes, Vol. 54, No.2, (December 2005) ISSN S87-S96

Favorova, O.O.; Kulakova, O.G. & Boĭko, A.N. (2010) Multiple sclerosis as a polygenic disease: an update. Genetika, Vol.46, No.3 (March 2010) ISSN 302-13

Fernando, MM.; Stevens, CR.; Walsh, EC.; De Jager, PL.; Goyette, P.; Plenge, RM.; Vyse, TJ. & Rioux, JD. (2008). Defining the role of the MHC in autoimmunity: a review and pooled analysis. Public Library of Science genetics, Vol.4, No.4, (April 2008), ISSN e1000024

Fernando, MM.; Stevens, CR.; Walsh, EC.; De Jager, PL.; Goyette, P.; Plenge, RM.; Vyse, TJ. & Rioux, JD. (2008). Defining the role of the MHC in autoimmunity: a review and pooled analysis. Public Library of Science genetics, Vol.4, No.4, (April 2008), ISSN e1000024

Ferreira, R.C.; Pan-Hammarström, Q.; Graham, R.R.; Gateva, V.; Fontán, G.; Lee, A.T.; Ortmann, W.; Urcelay, E.; Fernández-Arquero, M.; Núñez, C.; Jorgensen, G.; Ludviksson, B.R.; Koskinen, S.; Haimila, K.; Clark, H.F.; Klareskog, L.; Gregersen, P.K.; Behrens, T.W. & Hammarström, L. (2010) Association of IFIH1 and other

autoimmunity risk alleles with selective IgA deficiency. Nature genetics, Vol.42, No.9 (September 2010) ISSN 777-80

Fichna, M.; Zurawek, M.; Januszkiewicz-Lewandowska, D.; Fichna, P. & Nowak, J. (2010) PTPN22, PDCD1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Polish patients. International journal of immunogenetics, Vol.37, No.5 (October 2010) ISSN 367-72

Fourlanos, S.; Varney, M.D.; Tait, B.D.; Morahan, G.; Honeyman, M.C.; Colman, P.G. & Harrison, L.C. (2008) The rising incidence of type 1 Diabetes is accounted for by cases with Lower-Risk Human leukocyte Antigen genotypes. Diabetes Care, Vol.31, No.8 (August 2008) ISSN 1546-9

Giongo A, Gano KA, Crabb DB, Mukherjee N, Novelo LL, Casella G, Drew JC, Ilonen J, Knip M, Hyöty H, Veijola R, Simell T, Simell O, Neu J, Wasserfall CH, Schatz D, Atkinson MA, Triplett EW.; Toward defining the autoimmune microbiome for type 1 diabetes. ISME J. 2011 Jan;5(1):82-91. Epub 2010 Jul 8

Giongo, A.; Gano, K.A.; Crabb, D.B.; Mukherjee, N.; Novelo, L.L.; Casella, G.; Drew, J.C.; Ilonen, J.; Knip, M.; Hyöty, H.; Veijola, R.; Simell, T.; Simell, O.; Neu, J.; Wasserfall, C.H.; Schatz, D.; Atkinson, M.A. & Triplett, E.W. (2011) Toward defining the autoimmune microbiome for type 1 diabetes. The ISME journal, Vol.5, No.1 (January 2011) ISSN 82-91

Giuliani, L.; Mele, R.; Di Giovine, M.; Altieri, L.; Crinò, A.; Ravà, L. & Fierabracci. A. (2009) Detection of GAD65 autoreactive T-cells by HLA class I tetramers in type 1 diabetic patients. Journal of biomedicine & biotechnology, (2009) ISSN 576219

Green, E.A.; Eynon, E.E. & Flavell, R.A. (1998) Local expression of TNFalpha in neonatal NOD mice promotes diabetes by enhancing the presentation of islet antigens. Immunity, Vol.9, No.5 (November 1998) ISSN 733-43

Grey, S.T.; Longo, C.; Shukri, T.; Patel, V.I.; Csizmadia, E.; Daniel, S.; Arvelo, M.B.; Tchipashvili, V. & Ferran, C. (2003). Genetic engineering of a suboptimal islet graft with A20 preserves beta cell mass and function. The Journal of immunology, Vol.170, No.12 (June 2003) ISSN 6250-6

Hafler, J.P.; Maier, L.M.; Cooper, J.D.; Plagnol, V.; Hinks, A.; Simmonds, M.J.; Stevens, H.E.; Walker, N.M.; Healy, B.; Howson, J.M.; Maisuria, M.; Duley, S.; Coleman, G. & Gough, S.C. (2009) CD226 Gly307Ser association with multiple autoimmune diseases. Genes and immunity, Vol.10, No.1 (January 2009) ISSN 5-10

Hanifi-Moghaddam, P.; Schloot, N.C.; Kappler, S.; Seissler, J. & Kolb, H. (2003) An Association of Autoantibody Status and Serum Cytokine Levels in Type 1 Diabetes. Diabetes, Vol.52, No.5 (May 2003) ISSN 1137-42

Hayashi, T.; Hasegawa, K.; Morimoto, M. & Onodera, T. (2003) Effect of antibodies to intercellular adhesion molecule (ICAM)-1 and lymphocyte function-associated antigen (LFA)-1 on cytokine mRNA expression in reovirus type-2-triggered autoimmune insulitis in suckling DBA/1 mice. Journal of comparative pathology, Vol.128, No.4 (May 2003) ISSN 283-8

Hayashi, T.; Morimoto, M.; Iwata, H. & Onodera, T. (1998) Interferon-gamma plays a role in pancreatic islet-cell destruction of reovirus type 2-induced diabetes-like syndrome in DBA/1 suckling mice. International journal of experimental pathology, Vol.79, No.5 (October 1998) ISSN 313-20

Heli T.A. Siljander, Satu Simell, Anne Hekkala, Jyrki Lähde, Tuula Simell, Paula Vähäsalo, Riitta Veijola, Jorma Ilonen, Olli Simell and Mikael Knip; Predictive Characteristics

of Diabetes-Associated Auto-Abs Among Children With HLA-Conferred Disease Susceptibility in the General Population; December 2009 2835-2842

Hermann, R.; Lipponen, K.; Kiviniemi, M.; Kakko, T.; Veijola, R.; Simell, O.; Knip, M. & Ilonen, J. (2006) Lymphoid tyrosine phosphatase (LYP/PTPN22) Arg620Trp variant regulates insulin autoimmunity and progression to type 1 diabetes. Diabetologia, Vol.49, No.6 (June 2006) ISSN 1198-208

Herrath, M.; Sanda, S. & Herold, K. (2007). Opinion Type 1 diabetes as a relapsing-remitting desease? Nature reviews. Immunology. Vol.7, No.12, (December 2007), ISSN 988-94

Hilger, C.; Grigioni, F.; De Beaufort, C.; Michel, G.; Freilinger, J. & Hentges, F. (2001) Differential binding of IgG and IgA antibodies to antigenic determinants of bovine ser&um albumin. Clinical and experimental immunology, Vol.123, No.3 (March 2001) ISSN 387-94

Hirasawa, K.; Jun, H.S.; Han ,H.S.; Zhang, M.L.; Hollenberg, M.D. & Yoon, J.W. (1999) Prevention of encephalomyocarditis virus-induced diabetes in mice by inhibition of the tyrosine kinase signalling pathway and subsequent suppression of nitric oxide production in macrophages. Journal of virology, Vol.73, No.10 (October 1999) ISSN 8541-8

Hodgkinson, A.D.; Millward, B.A. & Demaine, A.G. (2000). The HLA-E locus is associated with age at onset and susceptibility to type 1 diabetes mellitus. Human immunology, Vol.63, No.3 (March 2000), ISSN 290-5

Hoffmann, A. & Baltimore, D. (2006) Circuitry of nuclear factor kappaB signaling. Immunological reviews, Vol.210 (April 2006) ISSN 171-86

Hongjie Wang, Yulan Jin, M. V. Prasad Linga Reddy, Robert Podolsky, Siyang Liu, Ping Yang, Bruce Bode, John Chip Reed, R. Dennis Steed, Stephen W. Anderson, Leigh Steed, Diane Hopkins, Yihua Huang, Jin-Xiong She. Genetically Dependent ERBB3 Expression Modulates Antigen Presenting Cell Function and Type 1 Diabetes Risk PLoS One. 2010 Jul 26;5(7):e11789

Howson, J.M.; Walker, N.M.; Clayton, D. & Todd, J.A. (2009) Confirmation of HLA class II independent type 1 diabetes associations in the major histocompatibility complex including HLA-B and HLA-A. Diabetes, obesity & metabolism, Suppl 1, (February 2009) ISSN 31-45

Hunger-Battefeld, W.; Fath, K.; Mandecka, A.; Kiehntopf, M.; Kloos, C.; Müller, U.A. & Wolf, G. (2009) [Prevalence of polyglandular autoimmune syndrome in patients with diabetes mellitus type 1]. [Article in German] Medizinische Klinik, Vol.104, No.3 (March 2009) ISSN 183-91

Jiang, H.; Canfield, S.M.; Gallagher, M.P.; Jiang, H.H.; Jiang, Y.; Zheng, Z. & Chess. L. (2010). HLA-E-restricted regulatory CD8(+) T cells are involved in development and control of human autoimmune type 1 diabetes. The Journal of clinical investigation, Vol. 120, No.10 (October 2010) ISSN 3641-50

Jun, H.S. & Yoon, J.W. (2001) The role of viruses in type I diabetes: two distinct cellular and molecular pathogenic mechanisms of virus-induced diabetes in animals. Diabetologia, Vol.44, No.3 (March 2001) ISSN 271-85

Kakleas, K.; Paschali, E.; Kefalas, N.; Fotinou, A.; Kanariou, M.; Karayianni, C. & Karavanaki, K. (2009) Factors for thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus. Upsala journal of medical sciences, Vol.114, No.4 (2009) ISSN 214-20

Karvonen, M.; Cepaitis, Z. & Toumilheto, J. (1999) Association between type 1 diabetes and Haemophilus influenza type B vaccination: birth cohort study. BMJ (Clinical research ed.), Vol.318, No.7192 (May 1999) ISSN 1169-72

Katona-Dureković, A. (2007) The role of virus infections in the pathogenesis of type 1 diabetes--a case report. Medicinski pregled, Vol.60, No.7-8 (July 2007) ISSN 397-400

Kawasaki, E.; Nakamura, K.; Kuriya, G.; Satoh, T.; Kuwahara, H.; Kobayashi, M.; Abiru, N.; Yamasaki, H. & Eguchi. K. (2010) Autoantibodies to insulin, insulinoma-associated antigen-2, and zinc transporter 8 improve the prediction of early insulin requirement in adult-onset autoimmune diabetes. The Journal of clinical endocrinology and metabolism, Vol. 95, No.2 (February 2010) ISSN 707-13

Kim, S.J.; Jeong, D.G.; Jeong, S.K.; Yoon, T.S. & Ryu, S.E. (2007) Crystal structure of the major diabetes autoantigen insulinoma-associated protein 2 reveals distinctive immune epitopes. Diabetes, Vol.56, No.1 (January 2007) ISSN 41-8

Kohno, T.; Kobashiri, Y.; Sugie, Y.; Takai, S.; Watabe, K.; Kaino, Y. & Kida, K. (2002) Antibodies to food antigens in Japanese patients with type 1 diabetes mellitus. Diabetes research and clinical practice, Vol.55, No.1 (January 2002) ISSN 1-9

Kordonouri, O.; Hartmann, R.; Charpentier, N.; Knip, M.; Danne, T. & Ilonen, J. (2010) Genetic risk markers related to diabetes-associated auto-Abs in young patients with type 1 diabetes in berlin, Germany. Experimental and clinical endocrinology and diabetes, Vol.116, No.4 (April 2010) ISSN 245-9

Lee, M.H.; Lee, W.H.; Todorov, I. & Liu, C.P. (2010) CD4+ CD25+ regulatory T cells prevent type 1 diabetes preceded by dendritic cell-dominant invasive insulitis by affecting chemotaxis and local invasiveness of dendritic cells. The Journal of immunology : official journal of the American Association of Immunologists, Vol.185, No.4 (August 2010) ISSN 2493-501

Lipponen, K.; Gombos, Z.; Kiviniemi, M.; Siljander, H.; Lempainen, J.; Hermann, R.; Veijola, R.; Simell, O.; Knip, M. & Ilonen, J. (2010). Effect of HLA class I and class II alleles on progression from autoantibody positivity to overt type 1 diabetes in children with risk-associated class II genotypes. Diabetes, Vol.59, No.12, (December 2010) ISSN 3253-6

Liu, Y.; Stanford, S.M.; Jog, S.P.; Fiorillo, E.; Orrú, V.; Comai, L. & Bottini, N. (2009) Regulation of lymphoid tyrosine phosphatase activity: inhibition of the catalytic domain by the proximal interdomain. Biochemistry, Vol.48, No.31 (August 2009) ISSN 7525-32

Liuwantara, D.; Elliot, M.; Smith, M.W.; Yam, A.O.; Walters, S.N.; Marino, E.; McShea, A. & Grey, S.T. (2006) Nuclear factor-kappaB regulates beta-cell death: a critical role for A20 in beta-cell protection. Diabetes, Vol. 55, No.9 (September 2006) ISSN 2491-501

Martinov L.A., Salafet O.V., Kimova M.V., O. Neuhaus., Y. Shoenfeld., M.A. Paltsev., S.V. Suchkov (2010) The demyelination phenomenon and control over its progression: basic preventive protocols of the future.; Efferent and physico-chemical medicine.; (February 2010) pp. 47-52

Mayr, A.; Schlosser, M.; Grober, N.; Kenk, H.; Ziegler, A.G.; Bonifacio, E. & Achenbach, P. (2007) GAD Autoantibody Affinity and Epitope Specificity Identify Distinct Immunization Profiles in Children at Risk for Type 1 Diabetes. Diabetes, Vol.56, No.6 (June 2007) ISSN 1527-33

Metz, T.O.; Qian, W.J.; Jacobs, J.M.; Gritsenko, M.A.; Moore, R.J.; Polpitiya, A.D.; Monroe, M.E.; Camp, D.G.; Mueller, P.W. & Smith, R.D. (2008) Application of proteomics in the discovery of candidate protein biomarkers in a diabetes autoantibody

standardization program sample subset. Journal of proteome research, Vol.7, No.2 (February 2008) ISSN 698-707

Noble, J.A.; Valdes, A.M.; Varney, M.D.; Carlson, J.A.; Moonsamy, P.; Fear, A.L.; Lane, J.A.; Lavant, E.; Rappner, R.; Louey, A.; Concannon, P.; Mychaleckyj, J.C. & Erlich, H.A. (2010). HLA class I and genetic susceptibility to type 1 diabetes: results from the Type 1 Diabetes Genetics Consortium. Diabetes, Vol.59, No.11 (November 2010), ISSN 2972-9

Oresic, M.; Simell, S.; Sysi-Aho, M.; Näntö-Salonen, K.; Seppänen-Laakso, T.; Parikka, V.; Katajamaa, M.; Hekkala, A.; Mattila, I.; Keskinen, P.; Yetukuri, L.; Reinikainen, A.; Lähde, J.; Suortti, T.; Hakalax, J.; Simell, T.; Hyöty, H.; Veijola, R.; Ilonen, J.; Lahesmaa, R.; Knip, M. & Simell, O. (2008) Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes. The Journal of experimental medicine, Vol.205, No.13 (December 2008) ISSN 2975-84

Qu, H.Q. & Polychronakos, C. (2009). The effect of the MHC locus on autoantibodies in type 1 diabetes. Journal of medical genetics, Vol.46, No.7 (July 2009), ISSN 469-71

Rajasalu, T.; Haller, K.; Salur, L.; Kisand, K.; Tillmann, V.; Schlosser, M. & Uibo, R. (2007) Insulin VNTR I/III genotype is associated with autoantibodies against glutamic acid decarboxylase in newly diagnosed type 1 diabetes. Diabetes/metabolism research and reviews, Vol.23, No.7 (October 2007) ISSN 567-71

Riachy, R.; Vandewalle, B.; Kerr Conte, J.; Moerman, E.; Sacchetti, P.; Lukowiak, B.; Gmyr, V.; Bouckenooghe, T.; Dubois, M. & Pattou, F. (2002). 1,25-dihydroxyvitamin D3 protects RINm5F and human islet cells against cytokine-induced apoptosis: implication of the antiapoptotic protein A20. Endocrinology. Vol.143, No.12 (December 2002) ISSN 4809-19

Saukkonen, T.; Virtanen, S.M.; Karppinen, M.; Reijonen, H.; Ilonen, J.; Räsänen, L.; Akerblom, H.K. & Savilahti, E. (1998) Significance of cow's milk protein antibodies as risk factor for childhood IDDM: interactions with dietary cow's milk intake and HLA-DQB1 genotype . Childhood Diabetes in Finland Study Group. Diabetologia, Vol.41, No.1 (January 2998) ISSN 72-8

Sepiashvili R.I., Kimova M.V., Kalinina E.V., Martinov L.A., D.S. Kostyushev., Y.Shoenfeld, Suchkov S.V (2010) Antibodies in the pathogenesis of demyelinating autoimmune diseases. Allergology and Immunology.; Vol. 11 No.1 pp. 20-30

Severinski, S.; Banac, S.; Severinski, N.S.; Ahel, V. & Cvijović, K. (2009) Epidemiology and clinical characteristics of thyroid dysfunction in children and adolescents with type 1 diabetes. Collegium antropologicum, Vol.33, No.1 (March 2009) ISSN 273-9

Siljander, H.T.; Simell, S.; Hekkala, A.; Lähde, J.; Simell, T.; Vähäsalo, P.; Veijola, R.; Ilonen, J.; Simell, O. & Knip, M. (2009) Predictive characteristics of diabetes-associated autoantibodies among children with HLA-conferred disease susceptibility in the general population. Diabetes, Vol. 58, No.12 (December 2009) ISSN 2835-42

Solomon, M.; Balasa, B. & Sarvetnick, N. (2010) CCR2 and CCR5 chemokine receptors differentially influence the development of autoimmune diabetes in the NOD mouse. Autoimmunity, Vol.43, No.2 (March 2010) ISSN 156-63

Somers, E.C.; Thomas, S.L.; Smeeth, L. & Hall, A.J. (2009) Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder? American journal of epidemiology, Vol.169, No.6 (March 2009) ISSN 749-55

Suchkov.; L.A. Martynov.; I.A. Vinokurov.; D.S. Kostyushev.; A.A. Andreeva.; S.I. Gadzhieva.; D.A. Gnatenko.; Y. Shoenfeld.; Y.M. Lopuhin.; A. Notkins.; M.A.

Paltsev (2010) On the prospects of preclinical diagnostics within the objectives of preventive and predictive medicine. Efferent and Physico-Chemical medicine.; (March 2010)

Svejgaard, A. (2008) The immunogenetics of multiple sclerosis. Immunogenetics, Vol.60, No.6 (June 2008) ISSN 275-86

Taniyama, M.; Maruyama, T.; Tozaki, T.; Nakano, Y. & Ban, Y. (2010) Association of PTPN22 haplotypes with type 1 diabetes in the Japanese population. Human immunology, Vol.71, No.8 (August 2010) ISSN 795-8

Tavares, R.M.; Turer, E.E.; Liu, C.L.; Advincula, R.; Scapini, P.; Rhee, L.; Barrera, J.; Lowell, C.A.; Utz, P.J.; Malynn, B.A & Ma, A. (2010) The ubiquitin modifying enzyme A20 restricts B cell survival and prevents autoimmunity. Immunity, Vol.33, No.2 (August 2010) ISSN 181-91

Thrower, B.W. (2007) Clinically isolated syndromes: predicting and delaying multiple sclerosis. Neurology, Vol.68, No.24 (June 2007) ISSN S12-5

Tsai, S.J.; Sen, U.; Zhao, L.; Greenleaf, W.B.; Dasgupta, J.; Fiorillo, E.; Orrú, V.; Bottini, N. & Chen, X.S. (2009) Crystal structure of the human lymphoid tyrosine phosphatase catalytic domain: insights into redox regulation. Biochemistry, Vol.48, No.22 (June 2009) ISSN 4838-45

Valdes, A.M. & Thomson, G. (2006). Several loci in the HLA class III region are associated with T1D risk after adjusting for DRB1-DQB1. Diabetes, obesity & metabolism, Vol.11, No.1, (February 2006) ISSN 46-52

Viken, M.K.; Blomhoff, A.; Olsson, M.; Akselsen, H.E.; Pociot, F.; Nerup, J.; Kockum, I.; Cambon-Thomsen, A.; Thorsby, E.; Undlien, D.E. & Lie, B.A. (2009) Reproducible association with type 1 diabetes in the extended class I region of the major histocompatibility complex. Genes and immunity, Vol.10, No.4 (June 2009) ISSN 323-33

Villano, M.J.; Huber, A.K.; Greenberg, D.A.; Golden, B.K.; Concepcion, E. & Tomer, Y. (2009) Autoimmune thyroiditis and diabetes: dissecting the joint genetic susceptibility in a large cohort of multiplex families. The Journal of clinical endocrinology and metabolism, Vol.94, No.4 (April 2009) ISSN 1458-66

Werner, S.L.; Barken, D. & Hoffmann, A. (2005) Stimulus specificity of gene expression programs determined by temporal control of IKK activity. Science, Vol.309, No.5742 (September 2005) ISSN 1857-61

Wertz, I.E.; O'Rourke, K.M.; Zhou, H.; Eby, M.; Aravind, L.; Seshagiri, S.; Wu, P.; Wiesmann, C.; Baker, R.; Boone, D.L.; Ma, A.; Koonin, E.V. & Dixit, V.M. (2004) De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signaling. , Nature. Vol. 430, No.7000 (August 2004) ISSN 694-9

Williams, A.J.; Bingley, P.J.; Moore, W.P. & Gale, E.A. (2002) Islet auto-Abs, nationality and gender: a multinational screening study in first-degree relatives of patients with Type I diabetes. Diabetologia, Vol.45, No.2 (February 2002) ISSN 217-23

Witas, H.W.; Jedrychowska-Dańska, K. & Zawicki, P. (2010) Changes in frequency of IDDM-associated HLA DQB, CTLA4 and INS alleles. International journal of immunogenetics, Vol.37, No.3 (June 2010) ISSN 155-8

Yamaji, K.; Ikegami, H.; Fujisawa, T.; Noso, S.; Nojima, K.; Babaya, N.; Itoi-Babaya, M.; Kobayashi, M.; Hiromine, Y.; Makino, S. & Ogihara. T. (2006). Contribution of class III MHC to susceptibility to type 1 diabetes in the NOD mouse. Annals of the New York Academy of Sciences, (October 2006) ISSN 114-7
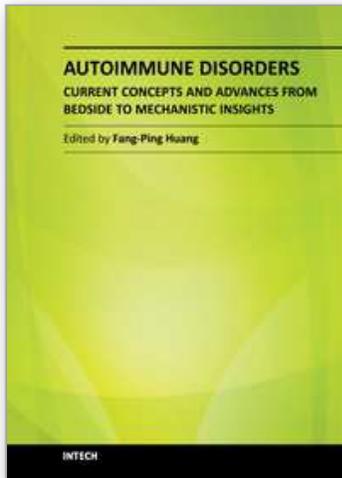
Autoimmune Disorders - Current Concepts and Advances from Bedside to Mechanistic Insights

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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