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VARIOUS CHROMATIN AND NUCLEAR MATRIX PROTEINS AS AUTOANTIGENS: A POSSIBLE LINK TO THE PROTEIN DEGRADATION MECHANISMS

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MINI-REVIEW

ABSTRACT. DEVELOPMENT OF autoantibodies to DNA and nuclear proteins is a characteristic feature of several autoimmune diseases. These are widely used in clinical practice for diagnostic purposes and are known as "nuclear antigens" or "extractable nuclear antigens" as autoantibodies to given nuclear protein or group of proteins appear to be disease-specific. It was suggested that autoantoibodies to nuclear proteins develop in the case when the nuclear proteins are degraded in ubiquitin-proteasome system. To our opinion hereditary individual peculiarities of the proteasomal proteins can also provoke development of nuclear autoantibodies. Data on associations of autoimmune diseases with proteasome gene polymorphism confirm our point of view. The present review summarizes data on development of autoantibodies to groups of nuclear proteins and individual proteins (histones, HMG-proteins, transcriptions factors, RNP proteins, nuclear envelope and nuclear matrix proteins) in patients with autoimmune diseases. Data on proteasomal degradation of nuclear proteins and polymorphism of the ubiquitin-proteasome system in humans are discussed in context of the above hypothesis.

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INTRODUCTION

Development of autoantibodies to DNA and nuclear proteins is a characteristic feature of several autoimmune diseases. These are widely used in clinical practice for diagnostic purposes and are known as “nuclear antigens” or “extractable nuclear antigens”. The increasing data on autoantigens to individual nuclear proteins enables to evaluate the role of these antibodies in pathogenesis of various autoimmune diseases. In the present review we will summarize data on antibodies to individual nuclear proteins or functional groups of the nuclear proteins found in patients with autoimmune diseases. Eventual mechanism of the nature of the phenomenon will be also discussed.

FIG. 1 presents a simplified scheme of the nucleus. The whole organelle is covered with nuclear envelope, the nuclear lamina and nuclear pores being the most important components of the structure. The inner space of the nucleus is structured by the inner nuclear matrix fibrils. The latter with the lamina and residual nucleoli are considered to form the nucleoskeleton, or nuclear matrix. The nuclear matrix contains proteins that contribute to the preservation of nuclear shape and its organization, many enzymes, including enzymes of DNA replication, repair and transcription, numerous transcription factors [1,2]. Chromatin loops formed of “beads on a string” nucleosome structures formed by histones are attached to the nuclear matrix fibrils. Replication occurs in the sites of chromatin loop attachment to the nuclear matrix, but transcription sites harbouring transcription enzymes and regulatory factors are localized in along the loops, often in contact with the nuclear matrix fibrils. RNA processing enzymes form specific particles. We will analyze data on the autoantibody incidence to these groups of the nuclear proteins below. Early reports on the problem have been reviewed previously [3].

HISTONES AND OTHER PROTEINS OF NUCLEOSOMES

Anti-nucleosome (anti-chromatin) antibodies play a key role in the pathogenesis of systemic lupus erythematosus (SLE). Anti-chromatin antibodies are found more often in SLE patients as compared to anti-histone antibodies, apparently, other chromatin proteins than histones give rise to autoantibodies [4]. However existence of specific autoantibodies to histones is considered to be crucial for development of the lupus nephritis. The strongly cationic histone has been proposed as a potential "planted antigen"; it would decorate the glomerular basement membrane to function as a ligand for DNA in the DNA-immune complex. A specific anomalous IgG binds nucleosomes in lupus patients [5]. The dominant nucleosomal epitopes that are critical for cognate interactions between autoimmune T-helper cells and anti-DNA B cells in lupus have been identified. By scanning of overlapping synthetic peptides, and by mass spectrometry of naturally processed peptides, five major epitopes in nucleosomal histones were localized, namely H1'(22–42), H2B(10–33), H3(85–105), H4(16–39), and H4(71–94). The autoimmune T cells as well as B cells of lupus recognize these epitopes, and with age, autoantibodies against the peptide epitopes cross-react with nuclear autoantigens [6]. Knowledge of autoantigenic epitopes enables elaboration of the lupus treatment strategies based on nasal application of histone peptides [7]. H1 antibodies are the most specific marker for SLE [8]. H1'(22-42) epitope is much more potent than other nucleosomal epitopes in accelerating glomerulonephritis in lupus-prone (SWR×NZB)F(1) mice [abbreviated as SNF(1) mice] [9]. Insufficient repair of H2b histone and accumulation of isoaspartate in complex with this protein contribute to autoantigenicity of this histone [10].

Autoantibodies to histones are found also in patients with other autoimmune pathologies, not exclusively in SLE patients. For example, anti-histone autoantibodies were observed in beta-thalassemia major patients receiving iron chelators [11], autoimmune hepatitis [12]. Antihistone antibodies, predominantly anti-H1 antibodies are found in blood sera of some (17%) patients with polymyositis/dermatomyositis [13]. Injection of histone H1 suppresses development of collagen-induced arthritis in mice [14].

Antibody to Japanese encephalitis virus recog-

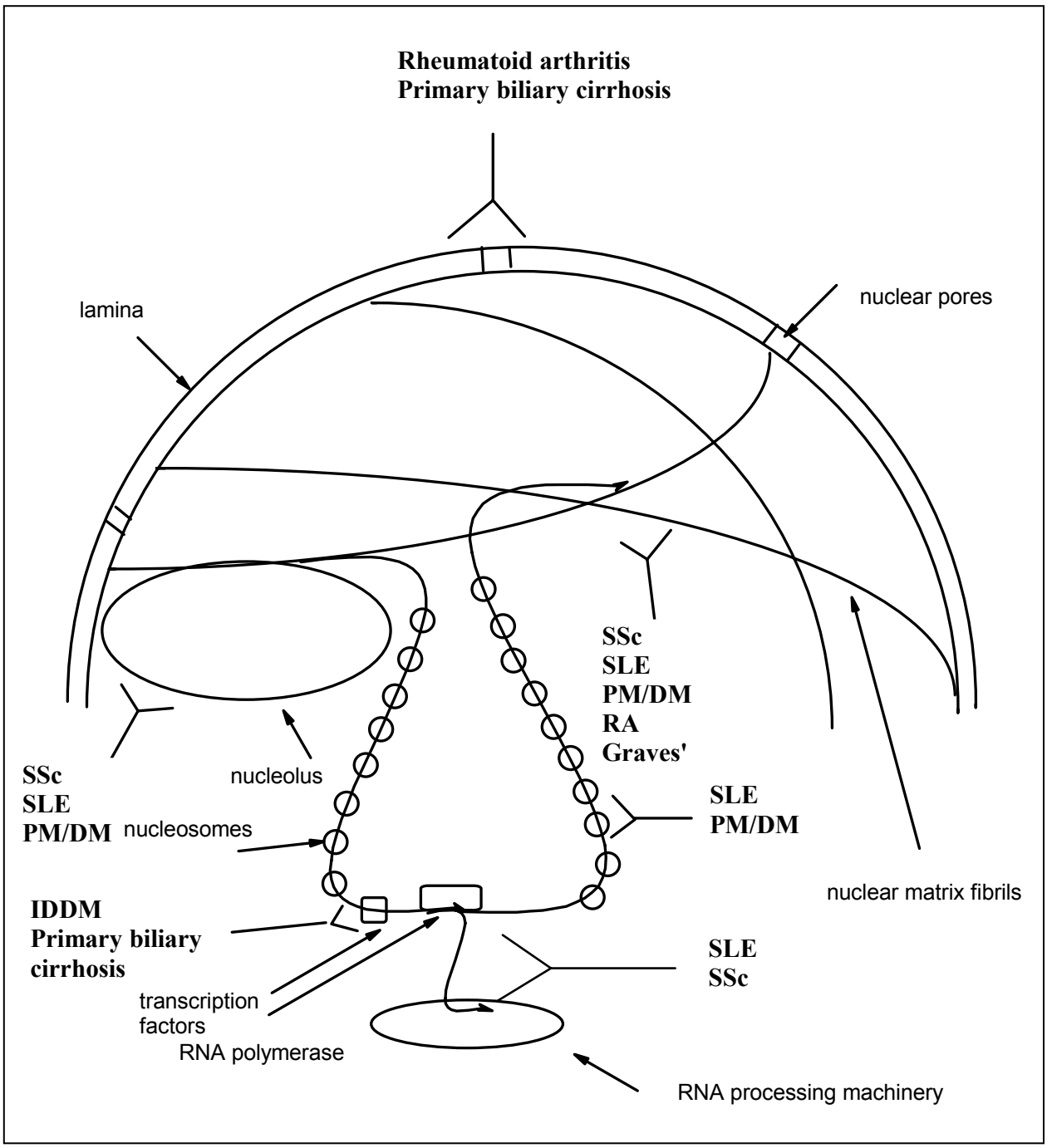

FIGURE 1. SCHEME OF THE STRUCTURE OF THE CELL NUCLEUS WITH INDICATION OF AUTOANTIGENIC PROTEINS FOR SOME DISEASES. Arrows indicate nuclear structures given in standard font. Names of pathologies are given in bold script. Autoantigenic proteins are indicated by "forks", simplified presentation of antibodies.

ABBREVIATIONS: SSc, systemic sclerosis; SLE, systemic lupus erythematosus; IDDM, insulin-dependent diabetes mellitus; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis.

nizes a cross-reactive epitope on nuclear histones, this feature of the antibody can trigger an autoimmune process [15]. In a similar way termination of human T cell tolerance to histones proceeds via presentation of histones and polyomavirus T when T antigen is complexed with nucleosomes [16].

HISTONE-MODIFYING ENZYMES

An autoantibody Anti-Mi-2, directed against an SNF2-superfamily helicase associated with the nucleosome remodeling and histone acetylation and deacetylation complex is characteristic of dermatomyositis [17].

HMG PROTEINS AND TRANSCRIPTION FACTORS

HMG group proteins take part in the chromatin structure alterations necessary for transcription, transcription factors are proteins that bind specific DNA sequences and trigger transcription of given genes in specific manner. Thus both groups of the proteins take part in regulation of transcription on different levels.

HMG-17 protein shares similar epitope with histone H1, thus autoantibodies to these chromatin proteins develop simultaneously [18]. Autoantibodies to HMG-17 were found in systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) and pauciarticular juvenile rheumatoid arthritis (JRA), but not in rheumatoid arthritis (RA). PKPEPKPK as the major epitope recognized by more than 70% of the HMG-17 positive JRA sera [19]. Anti-HMG-17 antibodies occur in one third of scleroderma patients, do not discriminate scleroderma variants and are not associated with other autoantibodies [20]. In patients with drug-induced lupus antibodies to the nucleosomal core HMGs (HMG-14 and HMG-17) occur more often than antibodies to HMG-1 and HMG-2 [21].

HMG1 and HMG2 are significant target antigens of perinuclear anti-neutrophil cytoplasmic antibodies in autoimmune hepatitis [22]. Autoantibodies against the nuclear high mobility group (HMG) protein SSRP1 is often found in sera from patients with systemic lupus erythematosus, but not other rheumatic diseases [23].

Among autoantibodies to transcription factors anti-SOX13 appear to be the most important in pathogenesis of autoimmune disease. SOX13 is a member of the SOX family of transcriptional regulatory proteins that contain a high mobility group (HMG) motif with structural similarity to HMG proteins 1 and 2. The molecule SOX13 was initially identified as an autoantigen (ICA12) in Type 1 diabetes [24]. Among the Latvian insulin-dependent *diabetes mellitus* (IDDM) patients ICA12 antibodies were found in 30% of the cases [25], in the Swedish population this autoantibody is identified in 9.8% of the cases [26]. Incidence of the antibodies depends of the MHC antigen expression in the patients. In the Indian population ICA 12 antibodies were increased in either DR3 or DR4 positive IDDM patients compared to non-DR3/DR4 IDDM patients. However in latent autoimmune diabetes of adults (LADA) patients ICA 12 is associated with non-DR3/DR4 patients [27]. Among the German patients SOX-13 antibodies are present in 8.8% of patients with newly diagnosed Type I diabetes and in 7.0% patients with latent autoimmune diabetes of adults [28]. Thus it appears to be a minor antigen for IDDM and LADA.

In primary biliary cirrhosis patients anti-SOX13 was detected in 18% of the cases. Anti-HMG1 and anti-HMG2 occur at frequencies of 30% and 35% respectively [29].

RNA TRANSCRIPTION AND PROCESSING ENZYMES

The spliceosomal Sm proteins are recognized by the so-called anti-Sm autoantibodies, an antibody population found exclusively in patients suffering from systemic lupus erythematosus. One of the Sm proteins, the Sm-F protein, is proteolytically cleaved in apoptotic cells, thus dying cells could be a potential reservoir of modified autoantigens that might initiate and drive systemic autoimmunity in susceptible hosts [30]. The U1 snRNP autoantigen is also modified during apoptosis [31]. Autoantibodies to the U1 snRNP are often found in SLE

patients, development of these antibodies is probably associated with cytomegalovirus infedtion [32]. Antibodies recognize the RNA-binding domain of the protein [33]. In patients with systemic sclerosis anti-U1 RNP antibodies are related to a high prevalence of arthritis and myositis, a low prevalence of calcinosis, and early disease onset [34].

The La (SS-B) autoantibody found in SLE an SSc patient recognizes a protein that is co-localized with splicesomes [35]. La protein is rapidly dephosphorylated and cleaved during the apoptosis [36]. The protein is considered to be a RNA chaperone, it interacts with a RNA-helicase [37]. Anti-SSB/La antibody develops in women with silicone breast implants [38].

An RNA-binding protein, the Ro 60 kDa autoantigen, is a major target of the immune response in patients suffering from two systemic rheumatic diseases, systemic lupus erythematosus and Sjogren's syndrome. In lupus patients, anti-Ro antibodies are associated with photosensitive skin lesions and with neonatal lupus, a syndrome in which mothers with anti-Ro antibodies give birth to children with photosensitive skin lesions and a cardiac conduction defect, third degree heart block. In vertebrate cells, the Ro protein binds small RNAs of unknown function known as Y RNAs. Although the cellular function of Ro has long been mysterious, recent studies have implicated Ro in two distinct processes: small RNA quality control and the enhancement of cell survival following exposure to ultraviolet irradiation. Most interestingly, mice lacking the Ro protein develop an autoimmune syndrome that shares some features with systemic lupus erythematosus in patients, suggesting that the normal function of Ro may be important for the prevention of this autoimmune disease [39]. The anti-Ro autoantibodies are found in almost all patients with neonatal lupus [40]. The Ro-60 kDa knockout mice develop lupus-like syndrome [41].

The exosome is a complex of 3'→5' exoribonucleases that functions in a variety of cellular processes, all concerning the processing or degradation of RNA. The human autoantigenic exosome subunit PM/Scl-75 is able to associate with the exosome complex. This interaction is most likely mediated by protein-protein interactions with two other exosome subunits, hRrp46p and hRrp41p. Autonatibodies to PM/Scl-75 and to protein PM/Scl-100 with similar functions are characteristic of the polymyositis (PM)/scleroderma overlap syndrome [42,43]. It is considered that the autoimmune response is initially directed to PM/Sc1-100, whereas intermolecular epitope spreading may cause the autoantobody response directed to the associated components [44].

Topoisomerase I (TopoI, SCL-70) is one of the key enzymes in the transcription. Autoantibodies against DNA topoisomerase I are found in 30% of the systemic sclerosis patients. Presence of the topoI autoantibodies in systemic sclerosis patients is largely determined by genetic factors, as it is associated with certain HLA class II DR52 and DQB1 alleles [45,46], but severe form of the disease is associated with the DRw11 allele [47]. In patients with systemic sclerosis antitopoisomerase I antibodies were shown to be associated with a high prevalence of digital joint deformity, distal osteolysis, radiological signs of pulmonary fibrosis, a low prevalence of calcinosis and late onset of disease [34]. Autoantibodies against DNA topoisomerase I (anti-topo I) have been reported to be specific not only to systemic sclerosis (SSc), however, anti-topo I was detected in patients with silicone breast implants, SLE without features of SSc, and rheumatic diseases. Ueki et al. (2001) have detected anti-topo I positive silicosis patients without any symptoms of autoimmune diseases. The correlation between anti-topo I autoantibody responses and HLA class II has been established in this study [48]. Expression of the systemic-sclerosis specific autoantigen genes, including the topoI gene and others (fibrillarin, centromeric autoantigen) is increased in the scleroderma fibroblasts [49]. Only fragments of the topoI and not the full-length enzyme can trigger the autoimmune response [50].

NUCLEOLAR PROTEINS

Autoantibodies specifically targeting nucleolar antigens are found most frequently in patients

suffering from systemic sclerosis (SSc) or systemic sclerosis overlap syndromes. Autoantibodies directed to nucleolar RNA-protein complexes, the so-called small nucleolar ribonucleoprotein complexes (snoRNPs) appear to be the most significant. Autoantibodies directed to snoRNPs were detected not only in patients suffering from SSc and primary Raynaud's phenomenon (RP), but also in patients suffering from SLE, rheumatoid arthritis (RA) and myositis (PM/DM). Antibodies against box C/D small snoRNPs can be subdivided in antifibrillarin positive and antifibrillarin negative reactivity. Antifibrillarin-positive patient sera were associated with a poor prognosis in comparison with antifibrillarin negative (reactivity with U3 or U8 snoRNP only) patient sera. Anti-Th/To autoantibodies were associated with SSc, primary RP and SLE and were found predominantly in patients suffering from decreased co-diffusion and oesophagus motility and xerophthalmia [51].

Antibodies to nucleolar proteins-fibrillarin and NOR-90/ hUBF are often found in then Chinese hepatocellular carcinoma patients [52].

NUCLEAR LAMINA, NUCLEAR MEMBRANE AND NUCLEAR PORE PROTEINS

The nuclear envelope consists of five interconnected regions: an outer nuclear membrane that is continuous with the endoplasmic reticulum, an intermembrane or perinuclear space, an inner nuclear membrane with a unique set of integral membrane proteins, the underlying nuclear lamina, and the pore domains that are regions where the two membranes come together. The pore domains are sites of regulated continuity between the cytoplasm and nucleus that are occupied by supramolecular structures, termed nuclear pore complexes. The nuclear envelope is one of many intracellular targets of the autoimmune response in patients with autoimmune liver disease, systemic lupus erythematosus, and related conditions. Human autoantibodies identified to date bind include the lamins A, B, and C of the nuclear lamina, gp210, p62 complex proteins, Nup153, and Tpr within the pore complex, and LBR, MAN1, LAP1, and LAP2 that are integral proteins of the inner nuclear membrane (reviewed in Enarson et al., 2004). The nuclear lamina of mammalian cells consists of three major proteins, lamins A, C, and B, and a fourth minor protein, lamin B2. Lamins belong to the family of intermediate filaments and are highly similar both in structure and primary sequence. They are organized in three well-defined domains: (i) a central alpha-helical rod, which is a secondary structure shared by all types of intermediate filaments, formed by three alpha-helices (coils 1A, 1B, and 2) and surrounded by (ii) an amino-terminal head and (iii) a carboxyl-terminal tail. The ability to recognize a protein domain seemed to differ with the pathology. Chronic active hepatitis sera are reactive to two or more lamin domains and reacting SLE sera always give positive signals to coil 2 and/or coil 1B. Coil 2 was preferentially recognized by rheumatoid arthritis sera. Polymyalgia rheumatica sera differed from all of the others because of their low reactivity to the rod domain and preference for the C terminus, a lamin-specific domain [53]. The nuclear pore protein gp210 autoantibody is characteristic of primary biliary cirrhosis, it is found in 25% of the patients. Autoantibodies against a lamin-intercting protein LBR are found in some patients with primary biliary cirrhosis [54].

NUCLEAR MATRIX PROTEINS

In part, the autoimmune response in autoimmune diseases is aimed on nuclear matrix proteins. Nuclear matrix proteins are prone to degradation in early stages of apoptosis, thus nuclear matrix proteins or antibodies against them sometimes mark conditions coupled to massive cell death. This subset includes such nuclear-matrix-bound proteins as poly (ADP-ribose) polymerase, the 70-kD protein of the U1 small nuclear ribonucleoprotein particle, lamin B, the nuclear mitotic apparatus protein NuMA, DNA topoisomerases II, and the RNA polymerase I upstream binding factor UBF [55]. This makes nuclear matrix proteins valuable markers of autoimmune diseases and other pathologies coupled to massive cell death.

Sera from patients with systemic lupus erythe-

matosus, rheumatoid arthritis, Graves' disease, systemic sclerosis and mixed connective tissue disease contain significantly more nuclear matrix antibodies than sera of healthy persons [56-59]. Peptides with molecular weights of 70 kDa, 50 kDa and 25 kDa are detected the most frequently [60]. Autoantibodies react also with MARs, the "matrix attachment regions", specific AT-rich DNA sites with high affinity to the nuclear matrix proteins [61]. Human autoimmune serum contains also antibodies that recognize PML proteins), proteins of a nuclear matrix-associated body with probable roles in apoptosis, and in acute viral infections [62].

Antibodies present in sera of patients with primary biliary cirrhosis and autoimmune chronic active hepatitis react with some of the nuclear matrix proteins. The antibodies are mainly directed against chromatin-associated proteins and protein constituents of discrete RNP particles. In addition, antibodies found in autoimmune liver disease sera detect a novel nuclear matrix protein of approximately 150 kD. Antibodies recognizing a nuclear 25-kD doublet apparently constituted a marker antibody for autoimmune liver disease. Those directed at the 17 kD centromere protein were associated with the primary biliary cirrhosis-related CREST syndrome (C – calcinosis; R – Raynaud syndrome; E – eosophagitis; S – sclerodactilia; T – teleangiectasia), while those recognizing La antigen were related to cases of sicca syndrome associated with autoimmune liver diseases [63]. Autoantibody to the nuclear body protein sp100 is found in 20-30% of the primary biliary cirrhosis patients [54].

Autoantibodies to DNA topoisomerase II, a prominent nuclear matrix component, was detected in patients with primary liver cancer [64].

Nuclear matrix proteins (NMPs) are released from white blood cells during blood storage; this can lead to autoimmune response after the transfusion [65].

Heavy burns and their complications lead to increase of nuclear matrix proteins in blood serum as consequence of intensive apoptosis. In patients suffering of burns and following multiple organ dysfunction syndrome (MODS) nuclear matrix protein increases in blood serum. The NMP value in the group with MODS is significantly higher than in the group without MODS [66]. Between the patients with multiple organ dysfunction syndrome (MODS) the number of organs that failed was found to be significantly correlated with the NMP level. NMP levels in the group of patients that died significantly exceeded those in the surviving group [67]. Nuclear matrix protein levels also increase in patients with acute pancreatitis [68].

MITOTIC CHROMOSOMES

Some autoantibodies develop against proteins specific of mitotic chromosomes. It should be mentioned that in interphase some of these proteins are found in cytoplasm or are localized in some nuclear substructures (nuclear matrix, nucleoplasm, etc).

CENTROMERE PROTEINS

Anticentromere antibodies (ACA) are frequently observed in patients with Raynaud's phenomenon and in the CREST syndrome, a subclass of systemic sclerosis. Likewise, ACA are also found in other autoimmune and non-autoimmune diseases [69]. The anti-centromere-associated protein A (CENP-A) immune response is directed against an autoantigenic motif, G/A-P-R/S-R-R, that occurs three times in the N-terminal amino acids of CENP-A. Mimotopes of this motif are present in a vast number of autoantigens and in the Epstein-Barr nuclear antigen 1. Autoantibodies against this motif are polyclonal and cross-react with several autoantigens [70].

In patients with systemic sclerosis the anti-centromere antibodies were found to be related to specific symptoms of the disease: a high prevalence of calcinosis, telangiectasia, digital ulcers, acro-sclerosis, primary biliary cirrhosis, isolated reduction of pulmonary diffusing capacity, and a low prevalence of radiological evidence of pulmonary fibrosis [34]. CENP-A and CENP-B antibodies are rather often in limited systemic sclerosis, but rear in patients with diffuse systemic sclerosis [71]. An

antibody against centromeric CENP-F protein, a cell cycle-related nuclear protein with maximum expression in the G2 and M phases of the cell cycle appears during the transition period from chronic liver disease to hepatocellular carcinoma [72].

ARMS OF MITOTIC CHROMOSOMES

Autoantibodies reacting with arms of mitotic chromosomes were found in sera of patients with discoid lupus erythematosus, chronic lymphocytic leukemia, Sjogren's syndrome, and polymyalgia rheumatica [73].

REASONS FOR SPECIFICITY OF NUCLEAR ANTIGENS

Trying to summarize these abundant and apparently chaotic data we can conclude that nuclear antigens are rather specific markers of the autoimmune diseases. Apparently novel groups of nuclear antigens, nuclear matrix proteins amd lamins, for example, will be soon added to a set of antibodies used in clinical practice. Some examples are illustrated in FIG 1. The most spectacular specificity is observed in cases of SLE, when autoantibodies are developed mostly against the nucleosomal proteins and systemic sclerosis, when autoantibodies are raised against RNA processing factors, topoisomerase I and nucleolar proteins. The origins of this specificity should be sought in mechanism of degradation of different nuclear proteins. Several reports indicate that antinuclear antibodies recognize cellular autoantigens driven by apoptosis, namely the autoantibodies recognize the protein cleavage products by caspases. This was shown for U1-RNP, Jo1, topoisomerase I, CENP-B, NuMA and the RNA polymerase I upstream binding factor (UBF) [74,75]. Taken together these autoantigens represent the autoantibody spectrum found mostly in systemic sclerosis patients. On the contrary, nucleosomal proteins are degraded predominantly by the ubiquitin-proteasome system, which was convincingly shown in a series of works of A. von Mikecz and co-workers. The studies revealed, that histones, splicing factor SC35, spliceosomal components, such as U1-70k or SmB/B', and PML partially colocalize with 20S proteasomes in nucleoplasmic substructures, whereas the centromeric and nucleolar proteins topoisomerase I, fibrillarin, and UBF did not overlap with proteasomes. The specific inhibition of proteasomal processing with lactacystin induced accumulation of histone protein H2A, SC35, spliceosomal components, and PML, suggesting that these proteins are normally degraded by proteasomes. In contrast, concentrations of centromeric proteins CENP-B and CENP-C and nucleolar proteins remained constant during inhibition of proteasomes [76]. Further studies showed that also the topoisomerase I and fibrillarin are degraded by the ubiquitin-proteasome system if treated with xenobiotics (topoI inhibitor campthotecin and heavy metals). In the same time these proteins acquire autoantigenic properties [77,78]. The authors hypothesize that altered proteasomal processing of antigens, especially when enhanced by the xenobiotic treatment, is an important step of the systemic sclerosis pathogenesis [79, 80]. In our opinion, this idea can be extended by establishing a link between proteasomal degradation and heredity.

The first indication on possible role of proteasomes in development of autoimmune diseases was obtained after discovery of two genes of low molecular weight proteins in the class II Major Histocompatibility Locus. These genes named LMP2 and LMP7 were localized in the proximity of transporter genes TAP1 and TAP2. TAP1 and TAP2 proteins move the newly formed antigens to the endoplasmatic reticulum. They are considered to perform antigen processing. LMP2 and LMP7 proteins are not absolutely necessary for the antigen processing, as deletion of these genes is not lethal. However these proteins are rather important for the process. Lymphocyte induction with interferon causes replacement by LMP2 and LMP7 of two other proteasomal core proteins, MB1 and Delta (reviewed in [81]). Recently it was postulated that development of autoimmune status is largely due to deceased expression of the proteasome protein LMP2. This defect prevents the proteolytic processing required for the production and activation of the transcription factor nuclear factor-

kappaB, which plays important roles in immune and inflammatory responses, as well as increases the susceptibility of the affected cells to apoptosis induced by tumor necrosis factor-alpha [82]. The altered expression of the gene might be associated to some its alleles. High degree of LMP2 and LMP7 polymorphism was detected soon after discovery of the genes [83]. Taken in general, results of association studies on LMP gene polymorphism with autoimmune diseases remain contradictory (reviewed in [84-87]. Among many diseases studied data on juvenile rheumatoid arthritis association appear to be the most convincing. It was clearly shown that LMP2 gene polymorphism gives a strong impact on susceptibility to, and severity of HLA-B27 associated juvenile rheumatoid arthritis [88]. Several years ago we have formulated the question about eventual role of the proteasome gene polymorphism in the genetic susceptibility to autoimmune diseases. As already mentioned above, these types of studies were restricted to LMP2 and LMP7 gene polymorphism associations to autoimmune diseases. However variations of proteasome genes structure may play a significant role in the function of proteasomal assembly and have important impact in the development, progress and treatment of human disorders. Unlike the authors of preceding polymorphism studies, we have chosen "conventional", not immunity-related and highly evolutionary conserved PSMA6 gene as object of our research. The PSMA6 gene is one of the best-conserved representatives of the alpha-family, and it is encoded by a single-copy gene on chromosome 14q13.2, pseudogene named PSMA 6P is located on Y chromosome [89]. We have studied polymorphism of its intronic microsatellite [90]. Further studies showed that polymorphisms of this and several neighbouring markers are associated with Graves' disease [91]. Several single nucleotide polymorphisms (SNPs) have been described in the gene; our preliminary data indicate that one of the found alleles is associated with juvenile idiopathic arthritis. Complex nature of proteasomes (14 core proteins belonging to two families, ATPase proteins, regulators) require equilibrated expression of numerous genes. Decreased or increased expression of proteasome proteins due to inborn structural peculiarities of the genes in regulatory sequences (enhancers, silencers, insulators, untranslated regions (UTR)) usually known as intronic or UTR SNPs or microsatellites could lead to production of abnormal proteolysis products that possess autoantigenic properties. We speculate that this might be the cause of autoantigenicity of nuclear proteins in some autoimmune diseases. Vast association studies of autoimmune diseses with proteasome gene polymorphism are necessary to prove or decline our hypothesis.

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