Natural catalytic antibodies in norm, autoimmune and viral diseases

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Abstract: - In patients with autoimmune diseases (ADs) autoantibodies (Abs) directed to polysaccharides, nucleic acids, proteins, peptides, nucleoprotein complexes, and enzymes with different catalytic functions may be induced spontaneously by primary antigens and can have characteristics of the primary antigen, including the catalytic activity of idiotypic and/or antiidiotypic Abs. The discovery of IgG specifically hydrolyzing intestinal vasoactive peptide in the sera of asthma patients (Paul S., 1989) stimulated of the studies of natural catalytic Abs (abzymes; Abzs). Detection of Abzs was shown to be the earliest indicator of development of different ADs. At the early stages of ADs, the repertoire of Abzs is usually relatively small but it greatly increases with the progress of the disease, leading to the generation of catalytically diverse abzymes with different activities and functions. Some Abzs are cytotoxic and can play an important negative role in the pathogenesis of AI pathologies, while positive roles have been proposed for other abzymes.During the spontaneous development of profound SLE-like pathology in mice, a specific reorganization of the immune system leads to conditions associated with production of Abzs with low catalytic activities (conditionally pre-diseased mice). A significant increase in the relative Abz activities associated with a transition from pre-diseased to diseased mice is correlated with additional changes in the differentiation and proliferation of bone marrow hematopoietic stem cells and lymphocyte proliferation in different organs. Different mechanisms of Abzs production are observed for healthy mice immunized externally and for autoimmune mice during the spontaneous development of pathology. New data concerning Abzs with different catalytic activities in various ADs, possible reasons of their catalytic heterogeneity, possible roles of abzymes and their exceptional multiplicity in the pathogenesis of different ADs, and possible uses of the abzyme activity for diagnostic of AI diseases are discussed.

Key-Words: - Key-Words: - Natural abzymes; healthy donors; autoimmune, viral, diseases

1 Introduction

Traditionally, antibodies (Abs) have been characterized as proteins produced by the immune system, which have the sole function of binding other molecules, called antigens (AG), with the goal of eliciting an immune response. In 1986, two groups were able to produce the first artificial monoclonal Abs with catalytic properties, which were generated against hapten analogs of the transition states for *p*-nitrophenylphosphorylcholine or for monoaryl phosphonate esters (reviewed in [1-5]). These catalytic Abs were termed abzymes (derived from antibody enzyme). Artificial Abzs against transition states of reactions catalyzing more than 100 distinct chemical reactions are novel biological catalysts that attracted much interest in the past years (for review see [1-5]).

2 Problem Formulation

New data concerning Abzs with different catalytic activities in various autoimmune diseases (Ads), possible reasons of their catalytic heterogeneity, possible roles of abzymes and their exceptional multiplicity in the pathogenesis of different ADs, and possible uses of the abzyme activity for diagnostic of AI diseases are discussed.

3 Problem Solution

The origin of natural abzymes

The development of ADs is characterized by spontaneous generation of primary Abs to proteins, nucleic acids and their complexes, polysaccharides, nucleotides etc. [1-5]. The first example of a natural Abz was an IgG found in bronchial asthma patients, which hydrolyzes vasoactive intestinal peptide (VIP; Paul S., 1989), the second was an IgG with DNase activity in systemic lupus erythematosus (SLE), and the third was an IgG with RNase activity in SLE [1-5]. Later, a number of natural catalytic IgG, IgA, and IgM hydrolyzing DNA, RNA, nucleotides, and polysaccharides were detected in the sera of patients with several ADs and viral pathologies [1-5]). The origin of natural Abzs in different AI diseases is complex. Similarly to artificial Abzs against analogs of transition states of catalytic reactions, naturally occurring Abzs may be Abs raised directly against the enzyme substrates acting as

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haptens, which, bound to different proteins, could resemble transition states of catalytic reactions [1-5]. For example, AD Abzs hydrolyzing different proteins are Abs against these proteins. ADs and viral diseases were found to stimulate production of IgG and/or IgM and IgA abzymes hydrolyzing thyroglobulin (Hashimoto's thyroiditis (HT) and rheumatoid arthritis), prothrombin (multiple myeloma), protein factor VIII (hemophilia A), myelin basic protein (multiple sclerosis; MS) [1-8]. pIgGs from AIDS patients hydrolyzing HIV reverse transcriptase and integrase were the first examples of proteolytic Abzs appearing in humans directly against these proteins due to a viral infection and immune reactions [9, 10]. On the other hand, artificial antiidiotypic Abs can also possess catalytic activity [1-5].

Natural Abzs hydrolyzing DNA and RNA from the sera of patients with several AI (SLE, MS, HT, polyarthritis, etc.) and viral diseases (viral hepatitis and AIDS) demonstrated extreme diversity in their affinity for DNA and human nucleases [1-5]. To find out which antigens can induce Abzs with nuclease activities in AI diseases, we have immunized rabbits with DNA, RNA, DNase I, DNase II, and pancreatic RNase A. In all cases, total Abs contained Abzs hydrolyzing both DNA and RNA, while Abs from non-immunized rabbits did not hydrolyze nucleic acids [11]. In addition, it was shown that nuclease Abzs after the immunization of rabbits with DNase I, DNase II, and RNase contain both antiidiotypic Abs against these enzymes and Abzs against nucleic acids complexed with these nucleases. Taking into account all the data obtained, we have concluded that polyclonal DNase and RNase Abs of AI patients are "cocktails" of Abs against DNA and RNA and their complexes with proteins, and antiidiotypic Abzs to active centers of different DNA-hydrolyzing enzymes.

3.2 Association of Abzs formation with changes in colony formation of hematopoietic progenitors

It was shown that IgGs from the sera of 2-7 month-old control non-autoimmune (CBAxC57BL)F1 and BALB/c mice and 2-3 months-old autoimmune prone MRL-lpr/lpr mice (conditionally healthy mice) are catalytically inactive [12]. During spontaneous development of deep SLE-like pathology a specific reorganization of immune system of these mice leads to conditions associated with a production of IgGs hydrolyzing DNA, ATP, and polysaccharides with low catalytic activities (conditionally pre-diseased mice). A significant increase in DNase, ATPase, and amylase IgG relative activities associated with a transition from pre-diseased to deep diseased mice is correlated with additional changes in differentiation and proliferation of mice bone marrow hematopoietic stem cells (HSCs) and lymphocyte proliferation in different organs. The highest increase in all abzyme activities was found in mice immunized with DNA, which in comparison with pre-diseased and diseased mice are characterized by a different profile of HSC differentiation and by a suppression of cell apoptosis. Overall, all mouse groups investigated are characterized by a specific relationship between abzyme activities, HSC differentiation profiles, levels of lymphocyte proliferation, and cell apoptosis in different organs. From our point of view, the appearance of ATPase, DNase activities may be considered the earliest statistically significant marker of mouse spontaneous SLE and a further significant increase in their activities correlates with the appearance of SLE visible markers and with an increase in concentrations of anti-DNA Abs and urine protein. A very important difference in immune system reorganizations during pre-disease, disease, and immunization of healthy mice leading to production of different auto-Abs and abzymes was revealed. The literature data and our findings suggest that AI diseases originate from specific changes in differentiation and proliferation of HSCs [12].

3.3 Biological function of abzymes

Abzs have been studied primarily in the context of AI diseases where their biological role remains unknown: do they have a function or represent a dysfunction? It is quite possible that some Abzs play positive roles while others are harmful [1-5]. VIP-hydrolyzing Abs of asthma patients can have an important effect in the pathogenesis by decreasing the concentrations of VIP, which plays an important role in asthma pathophysiology [5]. Recently, it was shown that hMBP-hydrolyzing activity is an intrinsic property of IgGs, IgMs, and IgAs from the sera of MS patients and the specific sites of the neural AG cleaved by Abs were established [7-9]. Recognition and degradation of hMBP peptides by serum auto-Abs was confirmed as a novel biomarker for MS. In MS, the protease activity of anti-hMBP Abzs can attack hMBP of the myelin-proteolipid sheath of axons. An established MS drug Copaxone appears to be a specific hMBP-hydrolyzing Abzs inhibitor [13]. Consequently, the Abzs may play an important negative role in MS pathogenesis.

DNase Abzs from SLE, lymphoproliferative diseases, MS patients, and DNA-hydrolyzing Bence-Jones proteins from multiple myeloma patients are cytotoxic, cause nuclear DNA fragmentation and induce cell death by apoptosis [1-5]. A decrease in Abzs hydrolyzing nucleic acids is most probably a positive sign in some diseases (SLE, MS, HT, etc.). For example, it was shown for HT patients that the relative activities of DNase Abzs correlate with the concentration of thyroid hormones and other biochemical and immunological indices of this pathology, and are related to the progressive deterioration of the clinical status, including exacerbation of thyroid gland damage [5]. The therapy of HT patients by thyroxine leads only to a temporary change in the hormone concentration in the blood but did not affect the level of DNase Abs. However, treatment with the immunosuppressive drug Plaquenil (7-chloro-4(β-diethylamino-α-methylbutyl-amino)quinoline), significantly decreases the DNase activity of Abs, which correlates with rising thyroid hormone concentrations, enhanced thyroid gland function,

and an improvement of the clinical state of the patients [5]. However, Abzs obtained by immunization of healthy animals and from patients with various bacterial and viral infections are not cytotoxic toward tumour and normal cells. Therefore, it is possible that the formation of cytotoxic nuclease Abzs is a consequence of specific immune processes in AI patients associated with changes in the differentiation profile and the levels of proliferation of HSCs and widening of the repertoire of Abzs in AI mammals [12]. Because of their ability to bind a variety of foreign AGs, natural pAbzs of patients with bacterial and viral infections can play a major role in the primary line of defense against infections. It was shown that the presence of IgGs with serine protease-like activity hydrolyzing small peptides in the serum strongly correlates with survival after sepsis [5]. In HT, Abzs hydrolyzing thyroglobulin have been considered a positive factor, since they could minimize AI responses to thyroglobulin and prevent formation of immunocomplexes [5]. We have recently found that the serum of HIV-infected patients contains IgG fractions specifically hydrolyzing only viral integrase or reverse transcriptase, but not many other tested proteins [8-10]. Abzs hydrolyzing integrase significantly suppress 3'-processing and integration reactions catalysed by this enzyme. Abzs from AIDS patients also hydrolyze DNA. The immune response to virus components is the most important factor slowing down the transition of HIV infection to the stage of AIDS. Therefore, reverse transcriptase-, integrase-, and DNA-hydrolyzing Abzs may cooperatively protect HIV-infected patients from the development of AIDS..

4 Conclusion

Taken together, it is obvious that the biological roles of various Abzs may be very different. At the early stages of ADs, the repertoire of Abzs is usually relatively small but it greatly increases with the progress of the disease, leading to the generation of catalytically diverse Abzs with different activities and functions. In this respect it should be mentioned that even pools of Abzs from AI patients contain different sets of abzymes, which may be toxic or nontoxic toward different cells; the number of toxic ones increased with development of deep pathology. It may be a consequence of an extreme diversity of the variable fragments and active centers of various Abzs. In conclusion, a number of studies of Abzs show the extremely wide potential of the immune system in producing Abzs possessing very different enzymatic activities, which very often are not comparable with those of known enzymes, and natural Abzs with specified and novel functions may have wide potential for biotechnology and medicine.

References:

[1] Keinan EE. (Eds.), *Catalytic antibodies*, Weinheim: Wiley-VCH Verlag GmbH and Co. KgaA, 2005, pp. 1-586.

[2] Nevinsky GA, Buneva VN., Human catalytic RNA- and DNA-hydrolyzing antibodies. *J. Immunol. Methods,* Vol.269, 2002, pp. 235-245.

[3] Nevinsky GA, Favorova OO, Buneva VN., Natural Catalytic Antibodies - New Characters in the Protein Repertoire. In E. Golemis (Eds.), *Protein-protein interactions; a molecular cloning manual*, New York, Cold Spring Harbor: Cold Spring Harbor Lab. Press, 2002, pp. 532-534.

[4] Nevinsky GA, Buneva VN., Catalytic antibodies in healthy humans and patients with autoimmune and viral pathologies, *J. Cell. Mol. Med.,* Vol.7, 2003, pp. 265-276.

[5] Nevinsky GA, Buneva VN., Natural catalytic antibodies-abzymes. In E. Keinan, (Eds.), *Catalytic antibodies*, Weinheim: Wiley-VCH Verlag GmbH and Co. KgaA, 2005, pp. 503-567.

[6] Polosukhina DI, Kanyshkova T, Doronin BM, et al., Hydrolysis of myelin basic protein by polyclonal catalytic IgGs from the sera of patients with multiple sclerosis. *J. Cell. Mol. Med.,* Vol.8, 2004, pp. 359-368.

[7] Polosukhina DI, Buneva V.N., Dorinin B.M. et al., Hydrolysis of myelin basic protein by IgM and IgA antibodies from the sera of patients with multiple sclerosis, *Med. Sci. Monit.,* Vol.11, 2005, pp. BR266-BR 272.

[8] Polosukhina DI, Kanyshkova TG, Doronin BM, et al., Metal-dependent hydrolysis of myelin basic protein by IgGs from the sera of patients with multiple sclerosis. *Immunol. Lett*., Vol.103, 2006, pp. 75-81.

[9] Baranova SV, Buneva VN, Kharitonova MA, et al., HIV-1 integrase-hydrolyzing antibodies from sera of HIV-infected patients. *Biochimie*, Vol.9, 2009, pp.1081-1086.

[10] Baranova S.V., Buneva V.N., Kharitonova M.A., et al., HIV-1 integrase-hydrolyzing IgM antibodies from sera of HIV-infected patients. *Int. Immunol.,* Vol.22, 2010, pp. 671-680.

[11] Nevinsky G.A., Buneva V.N., Natural Catalytic antibodies in norm, autoimmune, viral, and bacterial diseases. *ScientificWorldJournal,* Vol.10, 2010, pp. 1203-1233.

[12] Andryushkova AS, Kuznetsova IA, Buneva VN, et al., Formation of different abzymes in autoimmune-prone MRL-lpr/lpr mice is associated with changes in colony formation of haematopoetic progenitors, *J. Cell. Mol. Med.,* Vol.11, 2007, pp. 531-551.

[13] Belogurov AA, Kurkova IN, Friboulet A, et. al., Recognition and degradation of myelin basic protein peptides by serum autoantibodies: novel biomarker for multiple sclerosis, *J. Immunol.,* Vol.180, 2008, pp. 1258-1267.