Antibodies Possessing a Catalytic Activity (Natural Abzymes) at Norm and Pathology

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Abstract: The review is focused on the analysis of published data and the results obtained by the authors about the catalytic activity of antibodies (abzymes) at norm and pathology. Potential pathogenic and beneficial role of natural abzymes is discussed.

Keywords: Antibodies, Abzymes, Blood serum, Catalytic activity, Biological activity.

INTRODUCTION

After comparing the characteristics of antigen-antibody and enzyme-substrate complexes, L. Pauling in 1948 came to the conclusion that antibodies, similar to enzymes, can catalyze chemical reactions under certain conditions [1]. The idea of obtaining antibodies with catalytic activity by immunization of animals with hapten-immobilized analogs of the stable transition states of chemical reactions belongs to B. Jenks [2] and was experimentally confirmed in 1986 by two groups researchers [3, 4]. They obtained antibodies possessing the ability to accelerate hydrolysis of esters in 1000 times. These antibodies were named as "catalytically active antibodies" or "artificial abzymes". These antibodies were named as "catalytically active antibodies" or "artificial abzymes". Combining the immunization of animals with the technology of monoclonal antibodies allowed to obtain abzymes, are capable of catalyzing more than 100 chemical reactions [5]. All this, gave a reason to speak about a new biological discipline - abzymology.

New stimulus for enzymology has done in 1989 by a group of S. Paul, when they purified from a blood serum of bronchial asthma patients antibodies, are capable of hydrolyzing vasoactive intestinal neuropeptide (VIP) [6]. During the following years it was revealed that many human diseases (autoimmune, viral, cancer) are associated with appear in a blood serum of patients of different enzymes with peptidase, protease, DNase, RNase and others activities (see reviews [7-9]). Such catalytically active antibodies are called "natural" abzymes. Since abzymes were not detected in the body of healthy people, it was suggested that their production is linked with pathological processes. The suggestion about existence of natural abzymes in norm has done, when was shown that colostrum and milk of healthy women could contain secretory immunoglobulin A (sIgA), possessing the ability to catalyze the casein phosphorylation [10]. During the following years in colostrum and milk of humans were revealed different antibody isotypes, are capable of hydrolysing DNA [11-14], RNA [14-15], nucleotides [16], proteins [17, 18], polysaccharides [19], as well as to phosphorylate of proteins [20-22], lipids [23-26] and polysaccharides [27].

Next studies revealed that natural abzymes are present in blood serum of healthy humans [28 - 31]. Catalytical activity of such abzymes are directed toward a different autological antigens.

The ability to catalyze the reaction between oxygen radicals and water, which leads to the formation of hydrogen peroxide and ozone was shown as the property of all classes of immunoglobulins of mammals. This activity is determined by amino acid residues of tryptophan (Trp 36 and Trp37), which is a constitutive part of 99% of all immunoglobulin molecules [32 - 34] and don't depend on antibody-antigen specificity or their origin. Similar catalytic activity was also detected for some proteins with non imunoglobuline nature - beta-galactosidase and chicken egg ovalbumin [33, 34]. Since variable regions are not involved in catalysis, it is believed that the oxidoreductase activity of antibodies not belongs to abzymatic activity.

PROTEASE-LAKE ABZYMES (PROTABZYMES)

Abzymes, possessing protease activity were named as "protabzymes". As was mentioned above, protabzymes, capable of hydrolyzing intestinal

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E-ISSN: 2410-3802/14

vasoactive peptide (VIP), were firstly isolated from blood serum of patients with bronchial asthma in 1989 [6]. Also has been developed some criteria of proving of abzymatic activity.

This is including such requirements:

1 - high homogeneity of immunoglobulin samples,

2 - affinity of antibodies to reaction substrates,

3 - catalytic activity of the antibody Fab-fragments,

4 - saving of the capability of hydrolyzing substrate after dissociation of immune complex

Another example of protabzymes, associated to human autoimmune diseases is thyroglobulin-hydrolyzing abzymes, isolated from blood serum of patients with acute Hashimoto thyroiditis [9, 35]. The use of radioactive labeled thyroglobulin allowed to find that abzymes are capable of hydrolyzing of this protein to low molecular weight peptides. The Km value of this reaction was in the order of nanomolar concentrations of thyroglobulin. These abzymes catalyzed hydrolysis of a synthetic tripeptide methylcoumarin, but with essentially lowest activity. Catalytic activity toward tripeptide methylcoumarin has been shown also for a human myeloma Bence-Jones proteins (multimeric light chains of immunoglobulins) [36, 37]. It was shown, that such proteins are capable of hydrolyzing synthetic chromogenic substrates of trypsin (chromasines TRY and BApNa). pH optimum of these reactions is 8,4, and Km value is in range of 140-730 μM (for TRY) and 18-27 μM (for BApNa). Fact that protabzymes can play an essential role in the development of pathological processes in autoimmune diseases has forced researchers to search for new abzymes with catalytic activity and with unknown substrate specificity. As a result of this investigation have been discovered IgGs, isolated from cerebrospinal fluid and blood serum of multiple sclerosis patients with hydrolyzing activity toward myelin basic protein (MBP) [38 - 40]. Since the destruction of the MBP causes demyelination of axons, it is reasonable to assume that these sabzymes are involved in development of pathology of multiple sclerosis.

Followed studies revealed that protabzymes is hallmark to factor VIII - resistant hemophilia A patients [41]. Following studies revealed that protabzymes is a hallmark for factor VIII - resistant hemophilia A patients [41]. Abzym's activity level in blood serum significantly correlated with the resistance of these patients to effect of FVIII therapeutic drugs. Protabzymes also was fond in human colostrum and milk of healthy women. As substrate of there activity could serve human milk casein [42], histone H1 and myelin basic protein [43, 44]. Hydrolysis of protein antigens by a mechanism similar to serine proteases is typical to abzymes of healthy humans [45]. It was shown that antibodies isolated from blood serum of healthy donors, belong to the IgM class and are capable of hydrolyzing some viral and bacterial superantigens [29, 30]. Also, it was found, that IgM and IgG from blood serum of elderly people can hydrolyze neurotoxic beta-amyloid peptide, which is involved in the development of Alzheimer's disease. According to this data, abzymes detected in healthy humans possesses preferentially a protective function.

PROTEIN KINASE-LIKE ABZYMES

In 1991 we described for the first time the capability of antibodies having ability to catalyze protein phosphorylation [46]. It was found that electrophoretically homogeneous sIgA, purified from milk of healthy mothers are capable of phosphorylate human milk casein on a serine residues. This work has stimulated subsequent study of human milk abzymes. As was mentioned above, the main problem of natural abzyme is contamination of antibody samples with native enzyme possessing similar catalytic activity. To satisfy criteria of purity of antibodies which belong to abzymes, there was developed a number of purification schemes [20 - 22]. Usually this purification includes a multistep procedure consisting with affinity and ion exchange chromatography.

The method of sIgA-abzyme isolation we have developed is based on higher affinity of catalytically active fraction of sIgA to Protein A-Sepharose in compare with catalytically inactive antibodies [10]. Purified antibodies were additionally separated by ion-exchange chromatography on DEAE-sorbent. As a next step, electrophoretically homogeneous preparations of sIgA were performed by chromatography on matrix containing immobilized of protein kinase reaction - ATP-sepharose and casein-sepharose. To determine the localization of catalytic center into the molecule of the catalytically active sIgA we used two reactive ATP analogues - dialdehide derivative [α-^{32}P] ATP (oxyATP) and alkylating

derivative o [α-^{32}P] ATP (RCl-ATP) [20]. This approach allows detecting ATP-binding sites preferentially located on light chain of a sIgA molecule. The high affinity of the light chain to ATP was also confirmed by affinity chromatography of sIgA-abzymes on ATP-sepharose under conditions of dissociation of immunoglobulin polypeptide chains [10]. It was found that IgA-abzymes can phosphorylate variety of human milk proteins, and under certain conditions, have capacity to autophosphorylation [21-22]. Some unexpected results were obtained when for phosphorylation reaction were used other nucleotide triphosphates. It was found that all purine and pyrimidine nucleotide triphosphates can serve as the substrates of protein kinase activity of sIgA-Abzyme [20]. This date demonstrate the unique properties of abzymes in comparison to common protein kinases, which are capable of using as a phosphate donor ATP or GTP. Thus, sIgA-abzymes are classified as protein kinases, which have multi substrate specificity and properties, which are significantly different from other protein kinases.

LIPID KINASE-LIKE ABZYMES

Lipid kinase activity of abzymes was discovered during analysis of the phosphorylated products of a protein kinase activity of the sIgA-abzymes [23, 24]. Phosphorylated products, labeled with radioactive phosphorus, were isolated from the reaction mixture with chloroform-methanol solution and separated into three fractions, using thin layer chromatography. Following studies showed that isolated phospholipids form complexes with sIgA-abzymes [25]. Detailed analysis of the structure of phosphorylated lipid was carried out in G. Nevinsky lab. of Institute of Chemical Biology and Fundamental Medicine [26, 27]. To do this the authors used combined methods of enzymatic and chemical degradation, including processing with neuraminidase, alkaline hydrolysis in methanol and oxidation with periodic acid. The authors concluded that milk sIgA-abzymes can use as alternative to casein also two minor milk glycolipids, containing one sialic acid and 4-5 fatty acid residues.

NUCLEOTIDE-HYDROLYSING ABZYMES

Nucleotide-hydrolyzing activity in first time was discovered to sIgA [10], but in detail it was studied to human milk IgGs [16]. To purification of these abzymes was used earlier developed schema including chromatography human milk proteins on columns with Protein A-Sepharose, DEAE-cellulose, immobilized on sepharose monospecific antibodies to human IgGs and ATP-Sepharose. It was shown that electrophoretically homogeneous human milk IgGs and their Fab-fragments are capable of hydrolyzing ribonucleotide and deoxyribonucleotide 5'-mono-, two- and triphosphates. To detection of position catalytically active sites located in the IgG molecule was used method of affinity modification of IgG molecules with alkylating analogues of radiolabeled ATP. It was discovered that the ATP-binding site is located at light (L) chain of IgG molecules. It was developed an original method of determining the catalytic activity of abzymes, based on the nucleotide-hydrolyzing activity of IgG in polyacrylamide gels after their separation by electrophoresis in denaturing conditions [16]. This method revealed that the nucleotide-hydrolyzing activity is inherent to entire molecules of IgG-abzymes or their oligomeric forms. Reduction of IgG with their subsequent dissociation to heavy and light chains leads to loss of catalytic activity. Based on these results there was concluded, that although ATP binding area is located on the L-chain of IgG molecules , H-chains are also required to provide the hydrolysis reaction.

Analysis of thermodynamic and kinetic parameters of this reaction with various nucleotides discovered that the lowest Km is 44 μM for the hydrolysis of ATP, and the highest (Km = 79 mM) - for dCTP. V_{max} for different nucleotide changes in range from 0.57 μM / min for dATP to 1.1 μmM / min for CTP.

DNA-HYDROLYZING ANTIBODIES (DNA-ABZYMES)

It should be note, that DNA-hydrolyzing antibodies belong to the most studied abzymes. IgG, having topoisomerase activity (catalyzing breaks of one-strain supercoiled forms of plasmid DNA) were isolated from blood serum of patients with systemic lupus erythematosus in 1992 by team of prof. A. Gabibov [27]. Following studies have shown that DNA-abzymes also presence in blood serum of patients with various autoimmune diseases (scleroderma, rheumatoid arthritis, thyroiditis, multiple sclerosis), AIDS patients, radiation syndrome, hepatitis and lymphoproliferative types of cancer [7, 12, 39 - 50]. DNA-abzymes were not found in blood serum of patients with influenza, pneumonia, tuberculosis, tonsillitis, some cancers, as well as in clinically healthy individuals. It is allow to suggest that the DNA-abzymes may be serve as

pathogenic factors at some autoimmune diseases. For example, in serum of SLE patients, DNA-hydrolyzing activity level of IgG is closely correlated with the clinical manifestation of the disease. It was found that pathogenic effect of DNA-abzymes may be directly linked with their cytotoxicity. DNA-abzymes can induce a caspase-dependent apoptosis in human promyelocyte cells line HL-60, human T-cell lymphoma line Raji, transformed mouse fibroblast line L929 and human erythroleukemia cell line K562 in vitro [50, 51]. Fab-fragments of these antibodies possess the same activity. The mechanism of their cytotoxic activity remains unknown. Existing data allow to suggest that cytotoxic activity of DNA-abzymes could be closely linked with their ability to internalized by cells, their translocation into the nucleus that induce the DNA degradation.

POLYSACCHARIDE-HYDROLYZING ABZYMES

The ability of antibodies to hydrolyze polysaccharides was firstly described in 1999 [52]. It was found that IgG and IgM from blood serum of patients with rheumatoid arthritis, multiple sclerosis, pyelonephritis, and some cancers are able to hydrolyze maltose-containing oligosaccharides, glycogen and similar compounds. As substrates of glycosidase activity of these abzymes the authors used para-nitrophenyl-maltoseoligosaccharides with different lengths. Reaction products were analyzed by thin-layer chromatography and reverse phase HPLC separation.

The presence of polysaccharide-hydrolyzing abzymes in colostrum and milk of healthy women was detected by the same group of researchers [22]. These abzymes were able to catalyze cleavage of maltose-containing oligosaccharides, glycogen and similar compounds. It is shown that Fab-fragments of these antibodies are capable of catalyzing the similar reactions.

SIALYDASE-LIKE ABZYMES (SIALIC-ABZYME)

Cell surface sialylation is known to be tightly connected with tumorigenicity, invasiveness, metastatic potential, clearance of aged cells, while the sialylation of IgG molecules determines their anti-inflammatory properties [61]. Four sialidases – hydrolytic enzymes responsible for cleavage of sialic residues – were described in different cellular compartments [62]. We have found and characterized first known IgG antibodies possessing sialidase-like activity in blood serum of multiplemyeloma patients [63]. Immunoglobulin fractions were precipitated with ammonium sulfate (50% of saturation) from blood serum of healthy donors and MM patients, and screened for the presence of sialidase activity by using 4-MUNA (2(-(4-methylumbelliferyl)-a-D-N-acetylneuraminic acid) as substrate. High level of sialidase activity was detected in some MM patients, but not in healthy donors. Subsequent antibody purification by protein-G affinity chromatography and HPLC size exclusion chromatography at acidic conditions demonstrated that sialidase activity was attributable to IgG molecules. Sialidase activity was also specific for (Fab)2 fragment of IgG and blocked by sialidase inhibitor DANA. Sialidase activity of IgG molecule was also confirmed by in gel assay. Kinetic parameters of the catalysis reaction were described by Michaelis–Menten equation with Km:44.4–108 mM and k_{cat}:2.7–23.1. The action of IgG possessing sialidase-like activity on human red blood cells leads to increase their agglutination by the peanut agglutinin, that confirms their desialylation. Sialidase active IgGs were also detected in blood serum of the systemic lupus erythematosis (SLE) patients, but were not found in healthy donors [64]. We have found that mucin, isolated from bovine submandibular glands and conjugated with Sepharose beads could serve as a useful matrix for purification of sialydase active abzymes from blood serum of the SLE patents. That allowed us to develop a scheme of double-step chromatography purification of sialidase-like IgGs from human blood serum [65].

Recently, we have created artificial sialidase abzyme by means of rabbit immunization with a synthetic hapten consisting of nonhydrolyzable inhibitor of sialidase reaction conjugated with bovine serum albumin [66]. Incubation of the apoptotic cells with both natural (purified from blood serum of SLE patient and artificial (obtained by rabbits immunization) sialidase-like IgGs and their F(ab)2 fragments significantly enhanced their clearance by the macrophages [67]. We suggest that sialidase abzyme can serve as a protective agent in autoimmune patients and those artificial abzymes could be of therapeutic value.

CONCLUSION

The pathogenic or beneficial effect of catalytic antibodies has been directly demonstrated in numerous studies . This is making abzymes as essential factor in

immune response of human organism to self and others antigens.

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Received on 21-11-2014 Accepted on 7-12-2014 Published on 31-12-2014

http://dx.doi.org/10.15379/2410-3802.2014.01.2