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REVIEW ARTICLE

Catalytic Antibodies: Design, Expression, and Their Applications in Medicine

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Abstract
Catalytic antibodies made it feasible to develop new catalysts, which had previously been the subject of research. Scientists have discovered natural antibodies that can hydrolyze substrates such as nucleic acids, proteins, and polysaccharides during decades of research, as well as several ways of producing antibodies with specialized characteristics and catalytic functions. These antibodies are widely used in chemistry, biology, and medicine. Catalytic antibodies can continue to play a role and even fully prevent the emergence of autoimmune disorders, especially in the field of infection and immunity, where the process of its occurrence and development often takes a long time. In this work, the development, design and evolution methodologies, and the expression systems and applications of catalytic antibodies, are discussed. Trial registration: not applicable.

Keywords Catalytic Antibodies · Design and Evolution · Expression Systems · Infection and Immunity · COVID-19

Introduction

The catalytic antibody, also known as antibody-enzyme, is a type of immunoglobulin with catalytic ability, meaning it can not only bind to antigen but also catalyze certain reactions like an enzyme [1–4]. Pauling developed the transition state theory to explain the nature of enzyme catalysis in 1946, stating that an enzyme has catalytic activity when it can selectively bind and stable the transition state of a chemical reaction, lowering the reaction energy level [5]. Jencks hypothesized in 1969, based on the transition state theory, that if the antibody could bind to the transition state of the reaction, it could theoretically acquire catalytic characteristics [6]. Lerner [7] postulated in 1984 that the antibody generated by the transition state analogs(TSA) might have complementary confirmation to the analog. The antibody could cause catalysis by forcing the substrate to enter the transition state after binding [7]. According to this hypothesis, in the research of antibodies against a tetrahedral charged phosphate hapten, Schultz and Lerner [8, 9] discovered that they could selectively

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catalyze the hydrolysis of corresponding carbonate and carboxylic esters in 1986. The catalytic antibody is the name for this type of antibody [8, 9]. In 1989, Paul et al. [10, 11] identified autoantibodies from human serum that can hydrolyze vasoactive intestinal peptide (VIP), indicating that the research was progressing. For the first time, the study demonstrates that antibodies with catalytic activity can be produced in the body without the use of synthetic chemicals as vaccines. A huge number of catalytic antibodies were promptly extracted from patients with various autoimmune disorders as a result of this investigation [12–19]. Patients with thyroiditis, multiple myeloma, and hemophilia, for example, have catalytic antibodies against thyroglobulin, prothrombin, and factor VIII (FVIII) [13, 16, 20, 21]. Patients with systemic autoimmune symptoms such as systemic lupus erythematosus, scleroderma, rheumatoid arthritis, or multiple sclerosis had catalytic antibodies with DNA and RNA hydrolysis activity isolated from their serum [12, 22, 23]. Catalytic antibodies with different activities have been found (summarized in Table 1). In addition, many approaches and tactics have been developed in order to obtain catalytic antibodies suited for a range of unique functions, particularly those that do not occur in nature [24].

Catalytic Antibody Design and Evolution Strategy

Production of Catalytic Antibodies Based on Transition State Analogs

Traditional catalytic antibody preparation involves in vivo immunization followed by cell fusion. Enzyme catalysis is attributed to the complementarity between enzyme and transition state rather than the substrate of catalytic activity, according to the transition state theory of enzyme catalysis (Fig. 1) [9, 12, 44–46]. A suitable and stable transition state analog is designed as a semi-antigen using the chemical molecular design method, and the desired catalytic antibody is tested using the hybridoma technique (Fig. 2A). The first catalytic antibodies were produced using alkaline hydrolysates of esters and carbonates. A negatively charged tetrahedral transition state is one of the hydrolysates of esters, which can be adequately imitated by phosphonates. After the hapten has been designed and manufactured, it binds to the carrier protein to create an antigen that is immunogenic enough [45]. The antibody produced by transition state theory binds to the transition state more strongly than the ground state of the substrate, resulting in a perfect catalytic antibody [45]. These transition state analogs have been utilized as haptens in the production of hydrolytic antibodies for a long time [46–51]. And catalytic antibodies that can catalyze peroxy reaction [52], decarboxylation [53–55], cyclization [56–58], lactonization [59], bimolecular amide-bond formation, and even reactions that are not catalyzed by natural enzymes [50]. The design of the transition state analog determines whether or not the desired catalytic antibody can be generated using this procedure. Reaction immunity [12, 22, 23, 60], induction and transformation design [58], "latent transition state" semi-antigen design [21], and so on are some of the most common design methodologies.

Production of Catalytic Antibodies by Genetic Engineering

Site-directed mutagenesis of the variable region of the antibody or the introduction of known catalytic amino acid residues into the antigen-binding site of the antibody can often yield the desired antibody with catalytic activity (Fig. 2B). Liu [64] combined antibody Jel42 with bacterial protein HPr, added glutamic acid to increase the

Table 1 Summary of spontaneously generated catalytic antibodies

Source	Antibodies	Activity	References
Healthy human	IgG	Hydrolyze Vasoactive intestinal peptide (VIP)	Paul et al. (1989) [10]
Patients with Hashimoto's thyroiditis	Anti-Tg antibodies	Hydrolyze thyroglobulin (Tg)	Li et al. (1995) [13]
Patients with lymphoproliferative diseases	IgG	DNA-hydrolyzing activity	Kozyr et al. (1998) [25]
Patients with systemic lupus erythematosus(SLE) and hepatitis B	IgG	RNA hydrolyzing activity	Vlassov et al. (1998) [22]
Patients with multiple myeloma	RHY	Prothrombinase activity	Thiagarajan et al. (2000) [16]
Patients with multiple sclerosis (MS)	IgG	Catalyze DNA hydrolysis	Baranovskii et al. (2001) [23]
Rabbit with thymomas	IgG	Creatine phosphokinase activity,	Kakinuma et al. (2002) [26]
Patients with multiple sclerosis	IgMs	Amylolytic activity	Ivanen et al. (2004) [27]
Urine of patients in different clinical stages of multiple myeloma	Bence Jones proteins (BJPs)	Chromozym TRY cleaving activity	Matsuura et al. (2006) [15]
Patient with Waldenström's macroglobulinaemia	IgM (Yvo)	Proteolytic activity	Ramasland et al. (2006) [28]
Patients with acquired hemophilia	IgG	FVIII-hydrolyzing activity	Wootla et al. (2008) [18]
Patients with autoimmune (AI) diseases	IgG	DNase and RNase activities	Krasnorutskii et al. (2008) [29]
Antiphospholipid syndrome(APS)patient	IS6 mAb	Prothrombinase activity	Yang et al. (2010) [17]
Autoimmune-prone MRL/MpJ-lpr mice	Polyclonal IgG	DNase activity	Kostrikina et al. (2011) [30]
Staphylococcus aureus infection	IgG from non-infected humans	Hydrolyzed *S. aureus* extracellular fibrinogen-binding protein (Efb)	Brown et al. (2012) [31]
Blood serum of multiple myeloma and systemic lupus Erythematosis patients	IgG	Sialidase-like activity	Kit et al. (2014) [32]
Healthy humans	IgGs	Peroxidase and oxidoreductase activities	Tolmacheva et al. (2015) [33]
Serum of mice and humans	IgM	Hydrolyze *Trypanosoma cruzi* Tc24 protein	Gunter et al. (2016) [34]
Primary open-angle glaucoma (POAG)	Antibodies (AB)	Hydrolyze myelin basic protein (MBP)	Frolov et al. (2017) [35]
Systemic lupus erythematosus patients	IgG	PFR-MCA hydrolysis activity	Pradhan et al. (2018) [36]
Systemic lupus erythematosus patients	NGTA2-Me-pro-Tr	Trypsin-like activity	Timofeeva et al. (2020) [37]
Human breast milk	sIgA	Ribonuclease activity	Kompaneets et al. (2020) [38]

Table 1 (continued)

Source	Antibodies	Activity	References
Multiple sclerosis (MS)	IgGs	Histone-hydrolyzing activity; myelin basic protein (MBP) hydrolysis activity	Ermakov et al. (2021) [40]
Patients with *Pseudomonas aeruginosa* infection	HuscFv	Elastase activity	Santajit et al. (2021) [41]
Mother's milk	Immunoglobulin G(IgG)	Histone-hydrolyzing activity; myelin basic protein (MBP) hydrolysis activity	Kompaneets et al. (2021) [42]
Neuropsychiatric-systemic lupus erythematosus (NP-SLE) patients	IgG	DNase activity	Ramesh et al. (2021) [43]

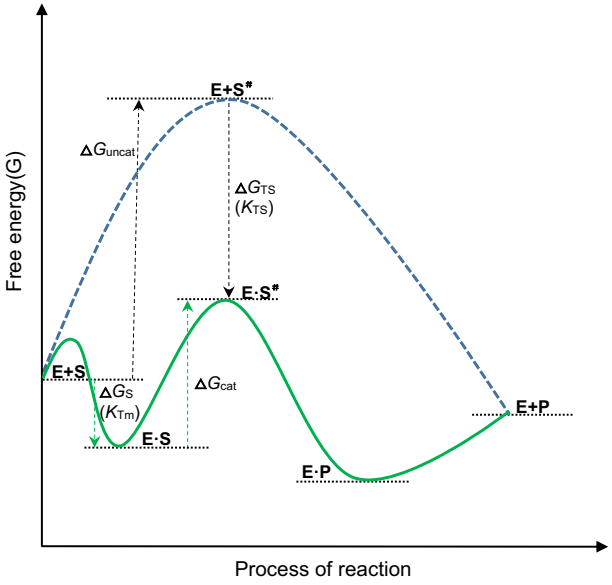

Fig. 1 Energy profiles for enzyme-catalyzed and uncatalyzed reactions. Chemical transformation proceeds through the high-energy transition state ($S^{\#}$) to make the products (P). In enzymatic reactions, an enzyme (E) strongly binds to the transition state to lower the activation energy (ΔG_{TS}) and thus catalyze the reaction. But an enzyme binds to the ground state of the substrate (S) very weakly. Enzyme achieves efficient catalysis by maximizing the differential binding affinities between the transition state (K_{TS}) and the substrate (K_S). The ratio of K_S to K_{TS} is equal to the ratio of K_{cat} to K_{uncat} [44]

nucleophilicity of nearby water molecules, lysine to increase the polarizability of water molecules, carbonyl and histidine to provide protons to convert amines into better-leaving groups, and changed the fourth residue to glycine to maintain the integrity of complementary determining region 3 of the heavy chain (CDRH3) at the binding interface. Finally, the bacterial protein HPr's single-chain antibody (scFV) possesses protease activity [64]. By adding a histidine residue into the antibody Jel103, Fletcher et al. [65] were able to create catalytic antibodies with RNA-specific ribonuclease activity. Okochi et al. [66] produced antibodies with peptidase activity by adding mutations to generate catalytic triplets among the residues of Asp1, Ser27a, and the original His93. These findings suggest that novel ways for tailoring catalytic antibodies beyond the restrictions of existing vaccination methods may be possible [50].

Manipulation Based on the Idiotypic Network to Produce Catalytic Antibodies

Jerne [67] proposed the "idiotypic network theory" in 1974. According to this theory, animals are immunized with enzymes as antigens to produce monoclonal antibodies (called Ab1). The antigen-binding site of the antibody is complementary to the active site of the enzyme, and the antibody is then vaccinated against the antigen-binding site of Ab1 (the variable region of Ab1). Finally, the catalytic antibody (called Ab2) is obtained (Fig. 2C). Antibodies with amidase activity were produced using this method [68], which used lactamase as an antigen and used subtilisin and acetylcholinesterase as antigens, the researchers created catalytic antibodies with serine protease [69] and esterase activity [47]. Antibodies containing allicin and carboxypeptidase activity were also produced [21, 70, 71]. This approach has been used to create antibodies with various catalytic activities [46–49, 62, 68, 69, 71, 72].

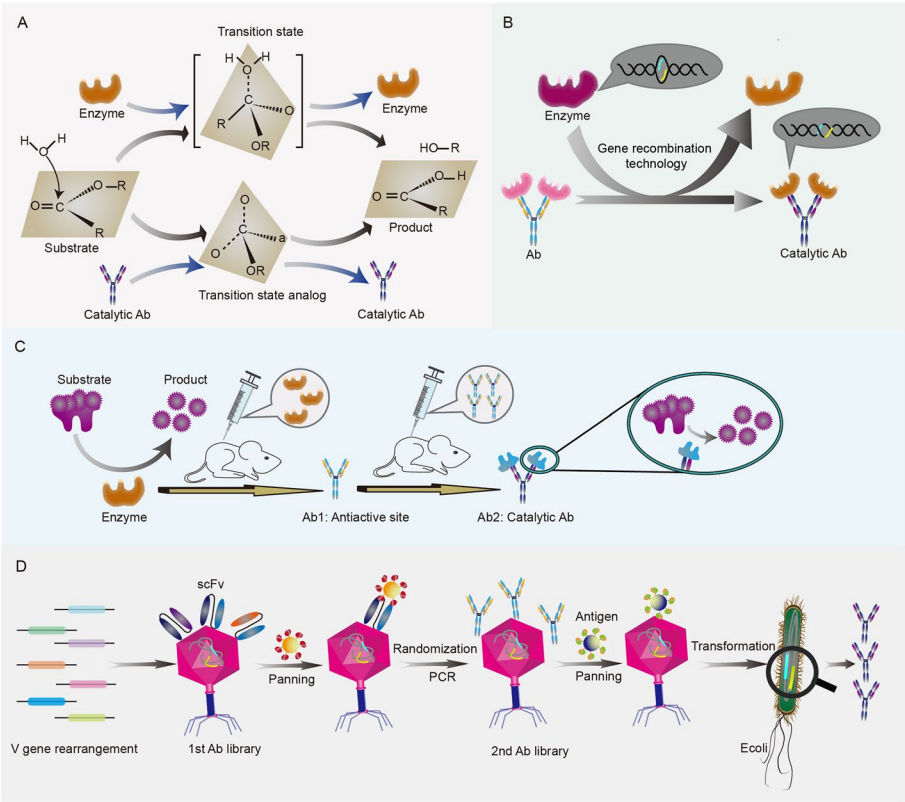

Fig. 2 Different methods to generate catalytic antibodies. **A**. Based on known chemical reactions, stable transition state analogs are synthesized and used as haptens to immunize animals. Monoclonal antibodies with high affinity and good complementarity to the transition state are selected,thus enabling the acceleration of catalysis when incubated with the substrate [50, 61]. **B**. The antibody with catalytic function is obtained by recombining or replacing the catalytic domain fragment of the enzyme with the variable region of the antibody [50]. **C**. Generation of catalytic antibodies based on "idiotypic network theory" [50, 62]. **D**. Generation of catalytic antibodies by phage display technology [45, 63]

Production of Catalytic Antibodies by Phage Display Technology

Phage display technology can introduce the DNA sequence of a foreign protein or peptide into the right position of the phage's coat protein structure gene as an in vitro selection system, allowing the foreign gene to be produced alongside the coat protein. At the same time, the foreign protein is displayed on the surface of the phage with the phage is reassembled, achieving the goal of antibody screening (Fig. 2D). Smith invented the technique in 1985 [73], which was later modified by McCafferty and his colleagues in 1990 [74–76]. In comparison to the other three methods, phage display technology offers the following advantages: high speed, a relatively straightforward screening process, and the ability to display recombinant antibody fragments using libraries for human applications. Nishi's team used transition state modeling technologies to create 6D9, a catalytic antibody with low catalytic activity. They then randomly altered 6D9 and showed a library of mutants on the phage before screening the catalytic antibody with 20 times higher activity [45, 62, 76].

By displaying the biased scFv produced from the spleen of mice previously immunized with cocaine phosphonate transition analog hapten, McKenzie et al. [77] were able to identify the antibody capable of binding and hydrolyzing cocaine. He then used site-directed mutagenesis to obtain the antibody with a three-fold increase in catalytic rate [75, 77]. To create catalytic antibodies, Li's team combined the idiotypic network method with phage display technology, combining numerous methodologies [49].

Other Methods of Producing Catalytic Antibodies

In addition to the methods mentioned above, catalytic antibodies can also be obtained by screening electrophilic covalent reactive analogs (CRA) [50]. Paul's team developed a monoclonal antibody against the HIV-1 gp120 coat protein and an scFv library against the amyloid β peptide generated from CRA-coupled gp120 as the immunogen [50, 78, 79]. In addition, normal or autoimmune mice immunized with ground state antigens could be examined for antibodies with expected catalytic activity [80–85]. In addition, bioinformatics methods can help understand the specificity of catalytic antibodies to assist repeated tests in the laboratory, thus saving time and money. The related tools are applicable for autoimmune analysis of binding sites, prediction of binding activity and most likely motifs of antibody binding, and dynamics simulation of catalytic reaction [41, 48, 86–88]. Luo designed the new catalytic ability into the antibody scFv2F3 by combining computational design and site-directed mutagenesis [89]. The resulting antibody enzyme Se-scFv2F3 showed high glutathione peroxidase activity, which was close to the natural enzyme activity. Molecular dynamics simulations showed that the designed catalytic triplet was very stable and the conformational flexibility caused by Tyr101 occurred mainly in the loop of complementary determination region 3. Docking studies showed that this loop facilitates the conformational transfer of Tyr54, Asn55, and Gly56 to stabilize substrate binding. Molecular dynamics free energy and molecular mechanics Poisson-Boltzmann surface area calculation estimated the pKa shifts of catalytic residues and the binding free energy of docking complexes, indicating that the dipole–dipole interaction between Trp29-Sec52-Gln72 leads to the change of free energy, which promotes the residual catalytic activity and substrate binding capacity [89].

In the above methods, catalytic antibodies are prepared based on transition state analogs, and the quality of the designed transition state analogues is the key to this method, and it is necessary to use transition state analogues as antigens or semi-antigens to immunize the host [22, 23, 60]. Genetic engineering techniques are usually used to design and introduce catalytic sequences or bases into antibodies [64, 65]. The "idiotypic network theory" method usually takes more time [68, 69]. However, It is usually possible to combine the above two or more methods to produce the required catalytic antibodies, assisted by bioinformatics analysis tools. Paul's team developed a platform for the preparation of catalytic antibodies (catabody) for age-related amyloid diseases [90]. First, electrophilic target analogues (ETA) were screened, and ETA mimics a high-energy covalent intermediate of the target protein, which recombines with the nucleophilic catalytic site. ETA capture the structure of specific covalent intermediates with their targets. Then the human antibody was produced by B cell library, and the catalytic antibody with a fast catalytic rate and no off-target reaction was screened by phage display, and finally, the cell lines producing therapeutic-grade CAT with different targets were isolated [90].

Catalytic Antibody Expression System

After the catalytic antibodies have been designed and modified using the methods described above, the catalytic antibodies must be produced with soluble and properly folded spatial structure before further research and application. As a result, it is crucial to select the appropriate expression system based on the characteristics of different catalytic antibodies, research goals, and application scenarios. The following are the three most often used catalytic antibody expression systems: prokaryotic expression system, eukaryotic expression system using yeast as host, and mammalian cell expression system.

Expression of Catalytic Antibodies in a Prokaryotic Expression System

Before catalytic antibodies are employed, they must be thoroughly examined, and the prokaryotic expression system offers the advantages of the fast growth of host cells, ease of operation, high yield, short production cycle, and low cost. It is frequently chosen as the method of expression for catalytic antibodies. In this technique, various catalytic antibodies have been effectively expressed (summarized in Table 2). The most common host is *Escherichia coli,* which can be expressed in cytoplasm or periplasm depending on the features of catalytic antibodies. The yield was rather high when expressed in the cytoplasm. However, because the catalytic antibody's binding antigen region is usually derived from the variable domain of the antibody's heavy chain or light chain (VH or VL), and the VH and VL domains are usually assembled in tandem during immunoglobulin folding, recombinant catalytic antibodies are often unstable and easy to aggregate [91, 92]. The crowded cytoplasmic environment allows molecules to interact easily, promoting antibody oligomerization and aggregation; also, the cytoplasmic redox environment prevents disulfide bonds from forming in the domain. Disulfide bonds play a crucial role in the stability of antibody structures [93, 94]. The catalytic antibodies cannot be folded appropriately during cytoplasmic expression because of the superposition of different circumstances, and they congregate to form inclusion bodies. Fortunately, there are several options for reversing this outcome. First, it might be expressed in terms of weekly quality. Periplasm is an oxidative environment that promotes the formation of disulfide bonds, and the type and quantities of proteins are modest, making it simple to create suitably folded catalytic antibodies. At the same time, due to the relatively small periplasmic space, catalytic antibody production is low. Second, catalytic antibodies are expressed on fusion lysozyme tags (Solubility-Enhancing Tags, SET). Using the properly folding of the lysolytic tag–enhanced protein and its fusion expression with the catalytic antibody, the active antibody can also be generated. A number of lysolytic tags have been discovered thus far, and researchers have successfully used tags like maltose-binding protein (MBP) [95, 96] and (FK506 binding protein) (KFBP) to obtain properly folded antibodies [97, 98]. There is also thioredoxin A (TrxA) [99], glutathione sulfhydryl transferase (GST) [100], NusA protein [101], small ubiquitin-like modified protein (SUMO) (102, GB1 [92], and other proteins [103]. Select the proper solubilization label for the label, then work with the appropriate carrier and host to achieve the soluble expression of the catalytic antibody. Third, by enhancing the cytoplasmic environment, soluble expression of antibody-enzyme can be obtained. The physical and chemical parameters of the cytoplasmic environment are directly related to the stability of the antibody, and the endogenous net charge of pH 7.4 in the cytoplasm impacts its aggregation tendency in the cytoplasm [104]. Furthermore, by increasing net negative

Table 2 Production of various catalytic antibodies using different expression systems [62]

Catalytic antibody fragment	Expression system	Activity	Host	References
Fab 1F7	EuK–Yeast	Chorismate mutase	*S. cerevisia*	Bowdish et al. (1991) [106]
scFv D2.3 and D2.4	ProK–Peripl. way	Ester hydrolysis	*E. coli*	Kim (1997) [107]
	ProK–Cytopl. way	Ester hydrolysis		
41S-2-L	Mamm.cell	Cleavage of gp41 peptides	Rabbits	Hifumi et al. (2002) [81]
scFv 4B2	ProK–Cytopl. way	allylic isomerization and Kemp elimination	*E. coli*	Robin et al. (2003) [108]
	EuK–Yeast		*P. pastoris*	
	EuK–Yeast		*K. lactis*	
mAb 9A8	Mammalian ascites	Acetylcholinesterase		Franqueville et al. (2003) [109]
Fab BV04-01	EuK–Yeast	DNA hydrolysis	*P. pastoris*	Kozyr et al. (2004) [110]
ECL2B-2	Mamm.cell	Cleaving a Chemokine Receptor CCR-5 Peptide	Mice	Mitsuda et al. (2004) [84]
Fab 6D9	Transcription/translation system	Ester hydrolysis	*E. coli cell-free expression system*	Ali et al. (2005) [111]
A.17	ProK	Amidase activities	*E. coli*	Reshetnyak et al. (2007) [112]
Ab2 6B8-E12	ProK	Proteolytic activity	*E. coli*	Ponomarenko et al. (2007) [48]
scFv GNL 3A6	ProK	Hydrolysis of cocaine	*E. coli* BL21-Gold	Mckenzie et al. (2007) [77]
	EuK–Yeast		*E. coli Rosetta*	
UA15-L	Mamm.cell	Proteolytic activity	Rabbits	Hifumi,et al. (2008) [85]
Humanized Ab A17	EuK–Mamm cells	Hydrolysis of organo-phosphorus compounds)	NSO-bcl2	Kurkova et al. (2009) [113]
HIV-1 gp120-specific IgG	ProK	Cleavaging gp120	*E. coli*	Durova et al. (2009) [82]
ETNF-6-H	Mamm.cell	Protease activity	Mice	Hifumi et al. (2010) [80]
scFv 9G4H9	ProK–Peripl. way	Cleavage of ß-lactam cycle	*E. coli*	Naya et al. (2012) [114]
VHHC10	ProK	Alliinase activities	*E. coli*	Li et al. (2012) [49]

Table 2 (continued)

Catalytic antibody fragment	Expression system	Activity	Host	References
14D9	ProK	Catalyses the highly enantioselective (> 99% ee) protonation of enol-ethers	*E. coli*	Marconi et al. (2014) [115]
2E6	Mamm.cell	Hydrolyzed Aβ	Mice	Planque et al. (2015) [116]
3D8	ProK	DNA-hydrolysing activity	*E. coli*	Lee et al. (2017) [117]
#7TR/#7GY	ProK	Degrade both a fluorescence resonance energy transfer-Aβ substrate and Aβ1-40 full peptide	*E. coli*	Hifumi et al. (2019) [118]
H34	ProK	Degrading the PD-1	*E. coli*	Hifumi et al. (2020) [119]
T-CAN	ProK	Asparaginolytic Activity	*E. coli*	Maggi et al. (2021) [120]

ProK/EuK prokaryotic and eukaryotic systems respectively, *Cytopl./Peripl* cytoplasmic and periplasmic ways respectively, *Mamm.cells* mammalian cells, *scFv* single chain Fragment variable

charge, fusing highly negatively charged peptide tags with scFvs can improve their solubility [92, 105]. As a result, the researchers fused peptide tags with a high negative charge and low isoelectric point to produce hyper-stable production of catalytic antibody in the prokaryotic host cytoplasm [104].

Expression of Catalytic Antibodies in a Yeast Expression System

Although the prokaryotic expression system has many advantages, it is difficult for the prokaryotic expression system to apply to all catalytic antibodies. Because the prokaryotic host lacks the function of protein post-translational modification in eukaryotic cells, which is critical for maintaining the stability of some catalytic antibodies. Furthermore, catalytic antibodies may be harmful to bacterial hosts, an issue that can be efficiently avoided by isolating heterologous proteins from eukaryotic cells [62, 110]. In this case, using a yeast expression system to express catalytic antibodies is a good idea [121]. *Pichia pastoris* is considered to be the most commonly used [108]. Yeast can produce soluble and correctly folded heterologous proteins, and correct post-translational modification is essential to their function. The safety of the system is also ensured by the absence of endotoxins and oncogenes in yeast. And it is usually stable and allows a high level of expression [62, 122].

Expression of Catalytic Antibodies in Mammalian Cell Expression System

The mammalian cell expression system is a complex glycosylated protein expression system. Protein folding and post-translational modification are functions performed by mammalian cells. In terms of molecular structure, physical and chemical properties, and biological function, the produced recombinant protein is the most similar to the natural higher biological protein molecule and is more likely to have the same biological activity as natural protein. It is particularly popular in the development and manufacture of therapeutic recombinant catalytic antibody drugs [62, 90]. The mammalian cells commonly used for antibody production are Chinese hamster ovary (CHO) and human embryonic kidney (HEK) cells, as well as transgenic mice [62, 113]. In the preparation platform of catalytic antibodies for age-related amyloid diseases developed by Paul's team, catalytic antibodies were produced through B cell library [90]. To summarize, each expression system has advantages and limitations, we should choose the appropriate expression system for the catalytic antibody to be expressed based on its properties and application situations.

Application of Catalytic Antibodies

Potential Application of Catalytic Antibodies in Clinical Oncology

Catalytic antibodies show remarkable potential as a new class of therapeutic molecules. They are widely used in biology and medicine (summarized in Table 3). Chemotherapy is a crucial treatment option for cancer patients. However, its success is limited due to the shortcomings such as insufficient drug concentration in the tumor site, systemic toxicity, and tumor cell drug resistance. Pre-enzymatic drug therapy is a promising avenue for improving tumor selectivity. Gene-directed enzyme prodrug therapy (GDEPT) and antibody-directed proenzyme therapy (ADEPT) are the two types of enzyme prodrug therapy that can deliver drugs to malignancies [123, 124]. Catalytic antibodies can

Table 3 Application of catalytic antibodies

Application	Antibodies	Activity	References
Addiction	3B9, 6A12	Hydrolyzes cocaine benzoyl ester	Landry et al. (1993) [140]
Addiction	15A10	Cocaine esterase	Briscoe et al. (2001) [141]
Acquired Immune Deficiency Syndrome (AIDS)	41S-2-L	Hydrolyze HIV-1 coat protein gp41	Hifumi et al. (2002) [81]
Acquired Immune Deficiency Syndrome (AIDS)	mAb YZ20	Hydrolyze HIV-1 coat protein gp120	Paul et al. (2003) [78]
Addiction	TD1-10E8, TD1-36H10	Oxidative degradation of Nicotine	Dickerson et al. (2004) [142]
Addiction	3F5, 3H9	Cocaine esterase	Mckenzie et al. (2007) [77]
Helicobacter pylori infection	UA15-L	Degrade both UreB and the intact urease	Hifumi et al. (2008) [85]
Catalytic antibody against cancers	84G3, 85H6, 90G8	Alliinase	Goswami et al. (2009) [143]
Prodrug activation			
Gene silencing	3D8-VL	mRNA of HER2 hydrolysis	Lee et al. (2010) [144]
Autoimmune inflammatory disorders	ETNF-6-H	Hydrolysis of TNF-α	Hifumi et al. (2010) [80]
Alzheimer disease	c23.5, polyclonal autoAb	Proteolytic cleavage of β-amyloid peptide aggregates	Paul et al. (2010) [145]
Catalytic antibody against coagulation factor	Polyclonal antibodies	Hydrolysis of FIX	Wootla et al. (2011a) [146]
Rabies virus infection	A18b	Proteolytic activity	Hifumi et al. (2011) [147]
Design new catalytic protein	Se-scFv2F3	Glutathione peroxidase (GPx) activity	Luo et al. (2013) [89]
Influenza	22F6	Amidase activity	Hifumi et al. (2013) [148]
Alzheimer disease (AD)	2E6	Hydrolyze amyloid β peptides (Aβ)	Nishiyama et al. (2014) [149]
Alzheimer disease	IgVL5D3	Hydrolyze amyloid β peptides (Aβ)	Kou et al. (2015) [150]
Avian influenza virus (H1N1)	3D8 scFv	RNA-hydrolyzing activity	Cho et al. (2015) [151]
Influenza infection	23D4	Peptidase and DNase activity	Hifumi et al. (2015) [152]
Generate a bioactive chloramphenicol	6D9, 9C10, and 7C8	Hydrolyze nonbioactive chloramphenicol monoester derivative	Oda et al. (2016) [153]
Potential prognosis marker	IgG	Hydrolyze proline-phenylalanine-arginine-methylcoumarin amide (PFR-MCA)	Mahendra et al. (2016) [154]
Kemp elimination reaction	D38N	Kemp Eliminase Activity	Lamba et al. (2017) [155]

Table 3 (continued)

Application	Antibodies	Activity	References
Multiple sclerosis (MS)	IGs	Recognize and hydrolyse distinct epitopes within myelin basic protein (MBP)	Lomakin et al. (2018) [156]
P-nitrobenzyl phosphonate transition-state analogue (TSA) 1	7B9	Hydrolyzes p-nitrobenzyl monoesters	Miyamoto et al. (2018) [157]
Triple-negative breast cancer (TNBC)	TrkB-targeting DVD-ADCs	h38C2 catalytic antibody	Lin et al. (2021) [158]
COVID-19	Recombinant antibody	Reporter enzyme Gaussia luciferase (Gluc) activity	Fellouse et al. (2021) [159]
COVID-19	3D8 scFv	Nucleic acid-hydrolyzing activity	Lee et al. (2021) [160]

be used as the window of the prodrug activation system in the latter, which has clear advantages: first, they can be chosen to catalyze reactions that endogenous enzymes cannot catalyze. Second, it has the potential to reduce the immunogenic response. Lerner's team devised a novel ADEPT method based on the catalytic antibody 38C2, which targets anticancer drugs like camptothecin, doxorubicin, and etoposide. The tandem reverse aldehyde alcohol inverse Michael reaction catalyzed by 38C2 activates the low hazardous prodrugs of these drugs [125–129]. The systemic toxicity of the etoposide prodrug was not found in the mouse neuroblastoma cell line NXS2 xenotransplantation model, where 38C2 was administered directly to the tumor site, and etoposide prodrug was delivered through systemic administration [130]. Simultaneously, researchers have developed several treatments based on various catalytic antibodies, including new esterase catalyzed antibody activated 5 fluorodeoxyuridine (5-FdU) prodrug therapy [131, 132] and catalytic antibody activated carbamate prodrug therapy with hydrolytic activity [133, 134]. Aldolase catalytic antibody treatment and cap catalytic antibody therapy based on an anti-idiotypic antibody approach are two examples of polymer-directed prodrug therapy [135–139].

The Use of Inactivation of Addictive Drugs

Illegal psychoactive substances like cannabis, methamphetamine, cocaine, and smoking, can cause disease and even death, posing a public health risk [125, 142, 161, 162]. Despite scientific attempts, no effective drugs to prevent drug abuse have been discovered so far. One of the strategies is immunotherapy, which combines and neutralizes target drugs. The catalytic antibody is present in the cycle, and after delivery, the drug is converted into inactive metabolites, but the catalytic antibody remains in the cycle for the next catalytic turnover [77, 125, 163]. Cocaine can be hydrolyzed into non-psychoactive benzoic acid and methyl n-propylamine as benzoyl ester. Proteins that stimulate this response could be injected into cocaine addicts to aid in their recovery [125]. Several catalytic antibodies have been developed and thoroughly researched [77, 140, 164]. McKenzie identified catalytic antibodies 3F5 and 3H9 capable of binding and hydrolyzing cocaine by phage display from a biased single-chain antibodies library, which was produced in spleens of mice previously immunized with cocaine phosphonate transition analogue hapten, and increased the hydrolytic activity by three times [77]. Landry's team produced antibodies 3B9 and 6A12 that catalyze the hydrolysis of cocaine benzoyl esters by cocaine's phosphonate monoester transition state analogs. Egonine methyl ester and benzoic acid produced by benzoyl esterolysis lack the stimulating activity of cocaine. Passive immunization with this catalytic antibody could treat dependence by blunting reinforcement [140]. Zhu analyzed the crystal structures of catalytic antibody 7A1 Fab′ and six complexes with substrate cocaine. Transition state analogue, products ecgonine methyl ester, and benzoic acid have been analyzed. The mechanism of catalytic hydrolysis of cocaine by the catalytic antibody 7A1 was elucidated [163].

Furthermore, tobacco addiction has been linked to a variety of cancers and cardiovascular diseases. As a result, it has gotten a lot of attention as immunological drug therapy for nicotine addiction. The researchers created antibodies that can oxidize nicotine in the presence of riboflavin and visible light by synthesizing hapten TD1 from normal nicotine and glutaric anhydride [142]. Catalytic antibodies provide an effective strategy for treating substance use disorders and overdose for drugs [142].

Application of Anti-Alzheimer Catalytic Antibody in the Treatment of Alzheimer's Disease

Alzheimer's disease (AD) pathogenesis. Aggregates cause microglia to become inflammatory, create neurotoxic effects, and destroy the anatomical structure of the brain [116, 164]. A (1–42) (A42) deposits harm brain structures, whereas A A (1–40) (A40) accumulates in vessel walls, causing microvascular-related neuroinflammation and impaired blood–brain barrier (BBB) integrity, which leads to cerebral amyloid angiopathy (CAA) in almost all AD patients [116, 165]. Catalytic antibodies have the ability to break down antigens into soluble fragments without the assistance of inflammatory cells. According to Rangan et al. [166], AβP was hydrolyzed into neuropeptide vasoactive intestinal peptide by a cross-reactive light chain fragment of the antibody. According to another study, IgM human autoantibodies hydrolyze AβP [167]. According to studies, IgM activity in AD patients is considerably higher than in controls, and IgM with catalytic activity can inhibit the accumulation and toxicity of AβPin neuron culture in vitro [167]. The catalytic material for hydrolyzing AβP between His14 and Gln15 was isolated after the "covalent" single strand Fv was randomly selected from the phage display library [79, 116]. Researchers have also developed catalytic antibody 2E6 using a catalytic immunoglobulin V domain (IgV) derived from a human IgV library, which they utilize to break down and eliminate A without causing microglial activation or microhemorrhage [79].

In 2020, Planque et al. [90] developed an electrophilic target analogue based therapeutic grade catalytic antibody production platform. Researchers have developed catalytic antibodies for the treatment of Alzheimer's disease and anti-aging based on this technology [90]. According to the studies, catalytic antibodies may permanently remove target cells, and their efficacy is far superior to that of ordinary antibodies. Without developing or maintaining systemic amyloid pathology, human IgM antibodies selectively eliminate misfolded but usually non-aggregative fragments of TTR. Similarly, catalytic antibodies in the body break down Aβ into non-toxic, non-aggregative fragments without developing or perpetuating Alzheimer's disease [79, 116]. The catalytic antibody matrix complex is too short to activate inflammatory cells, whereas common antibodies create persistent immune complexes, which invariably cause inflammation. In mouse models, catalytic antibodies targeting brain Aβ were found to be effective [90, 116, 150].

It is believed that the utility of this catalytic antibody platform can be extended to a wide range of proteins involved in disease and aging damage to various organ systems, including protein targets involved in human susceptibility to microbial infections and autoimmune, nervous, cardiovascular, and oncological diseases [90]. Antibodies are made as needed from constitutive or immunogen-induced antibody libraries. In theory, the platform may manufacture catalytic antibodies to particularly every target protein using innate Darwinian immunity and acquired immunity triggered by immunogen [90].

Application of Catalytic Antibodies in the Field of Infection and Immunity

Septicemia

Septicemia is the most common cause of death in intensive care units, and it is caused by the toxic host's systemic response to infection [36, 168]. With the widespread use of

antibiotics, the incidence of septicemia caused by opportunistic pathogens has gradually increased in recent years, with the increase in drug-resistant strains, showing a trend of multidrug resistance [169, 170]. Selecting appropriate antibiotics based on the results of blood culture and drug sensitivity test is an effective method for the treatment of septicemia. but the results of bacterial culture cannot be obtained quickly. Antibiotics are usually selected based on clinical experience. The lack of pertinence is inevitable. Catalytic antibodies have been proposed to be involved in the removal of metabolic waste and the prevention of infection. It has been shown that high levels of catalytic antibodies are associated with a good prognosis of septicemia [36, 168]. IgG with serine protease-like hydrolysis activity is present in the plasma of the patients. The difference in IgG catalytic rate in patients with severe septicemia was higher than that in healthy blood donors, indicating that septicemia was related to the change of plasma hydrolyzed IgG level. The IgG catalytic rate of surviving patients was significantly higher than that of dead patients' IgG. Compared with patients with low hydrolysis rates, patients with high IgG-mediated hydrolysis rates had higher cumulative survival rates [168]. In addition, the IgG of three surviving patients hydrolyzed factor VIII, and one of them also hydrolyzed factor IX, suggesting that catalytic IgG may be involved in the control of diffuse microvascular thrombosis in some patients. Evidence that IgG-hydrolyzing antibodies may play a role in sepsis recovery [168]. Scientists predict that catalytic antibodies can reduce infection and inflammation in septicemia patients but that a lack of catalytic antibody response may accelerate the occurrence of the disease [36, 168]. It is a better potential way to treat septicemia.

Systemic Lupus Erythematosus

Antibodies against foreign antigens and autoantigens are usually produced in patients with autoimmune diseases [36, 37]. Systemic lupus erythematosus (SLE) is a chronic and potentially fatal autoimmune disease characterize[ed by deterioration and remission. The common symptom of SLE is conjunctival tissue disorder [36]. SLE patients often have large amounts of DNA and anti-DNA antibodies in their blood [171, 172]. Both cellular and soluble inflammatory mediators are involved in the pathogenesis of lupus [173–175]. SLE is marked by the presence of a series of IgG and IgM autoantibodies against one or more nuclear components, particularly double-stranded DNA. antibodies with catalytic properties against DNA or RNA are present in SLE [12, 176]. In the early 1990s, Gabipov's team reported that autoantibodies purified from the sera of patients with systemic lupus erythematosus and other autoimmune diseases could cleave phosphodiester bonds [12, 176, 177]. Polyclonal IgG antibodies purified from the sera of several SLE patients and hepatitis B patients showed RNA hydrolysis activity that differed from the weak RNAase type A activity of healthy donor IgG [22, 36]. However, these reports did not provide an indication of whether catalytic antibodies correlated with disease severity. Subsequently, Pradhan analyzed the hydrolytic activity of IgG from SLE patients in India and showed that the hydrolysis rate of PFRMCA by SLE IgG was also significantly higher than that of healthy donors. Catalytic antibody response may be part of the active disease process [36]. Therefore, the mechanism of origin of catalytic antibodies and the exact role of these antibodies in the pathogenesis of lupus should continue to be studied in a large number of SLE patients, to develop new biomarkers and treatment strategies for systemic lupus erythematosus [178, 179].

Acquired Immune Deficiency Syndrome

Some antibodies with different catalytic activities can be activated spontaneously by primary antigens and have primary antigen-like properties, such as the catalytic activity of idiotypic antibodies and/or anti-idiotypic antibodies [180]. They have the ability to degrade different peptides and proteins. For example, CD4 cells infected with HIV requires to bind the HIV surface glycoprotein gp120/gp41 to the CD4 receptor. Both Ig G and Ig M catalytic antibodies [78, 81, 180, 181] showed anti-gp120 polypeptidase activity. The catalytic antibody 41S-2-L developed by Hifumi was able to hydrolyze the glycoprotein gp41 and destroy non-autoantigen proteins by targeting them with immuno synthetic peptide antigens [81]. Long-term HIV infection was associated with a mild risk of catalytic secretory IgA (SIgA) of gp120 in patients who did not develop AIDS [181]. This activity was also found in the SIgA from non-HIV-positive patients, while RNA antibodies and anti-RNA antibodies have been found in the sera of numerous AIDS patients [182–185]. These antibodies have phosphodiester bond cleavage activity, implying that they are catalytic antibodies that contribute to resistance to infection.

Catalytic Antibodies that Inhibit New Coronavirus Infection

At the end of 2019, a new coronavirus spread over the globe, causing a new type of pneumonia disease (COVID-19) with high transmission and fatality [186–190]. A safe and effective vaccination is desperately needed, but development takes time. At the same time, very precise and effective antiviral therapies are required in the post-vaccine era. According to studies, SARS-CoV-2 enters host cells via contact between prickle glycoprotein and the angiotensin-converting enzyme 2 (ACE2) receptor. SARS-CoV-2 infection and transmission could be averted if this interaction could be blocked directly [190–193]. Single-stranded variable fragment (scFv) is a catalytic antibody with broad-spectrum antiviral activity against DNA and RNA viruses due to its nucleic acid hydrolysis properties. Lee evaluated the antiviral activity of the scFv 3D8 against SARS-CoV-2 and other coronaviruses in VeroE6 cell culture [160]. It was found that 3D8 inhibited the replication of SARS-CoV-2, human coronavirus OC43 (HCoV-OC43) and porcine epidemic diarrhea virus (PEDV). The preventive and therapeutic effects of catalytic antibody 3D8 against SARS-CoV-2 in VeroE6 cells were demonstrated. Immunoblotting and plaque analysis showed that the nucleoprotein and infected particles of coronavirus decreased in the cells treated with 3D8 [160]. These data indicate that 3D8 has broad-spectrum antiviral activity against SARS-CoV-2 and other coronaviruses [160]. Therefore, it can be considered a potential antiviral strategy against SARS-CoV-2 and zoonotic coronavirus.

Summary and Prospect

A large number of naturally occurring catalytic antibodies have been identified and intensively studied. The emergence of catalytic antibodies has been described in a variety of pathological conditions, including the autoimmune and alloimmune response. The emergence and increased titers of catalytic antibodies may represent a general phenomenon of inflammatory responses. With advances in engineering technology and the aid of

bioinformatics tools, scientists have developed antibodies with unique characteristics and catalytic properties. Catalytic antibodies can be used to destroy specific pathogens or tumor cells, remove autoimmune metabolites, protect normal cells from toxicity, and design catalysts suitable for passive immunotherapy of major diseases or stimulate catalytic immunity within the framework of preventive immunization. Although the reaction rates of catalytic antibodies are typically several orders of magnitude lower than that of typical enzymes, the concentration of catalytic antibodies in serum is much higher and can last for a long half-life. The combination of increased antibody concentration and longer action time can compensate for a low catalytic rate, especially in the case of chronic diseases or latent infections. where catalytic antibodies can play an important beneficial role in disease and immunity. Therefore, this paper summarizes the development, design, and evolution methodology of catalytic antibodies, as well as the expression system and application of catalytic antibodies.

However, catalytic antibody behaves as a double-edged sword. Naturally occurring catalytic antibodies are considered to play a pathogenic and beneficial role in a variety of autoimmune diseases. It is unclear whether the catalytic antibodies produced under pathological conditions play a pathogenic role or reflect the body's attempt to re-establish homeostasis in the body. The mechanism of origin of catalytic antibodies and the exact role of these antibodies in the pathogenesis of related diseases need to be studied in a large number of clinical trials. The fact that the stability of recombinant antibodies (including catalytic antibodies) is highly unpredictable in the physiological environment complicates the use of catalytic antibodies in research and clinical applications. Some problems still need to be further examined. However, catalytic antibodies are still considered promising tools for the treatment of human diseases due to the combination of high substrate/antigen specificity, enzyme-like turnover, relatively low catalytic efficiency, and high half-life.

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Data Availability Data and materials will be freely available in PubMed.

Declarations

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