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ABZYMES: A Comprehensive Review of Applications and Advances

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I. WHAT IS ABZYMES?

Abzymes, or antibody enzymes, are antibodies that have enzymatic activity. They can catalyze chemical reactions, similar to traditional enzymes. Abzymes have potential applications in medicine and biotechnology, as they can be engineered to target specific molecules, making them promising for therapies and diagnostics. They often called catmab (from catalytic monoclonal antibody).They can be artificial or naturally occurring, even in autoimmune diseases. They function by stabilizing reaction intermediates, making them valuable tools in biotechnology.

II. HISTORY OF ABZYMES

The possibility of catalyzing a reaction by means of an antibody which binds the transition state was first suggested by William P. Jencks in 1969. But * The first natural catalytic antibody, now termed abzyme, which hydrolyzes intestinal vasoactive peptide, was discovered by Paul et al. [Science 244 (1989) 1158].

III. NATURE OF ABZYMES

The nature of catalysis, specifically in the context of catalytic antibodies (abzymes), is characterized by their ability to process substrates through a Michaelis complex, similar to enzymes. Two key indices, kcat/kuncat and kcat/KM, are used to evaluate the catalytic efficiency of abzymes. The kcat parameter represents the rate of product formation when the antibody is saturated with substrate, while KM signifies the concentration of substrate producing half the maximal catalytic rate and serves as an approximate measure for the dissociation of the abzyme-substrate complex.

For abzymes, the kcat/kuncat values typically range from 10 to 106, and kcat/KM values are below those of diffusion-controlled processes. This suggests that the chemical step of the transformation is often rate-limiting, influenced by the antibody's affinity for its inducing hapten. Abzymes primarily catalyze reactions by restricting substrate movements within their active site cavity and, to a lesser extent, through acid/base or nucleophilic catalysis.

Covalent catalysis examples within abzymes tend to exhibit higher kinetic indices, but product inhibition can limit overall reaction flux. These abzymes may represent primitive forms of their enzyme counterparts, and the success of this technology relies on the selection and placement of catalytic active site residues.

Reactive immunization is a novel approach that generates catalytic antibodies by using highly reactive antigens to induce chemical reactions within the antibody's combining site. This method has been successfully applied to various reactions, including aldol condensation, where antibodies mimic natural Class-I aldolase enzymes.

The rate enhancement achieved by catalytic antibodies can vary significantly, with some reaching high values. However, off-the-shelf proteins like bovine serum albumin can exhibit similar rate enhancements, suggesting the challenges in achieving consistently high catalytic efficiency in abzymes. The ability to mimic the versatility and efficiency of enzymes with synthetic catalysts and antibodies remains a challenging task in the field of catalysis.

IV. CATALYTIC PROPERTIES OF ANTI-DSDNA ANTIBODIES (ABZYMES / CATMAB)

This passage discusses the catalytic properties of anti-double-stranded DNA (anti-dsDNA) antibodies, known as catalytic antibodies or abzymes. These antibodies have the ability to catalyze chemical reactions, particularly the hydrolysis of DNA. Catalytic antibodies are found in individuals with autoimmune diseases like lupus and even in response to viral and bacterial infections. These antibodies play a role in autoimmune diseases' pathogenesis, such as systemic lupus erythematosus (SLE), by cleaving DNA. However, their potential therapeutic application remains uncertain, as getting these antibodies into cell nuclei for a therapeutic effect is challenging.

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The study (Structure-Function in Antibodies to Double-Stranded DNA lYumin Xia *, Ertan Eryilmaz *, David Cowburn *, Chaim Putterman †) also highlights the isotype-dependent nature of anti-dsDNA antibodies' catalytic properties. The specific methods to detect catalytic antibodies vary, depending on the antigen and substrate involved. Techniques like agarose gel electrophoresis, microtiter plate assays, and mass spectrometry are used to assess their catalytic potential. The presence of catalytic antibodies can be a double-edged sword, as they can potentially block the interaction of lupus antibodies with glomerular antigens but may also cleave peptides designed for inhibition.

In conclusion, this passage explores the existence of catalytic antibodies, their isotype-dependent nature, and the challenges and potential applications in therapeutics. It emphasizes the need to identify specific cleavage sites and amino acid sequences to enhance the potential use of these antibodies in disease management.

V. USES OF ABZYMES IN BIOPHARMACEUTICAL INDUSTRIES

Antibodies, known for their role in the immune system, can also serve as catalysts, termed 'abzymes,' when engineered using transition state analogs as immunogens. These abzymes exhibit remarkable catalytic abilities, enhancing substrate hydrolysis by factors ranging from oi10^2 to 10^5 compared to their non-bound counterparts. This concept has been harnessed for therapeutic development.

While abzymes display esterase and amidase activities, their catalytic turnover is generally lower than natural enzymes due to high-affinity binding, which hinders product release. Researchers in academia and biotech startups have delved into enhancing abzyme efficiency and discovering therapeutic applications. Potential targets for abzyme-based therapies include combatting cocaine overdose and addiction, neutralizing bacterial endotoxins, and designing monoclonal antibodies conjugated with catalytic antibodies to activate cytotoxic prodrugs for cancer treatment.

Additionally, efforts are underway to create proteolytic abzymes with catalytic triads resembling those in serine proteases. These could be used to cleave key proteins like gp120 for HIV treatment, IgE for allergy management, or epidermal growth factor receptors in the context of cancer treatment. The exciting potential of abzymes opens doors to innovative solutions for a range of medical challenges, exemplifying the remarkable fusion of immunology and catalysis in the field of biotechnology.

VI. USES OF ABZYMES IN MEDICAL FIELD

Medical abzymology has significantly advanced our understanding of autoimmunity theory by elevating autoantibodies (Ab) to a central role. These Ab have been shown to possess catalytic capabilities, allowing them to directly and independently target and damage cellular and molecular structures. Natural catalytic autoantibodies, referred to as abzymes, represent a distinct group of physiologically active substances, combining canonical antibody properties with catalytic functions.This breakthrough opens the door for the development of new-generation biomarkers and tools for assessing disease progression and predicting patient disability. By investigating Ab-mediated autoantigen degradation and targeted Ab-mediated proteolysis, researchers can gain insights into autoimmune clinical cases, their role in disease development, and the potential for creating highly effective, personalized therapeutic drugs and protocols. In essence, this chapter highlights the current knowledge and future prospects of catalytic Abs in the context of autoimmunity, promising innovative approaches for the treatment of autoimmune diseases and the customization of therapeutic strategies.

A. Antigen-antibody Interactions

Antigen-antibody interactions play a pivotal role in the field of biotechnology, offering unique advantages when compared to natural enzymes. Antibodies, as well-characterized molecules, can be readily purified and produced in substantial quantities, making them easily accessible for various applications. What sets catalytic antibodies apart is their versatility - they can be specifically tailored for a wide range of chemical reactions, even those lacking a natural enzyme counterpart. Early catalytic antibodies initially exhibited lower catalytic rates compared to their natural enzyme counterparts, but with refined immunogen design, abzymes have emerged that match or even surpass the efficiency of native enzymes. Moreover, these ingenious antibodies have found novel applications, such as breaking down substances like cocaine into harmless by-products, potentially offering new avenues for drug addiction treatment. Beyond medicine, catalytic antibodies can be engineered to target environmental pollutants, opening up the possibility of designer bacteria equipped with these antibodies that can remediate hazardous chemical spills and pollutants. As this technology advances in complexity and sophistication, the utilization of abzymes in various industrial and non-industrial contexts is poised to expand.

VII. USSES IN ANTIBODY ENGINEERING

Over 45 years ago, Linus Pauling introduced the concept of transition state stabilization as the foundation of enzymatic catalysis. This notion was expanded upon by Jencks more than 25 years ago, suggesting that antibodies raised against transition state analogs could mimic natural enzymes. These ideas have significantly impacted enzymology, leading to the discovery of catalytic antibodies (abzymes) in 1986.Various strategies have been employed to enhance the catalytic activity of these abzymes. Site-directed mutagenesis has been used to introduce catalytic residues, engineer metal coordination sites, and leverage technologies like repertoire cloning and phage display. In specific cases, mutagenesis studies have been conducted to improve catalytic activity. For example, a mutation of VL-Tyr34 to His in one antibody led to a substantial increase in catalytic activity. Similarly, altering key heavy-chain residues in another antibody demonstrated the importance of electrostatic interactions in its catalytic mechanism. Metal coordination sites have been engineered into antibody light chains to enhance catalytic potential. For example, a zinc-binding site was introduced into a fluorescein-binding antibody, resulting in improved catalytic activity. Combinatorial libraries and modern molecular biology methods have been used to screen for catalytic antibodies, with the aim of improving their efficiency. Genetic selection schemes employing specific substrates have shown promise in enhancing catalytic activity. While these approaches have achieved some success in improving abzymes' catalytic efficiency, challenges remain. The development of new genetic engineering techniques holds the promise of further advancements in this exciting field of antibody engineering.

VIII. RECENT STUDIES

The recent studies said that , the focus shifts towards proteins, exploring various facets of their structure and function. Rémy Ricoux and Jean-Pierre Mahy delve into the world of catalytic antibodies, often referred to as 'abzymes,' in

Chapter 5.12. These biocatalysts, based on monoclonal antibodies, exhibit the remarkable ability to catalyze diverse chemical reactions, though their efficiency falls short of natural enzymes. Ute Kothe, in

Chapter 5.13, provides a comprehensive overview of ribosomal protein synthesis, shedding light on one of the most fundamental and conserved processes in all living cells. Recent crystal structures have enhanced our understanding of this intricate interplay between RNA and proteins.

Chapter 5.14, authored by Jonathan Huot, Jacques Lapointe, Robert Chenevert, Marc Bailly, and Daniel Kern, explores the intriguing biosynthetic pathways and functions of glutaminyl-tRNA and asparaginyl-tRNA. These unconventional routes hold great significance in biological processes. Posttranslation modifications of proteins take center stage in

Chapter 5.15, where Keith Green and Sylvie Garneau-Tsodikova present a contemporary perspective on these critical processes, influencing protein diversity and function. The subsequent article,

Chapter 5.16, penned by Hans Peter Bachinger, Kazunori Mizuno, Janice Vranka, and Sergei Boudko, offers an extensive examination of collagens, a vital component of the extracellular matrix crucial for tissue and organ structure.

Chapter 5.17, by Kristina Görmer, Luc Brunsveld, and Herbert Waldmann, delves into protein lipidation, a posttranslational modification impacting protein structure, activity, and cellular localization.Angela Parrish and Lei Wang, in

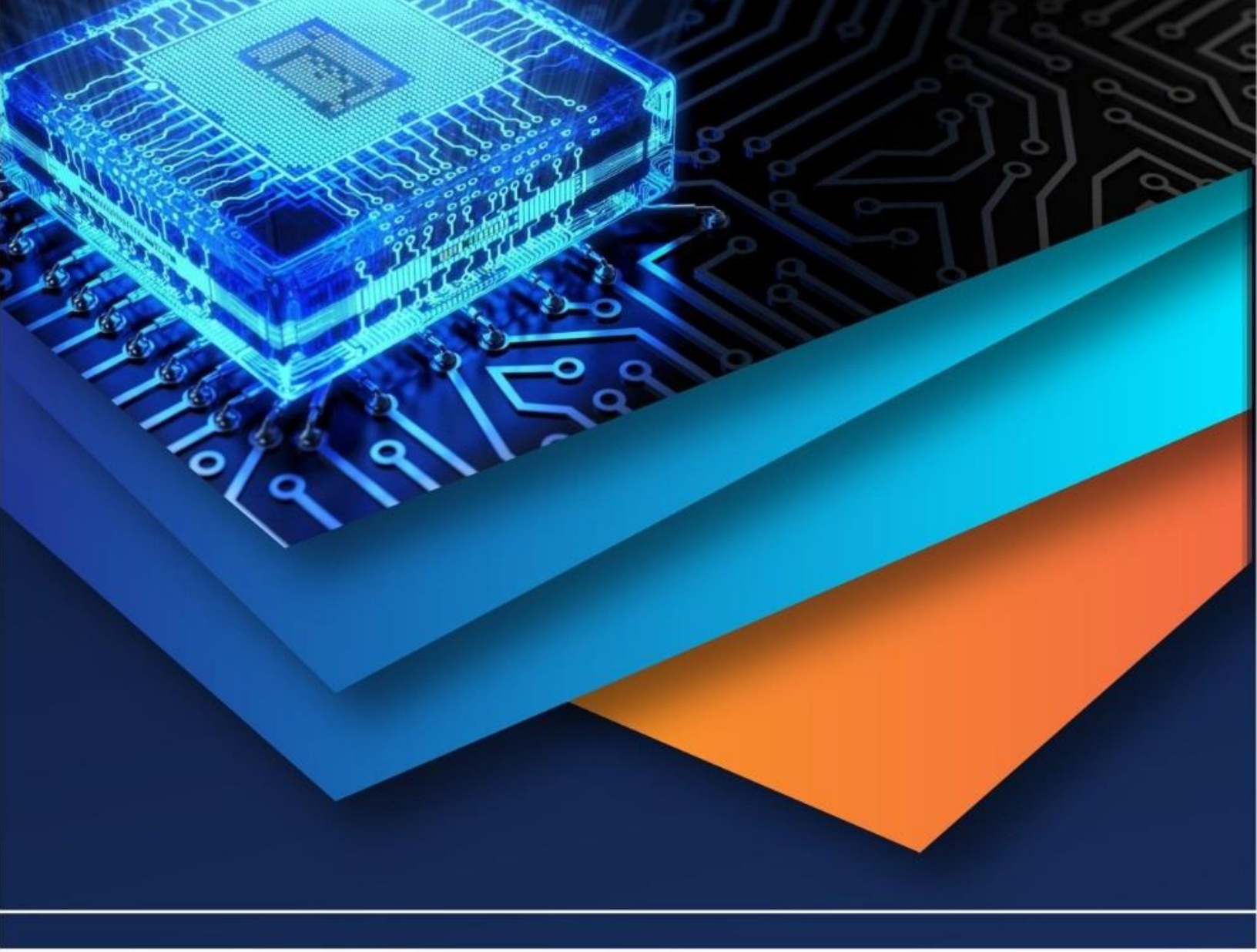
Chapter 5.18, explore the expansion of the genetic code through the incorporation of unusual amino acids into proteins, a breakthrough that has enabled the genetic encoding of over 40 novel amino acids.In Chapter 5.19, Timothy Montavon and Steven Bruner provide insights into the mechanisms and enzymes involved in nonribosomal peptide biosynthesis, which yields biologically and medicinally important compounds.

Chapter 5.20, by Petrus Milne and Gareth Kilian, focuses on 2,5-diketopiperazines, a family of cyclic dipeptides with diverse effects, including immunomodulation, hormone regulation, and anti-tumor properties.The volume concludes with a review in

Chapter 5.21 by Ashok Hegde, exploring ubiquitin-dependent protein degradation, a pathway of great importance in both physiological and pathological processes, including cancer and Alzheimer's disease.

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