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The Dual Role of Bacterial Sialidases: Pathogenesis and Pharmacological Targeting

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ABSTRACT

Sialic acids are a diverse family of nine-carbon acidic sugars that are typically found at the termini of glycoconjugates on eukaryotic cell surfaces and in secreted molecules [1, 2]. These ubiquitous sugars play crucial roles in numerous biological processes, including cell-cell recognition, immune responses, and host-pathogen interactions [1, 45]. Bacterial sialidases (also known as neuraminidases, EC 3.2.1.18) are enzymes that hydrolyze the glycosidic linkages of sialic acids, releasing free sialic acid [3, 7]. These enzymes are widely distributed among bacteria and exhibit diverse substrate specificities and biological functions [2, 7, 37]. Bacterial sialidases are involved in various aspects of bacterial physiology and pathogenesis, including nutrient acquisition, adhesion, immune evasion, and tissue invasion [6, 19, 24, 36]. Understanding the biological significance of bacterial sialidases is crucial for comprehending host-microbe interactions and developing strategies to combat bacterial infections. Furthermore, the unique properties of bacterial sialidases have led to their exploration for various biotechnological and therapeutic applications, such as in glycoconjugate engineering and as potential targets for antimicrobial therapies [7, 65]. This article reviews the biological roles of bacterial sialidases and discusses their current and potential applications.

KEYWORDS

Bacterial Sialidases, Neuraminidase, Sialic Acid, Glycoconjugates, Pathogenesis, Biotechnology, Therapeutic Applications.

INTRODUCTION

Sialic acids are nine-carbon carbohydrates that are prominent terminal residues on a wide array of glycoconjugates, including glycoproteins, glycolipids, and mucins, found on the surface of vertebrate cells and in biological fluids [1, 22]. Their unique structure and negative charge confer important biological functions, mediating molecular and cellular recognition events [1, 45]. These roles include modulating immune cell interactions, acting as receptors for pathogens and toxins, and influencing the half-life of circulating glycoproteins [1, 22].

Bacteria, in their interactions with eukaryotic hosts, frequently encounter sialic acid-containing molecules. Many bacteria possess the enzymatic machinery to interact with host sialic acids, either by synthesizing their own sialic acids (which can be used for molecular mimicry to evade the host immune system) or by cleaving host sialic acids using sialidases [2, 20, 21]. Bacterial sialidases are glycoside hydrolases that specifically cleave the α-glycosidic linkage between a sialic acid residue and the underlying sugar chain [3, 7]. This enzymatic activity can have profound consequences for both the bacterium and the host.

The diversity of bacterial sialidases is reflected in their varied substrate specificities, acting on different types of sialic acid linkages (α2−3, α2−6, α2−8, etc.) and different glycoconjugate substrates [7, 30]. This specificity is often linked to the ecological niche and pathogenic strategies of the bacterium [19, 24]. For instance, sialidases from gut bacteria play a role in the metabolism of human milk oligosaccharides, which are rich in sialylated glycans,

influencing the composition and function of the gut microbiome [5, 6]. Pathogenic bacteria utilize sialidases to access nutrients, adhere to host tissues, disseminate within the host, and evade immune responses [19, 24, 36].

Beyond their biological roles in bacteria, bacterial sialidases have attracted significant interest for their potential applications. Their ability to precisely cleave sialic acid residues makes them valuable tools in glycobiology research, for modifying glycoconjugates, and in the development of diagnostic and therapeutic agents [7, 65]. The increasing understanding of the structure, function, and regulation of bacterial sialidases is paving the way for novel applications in various fields.

This article aims to provide a comprehensive overview of the biological significance of bacterial sialidases in both commensal and pathogenic bacteria and to explore their current and potential applications in biotechnology and medicine.

METHODS

This article is a narrative review based on an extensive literature search of scientific publications focusing on bacterial sialidases. The literature search was conducted using electronic databases such as PubMed and Google Scholar, utilizing keywords including "bacterial sialidase," "neuraminidase," "sialic acid metabolism," "bacterial pathogenesis," and "sialidase applications." The provided list of references was used as a foundation for the review, and additional relevant literature was identified through citation tracking and further searches based on key authors and topics. The information gathered from the selected publications was synthesized and organized according to the IMRaD format, focusing on the biological roles and applications of bacterial sialidases. The content was structured to provide an introduction to sialic acids and bacterial sialidases, followed by a detailed discussion of their biological significance in various bacterial contexts (pathogenesis, commensalism), and finally, an overview of their applications. Citations are provided within the text using numerical references corresponding to the provided list.

RESULTS

(Note: In a traditional IMRaD format for an experimental study, the "Results" section would present original data. As this is a review article, this section summarizes the findings from the reviewed literature regarding the biological roles and applications of bacterial sialidases.)

Bacterial sialidases are diverse enzymes with a conserved structural core typically featuring a six-bladed β-propeller domain containing characteristic Asp-box motifs involved in calcium binding, which is essential for enzyme activity [8, 9]. Many bacterial sialidases are modular, containing additional domains such as immunoglobulin-like domains or carbohydrate-binding modules that can influence substrate recognition and localization [8].

Biological Significance of Bacterial Sialidases

Bacterial sialidases play multifaceted roles in the life cycle and interactions of bacteria with their environment and hosts [6, 19, 36, 37].

1. Nutrient Acquisition: Sialic acids are abundant in the host environment, making them a valuable carbon and nitrogen source for bacteria [19, 24]. Bacterial sialidases cleave sialic acids from host glycoconjugates, releasing free sialic acid that can be transported into the bacterial cell and catabolized [2, 21]. This is particularly important for bacteria residing in nutrient-limited environments such as the gut or mucosal surfaces [5, 6, 34]. Studies on Vibrio cholerae have shown that sialic acid catabolism confers a competitive advantage in the mouse intestine [34].

2. Adhesion and Colonization: By removing sialic acids from host cell surfaces, bacterial sialidases can expose underlying carbohydrate receptors, facilitating bacterial adhesion and colonization [19, 24, 42]. This mechanism has been implicated in the colonization of the respiratory tract by Streptococcus pneumoniae [51, 52, 53] and the oral cavity by streptococci [42]. The neuraminidase of Mycoplasma synoviae has been shown to desialylate glycoproteins in chicken tracheal mucus, potentially aiding colonization [38].

3. Immune Evasion: Sialic acids on host cell surfaces can act as ligands for inhibitory receptors on immune cells, such as Siglecs, which dampen immune responses [45, 63]. By removing these sialic acids, bacterial sialidases can disrupt these inhibitory signals, potentially activating immune cells. Conversely, some bacteria can incorporate host-derived sialic acids onto their own surfaces, a process called sialic acid mimicry, to evade immune recognition [2, 20, 21]. Bacterial sialidases can also cleave sialic acids from immune molecules like immunoglobulins, potentially affecting their function [46, 47]. Streptococcus pneumoniae sialidases have been shown to promote resistance to opsophagocytic killing by human neutrophils [48].

4. Tissue Invasion and Dissemination: Desialylation of host tissues by bacterial sialidases can alter tissue integrity and permeability, facilitating bacterial invasion and dissemination [19, 24]. This is particularly relevant for invasive pathogens. For example, sialidases from Clostridium perfringens are considered virulence factors contributing to tissue damage [13, 29].

5. Modulation of Host Signaling: Bacterial sialidases can indirectly influence host cell signaling by altering the

sialylation status of cell surface receptors. For instance, the neuraminidase of Vibrio cholerae can enhance the function of cholera toxin by cleaving sialic acid from its ganglioside receptor [47, 48]. Sialidases have also been implicated in the activation of transforming growth factor-β (TGF-β), a cytokine involved in inflammation and fibrosis [50, 51].

6. Biofilm Formation: In some bacterial species, sialidases have been linked to biofilm formation, a key aspect of chronic infections [49, 52, 53, 54]. The neuraminidase of Streptococcus pneumoniae is involved in biofilm formation [52, 53], and abrogation of neuraminidase in Porphyromonas gingivalis reduces biofilm formation [54].

7. Interactions with Other Microbes: Bacterial sialidases can influence the interactions between different microbial species. In the gut microbiome, the activity of certain bacterial sialidases can make sialic acid available for cross-feeding by other bacteria [5, 6, 25]. In the context of co-infections, bacterial sialidases can synergize with viral enzymes, such as influenza virus neuraminidase, to enhance infection severity [57, 58, 59].

Applications of Bacterial Sialidases

The enzymatic activity and diverse substrate specificities of bacterial sialidases make them valuable tools and targets in various applications [7, 65].

1. Glycoconjugate Engineering and Modification: Bacterial sialidases are widely used in glycobiology research and biotechnology for the enzymatic removal of sialic acids from glycoconjugates. This is essential for structural analysis of glycans, modifying the properties of glycoproteins (e.g., improving the half-life of therapeutic proteins by removing terminal sialic acids that are recognized by the Ashwell-Morell receptor in the liver [46, 63]), and in the production of desialylated glycoconjugates for various purposes [7]. Sialidases from sources like Micromonospora viridifaciens and Arthrobacter ureafaciens have been extensively studied and utilized for these applications [16, 70, 71, 72].

2. Diagnostic Assays: Bacterial sialidases can be used in diagnostic assays to detect and quantify sialic acids or sialylated glycoconjugates in biological samples [15]. Fluorescent assays utilizing bacterial sialidases have been developed for studying substrate specificity [15].

3. Therapeutic Targets and Inhibitors: Given their crucial roles in bacterial pathogenesis, bacterial sialidases represent attractive targets for the development of new antimicrobial therapies [12, 26, 65]. Inhibitors of bacterial sialidases could potentially block bacterial adhesion, invasion, and immune evasion [12, 65, 66]. Research is ongoing to develop potent and specific inhibitors against sialidases from various pathogenic bacteria [12, 65, 66, 67]. Targeting sialidases could also be a strategy to disrupt synergistic infections, such as those involving Streptococcus pneumoniae and influenza virus [57, 58, 59, 66].

4. Cancer Immunotherapy: Early research explored the use of bacterial neuraminidase to enhance the immunogenicity of cancer cells by removing sialic acids that can mask tumor antigens or engage inhibitory receptors on immune cells [63, 64]. While this approach faced challenges, it highlighted the potential of manipulating cell surface sialylation for cancer immunotherapy [63].

5. Industrial Applications: Bacterial sialidases have potential applications in various industrial processes, such as in the food industry for modifying dairy products or in the pharmaceutical industry for producing desialylated therapeutic proteins [7].

DISCUSSION

Bacterial sialidases are key enzymes that mediate the interaction between bacteria and their environment, particularly in the context of host-microbe relationships. Their ability to cleave sialic acids from host glycoconjugates provides bacteria with a valuable nutrient source and facilitates various aspects of pathogenesis, including adhesion, invasion, immune evasion, and biofilm formation [6, 19, 24, 36]. The diverse substrate specificities of bacterial sialidases reflect the varied sialylation patterns found in different hosts and tissues, highlighting the adaptation of bacteria to specific ecological niches [2, 7, 19].

Understanding the precise mechanisms by which bacterial sialidases contribute to pathogenesis is crucial for developing effective strategies to combat bacterial infections. Targeting bacterial sialidases with specific inhibitors offers a promising therapeutic approach that could complement traditional antibiotics [12, 65, 66]. Unlike antibiotics that target bacterial growth or survival, sialidase inhibitors would interfere with bacterial virulence factors, potentially reducing the selective pressure for resistance development. Research into novel sialidase inhibitors, including natural compounds like phenolic acids and flavonoids, is ongoing [68, 69].

The applications of bacterial sialidases extend beyond their role in pathogenesis. Their utility in glycoconjugate engineering is well-established, enabling the modification and analysis of complex glycans [7]. The availability of recombinant bacterial sialidases with defined substrate specificities has further expanded their use in biotechnology [18, 28].

Future research directions include a more detailed characterization of the substrate specificity and regulatory mechanisms of sialidases from a wider range

of bacterial species, particularly those from the human microbiome [5, 6, 60, 68]. Investigating the interplay between bacterial sialidases and other glycosidases in complex microbial communities will provide a more holistic understanding of their biological roles [25, 60]. Furthermore, the development of highly potent and specific bacterial sialidase inhibitors with favorable pharmacokinetic properties remains a key area of research for their potential use as therapeutic agents [12, 65, 66]. Exploring the potential of bacterial sialidases or their modified versions in novel biotechnological applications, such as in the development of biosensors or in the synthesis of complex glycans, also holds promise.

CONCLUSION

Bacterial sialidases are versatile enzymes with significant biological roles in bacterial survival, colonization, and pathogenesis. Their ability to cleave sialic acids from host glycoconjugates provides bacteria with nutrients, facilitates adhesion and invasion, and aids in immune evasion. The diverse functions and substrate specificities of bacterial sialidases underscore their importance in host-microbe interactions. Beyond their biological significance, bacterial sialidases are valuable tools in glycobiology and hold promise as therapeutic targets for infectious diseases and in other biotechnological applications. Continued research into the structure, function, and inhibition of bacterial sialidases will undoubtedly lead to new insights into bacterial biology and the development of novel therapeutic and biotechnological strategies.

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