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REVIEW

Nanoscale warriors against viral invaders: a comprehensive review of Nanobodies as potential antiviral therapeutics

Vaishali Verma [a], Nimisha Sinha [b], and Abhavya Raja [a,c]

[a]Department of Biotechnology, School of Engineering and Applied Sciences, Bennett University, Greater Noida, India; [b]Department of Biochemistry, Sri Venkateswara College, University of Delhi, New Delhi, India; [c]Department of Surgery and Cancer, Imperial College London, South, London, UK

ABSTRACT

Viral infections remain a significant global health threat, with emerging and reemerging viruses causing epidemics and pandemics. Despite advancements in antiviral therapies, the development of effective treatments is often hindered by challenges, such as viral resistance and the emergence of new strains. In this context, the development of novel therapeutic modalities is essential to combat notorious viruses. While traditional monoclonal antibodies are widely used for the treatment of several diseases, nanobodies derived from heavy chain-only antibodies have emerged as promising "nanoscale warriors" against viral infections. Nanobodies possess unique structural properties that enhance their ability to recognize diverse epitopes. Their small size also imparts properties, such as improved bioavailability, solubility, stability, and proteolytic resistance, making them an ideal class of therapeutics for viral infections. In this review, we discuss the role of nanobodies as antivirals against various viruses. Techniques used for developing nanobodies, delivery strategies are covered, and the challenges and opportunities associated with their use as antiviral therapies are discussed. We also offer insights into the future of nanobody-based antiviral research to support the development of new strategies for managing viral infections.

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Introduction

Viral infections present a persistent and formidable challenge to global health, underscored by the emergence and reemergence of various viral pathogens that can lead to epidemics and pandemics. Despite advancements in antiviral therapies, the development of effective treatments is frequently affected by issues such as immune evasion,[1] continuous emergence of new strains causing drug resistance, and costs associated with drug development.[2] This necessitates the development of new therapeutic strategies to overcome the existing challenges. Monoclonal antibodies (mAbs) have been recognized as an important class of targeted therapeutic agents for the treatment of a wide range of disease conditions.[3,4] Typically, they exhibit high specificity and affinity for their target with relatively low toxicity.[5] In addition to their use in the treatment of cancer, autoimmunity, and inflammation, they have also been recognized as potent antiviral molecules. MAbs have been developed to treat various viral infections, including infections caused by human immunodeficiency virus (HIV), respiratory syncytial virus (RSV), and SARS-CoV-2.[6–8] Primarily, mAbs neutralize viruses by disrupting binding between the host and viral proteins. This is achieved by targeting the viral[7] or host proteins.[5] They also promote clearance of infected cells through Fc-mediated effector functions.[7] However, their large size (~150 kDa) and complex multimeric structure may pose limitations, including reduced tissue penetration and potential immunogenicity.[9] Furthermore, mAbs are challenging to produce, with high costs and long development timelines.[10]

In recent years, nanobodies derived from the antigen-binding domain of heavy chain-only antibodies (HCAbs) expressed in camelids, have garnered attention as promising candidates for the fight against viral infections.[11] Discovered serendipitously by the research group of Raymond Hammers, these molecules have been extensively studied for diagnostic and therapeutic applications. Their unique structural properties enable the recognition of a broader range of epitopes, enhancing their versatility for targeting diverse viruses.[12] Their small size offers several advantages, including improved bioavailability, stability, solubility, and ease of genetic engineering for tailoring properties. Nanobodies are also economically produced through recombinant expression and purification, positioning them as cost-effective antiviral candidates.[13] In addition, their favorable biophysical characteristics allow for the exploration of alternative delivery routes for respiratory and intestinal viral infections.[14,15] Target-specific nanobodies are typically identified using phage-displayed libraries derived from immunized camelids.[11] Recently, phage-displayed semi-synthetic and synthetic libraries have become popular, eliminating the need for animal immunization.[16] In addition to phage display, other surface display technologies, including yeast display and ribosome display have also been used to discover nanobodies.

CONTACT Vaishali Verma vaishali.verma@bennett.edu.in Department of Biotechnology, School of Engineering and Applied Sciences, Bennett University (The Times Group), Plot number 8-11, Tech Zone 2, Greater Noida, Uttar Pradesh 201310, India