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Insights into Protein Delivery Mechanisms: Comparing Functional Transduction Domains with the NEMO Binding Domain Peptide

Bottino Karrasch *

Department of Genetics, Development & Molecular Biology, School of Biology, Aristotle University of Thessaloniki, 541 54, Greece

Introduction

Protein delivery into cells is a critical process in cell biology and has vast applications in therapeutics, including gene therapy, cancer treatment, and vaccine development. However, achieving efficient and targeted delivery of functional proteins into cells remains a significant challenge. Over the past few decades, the development of protein transduction domains (PTDs) has provided a solution to this challenge, offering a promising tool for delivering biologically active proteins across cellular membranes. Among the many PTDs, the NEMO binding domain (NBD) peptide has emerged as a key player in enhancing cellular protein delivery. In this review, we explore the mechanisms of protein delivery via PTDs, compare functional PTDs, and highlight the unique role of the NEMO binding domain peptide in improving cellular uptake and functional delivery of proteins.

Description

Protein transduction domains, also known as cell-penetrating peptides (CPPs), are short peptides that facilitate the delivery of proteins, peptides, and nucleic acids across cell membranes. PTDs are usually composed of cationic or amphipathic amino acid sequences that interact with the negatively charged components of the cell membrane. These peptides can penetrate cellular membranes through various mechanisms, including direct penetration, endocytosis, or macropinocytosis, enabling the internalization of otherwise membrane-impermeable substances. The efficiency and mechanism of protein delivery largely depend on the structure and properties of the PTD. Some PTDs are more efficient at internalizing proteins into specific cell types, while others may trigger cellular responses or induce endosomal escape to release the delivered proteins into the cytoplasm. Despite the diversity of PTDs, common sequences like TAT (from the HIV-1 transactivator protein) and penetratin (from the Antennapedia homeodomain) are among the most widely studied for their cell-penetrating abilities. [1].

The NEMO binding domain (NBD) peptide is derived from the nuclear factor-kappa B essential modulator (NEMO), which plays a central role in the NF-κB signaling pathway. NEMO is an essential scaffold protein in the NF-κB pathway, a critical regulator of immune responses, inflammation, and cellular survival. The NBD peptide, a functional fragment of NEMO, can specifically bind to and inhibit the activity of IκB kinase (IKK), a component of the NF-κB pathway. In addition to its functional role in inhibiting NF-κB activation, the NBD peptide has been utilized as a PTD due to its ability to facilitate the internalization of proteins into cells. The NBD peptide's unique ability to bind to and inhibit IKK provides it with an advantage over other PTDs in certain therapeutic applications, particularly those targeting inflammatory diseases and cancer. When conjugated to therapeutic proteins or peptides, the NBD peptide can enhance the delivery of these agents into cells, thus enabling their therapeutic effects [2].

The NBD peptide facilitates protein delivery into cells by exploiting cellular pathways that allow for the uptake of larger macromolecules. Once attached to a protein or therapeutic agent, the NBD peptide interacts with the cell membrane and promotes internalization, which can occur through direct penetration or endocytosis. After cellular entry, the NBD peptide helps direct the cargo protein to specific subcellular locations, such as the cytoplasm or nucleus, where it can exert its desired function. One key feature of the NBD peptide in protein delivery is its ability to enhance endosomal escape. Following internalization, many proteins delivered via PTDs are trapped in endosomes or lysosomes, where they are degraded before they can reach their target sites within the cell. The NBD peptide's interaction with cellular membranes may facilitate endosomal escape, allowing the protein to bypass degradation pathways and reach the cytoplasm or nucleus. This property is particularly valuable in therapeutic applications, where the functional integrity of the protein must be preserved for maximum efficacy [3,4].

The TAT peptide, derived from the HIV-1 TAT protein, is one of the most widely studied and utilized PTDs. TAT is a cationic peptide that interacts with negatively charged cell membranes, facilitating cellular entry via endocytosis or direct penetration. TAT has been used extensively for the delivery of nucleic acids, peptides, and proteins into a variety of cell types, including mammalian cells, neurons, and immune cells. Its widespread use is due to its ability to cross cellular membranes efficiently and deliver therapeutic cargo. However, TAT-mediated delivery has some limitations. For example, TAT has been shown to be less efficient in delivering larger protein cargo and may cause cytotoxicity at higher concentrations. Moreover, TAT-mediated delivery often results in the sequestration of the cargo within endosomal compartments, limiting its ability to reach the cytoplasm or nucleus. The NBD peptide, while less well-known than TAT and penetratin, offers a unique advantage in specific applications, particularly in inflammation and immune modulation. Unlike TAT and penetratin, which rely on general mechanisms of protein internalization, the NBD peptide has a more specific mechanism of action, targeting the IKK pathway involved in the NF-κB signaling cascade. This specificity makes the NBD peptide an excellent candidate for targeted therapies aimed at modulating immune responses or inhibiting inflammatory pathways. In terms of protein delivery, the NBD peptide's ability to facilitate endosomal escape and direct the protein to subcellular compartments enhances its overall delivery efficiency. Furthermore, NBD peptides are less likely to induce cytotoxicity compared to TAT and penetratin, making them more suitable for long-term therapeutic use [5].

Address for Correspondence: *Bottino Karrasch, Department of Genetics, Development & Molecular Biology, School of Biology, Aristotle University of Thessaloniki, 541 54, Greece, E-mail: aarsh@edu.gr*

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Conclusion

The use of PTDs like the NBD peptide has opened new avenues for therapeutic protein delivery, particularly in the treatment of inflammatory diseases, autoimmune disorders, and cancers. The NBD peptide, in particular, offers a targeted approach to modulating immune responses by facilitating the delivery of proteins that can specifically inhibit NF-κB activation. This has potential applications in diseases where NF-κB plays a critical role, such as rheumatoid arthritis, inflammatory bowel disease, and certain types of cancer. Additionally, the NBD peptide's ability to enhance endosomal escape could improve the delivery of therapeutic proteins that otherwise struggle to reach their target locations within the cell. By conjugating the NBD peptide to therapeutic proteins, researchers can enhance the bioavailability and therapeutic efficacy of these agents. Protein transduction domains (PTDs) are powerful tools for delivering therapeutic proteins and peptides into cells. The NEMO binding domain (NBD) peptide, with its unique ability to target and inhibit the NF-κB pathway, provides a promising platform for protein delivery, especially in immune modulation and inflammation. By comparing functional PTDs such as TAT, penetratin, and NBD, we gain valuable insights into their strengths, limitations, and potential applications in therapeutic development. As research continues, the NBD peptide and other PTDs will likely play an increasingly important role in advancing personalized medicine and improving the treatment of complex diseases..

Acknowledgment

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Conflict of Interest

There are no conflicts of interest by author.

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