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Proteins that have been Myristoylated and are Intrinsically Disordered Change in Structure and Hydration

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Abstract

Post-translational modifications play a crucial role in modulating the structure and function of proteins. Myristoylation, the attachment of a myristoyl group to the N-terminus of a protein, is a common modification that facilitates membrane association. While the effects of myristoylation on structured proteins have been extensively studied, its impact on intrinsically disordered proteins (IDPs) remains less explored. This abstract highlights the changes in structure and hydration of myristoylated IDPs. Intrinsically disordered proteins are a class of proteins that lack a well-defined structure but possess critical biological functions. Myristoylation can induce structural changes in IDPs by promoting the formation of transient secondary structure elements or modulating local folding propensity. The myristoyl group's presence can alter the conformational dynamics of IDPs, resulting in the adoption of specific structural motifs upon membrane binding. Additionally, myristoylation can facilitate protein-protein interactions, leading to changes in the overall structure of IDPs. Hydration, an essential factor for protein stability and function, is also affected by myristoylation in IDPs. Experimental studies have shown that myristoylated IDPs exhibit distinct hydration dynamics compared to their non-myristoylated counterparts. The myristoyl group can influence the hydration of specific regions of the IDP by shielding them from solvent exposure, while other regions may experience enhanced hydration. These hydration changes have implications for the interactions of myristoylated IDPs with partner proteins and membranes.

Keywords: IDPs; Myristoylated; Protein-protein interactions

Introduction

Proteins play a crucial role in various cellular processes, and their structure and function are tightly regulated. While many proteins adopt well-defined three-dimensional structures, a subset of proteins, known as intrinsically disordered proteins (IDPs), lack a fixed structure under physiological conditions. IDPs are involved in a wide range of biological functions, including cell signaling, transcriptional regulation, and protein-protein interactions. Recent research has revealed that post-translational modifications, such as myristoylation, can influence the conformational dynamics and hydration properties of IDPs [1]. This article explores the impact of myristoylation on the structure and hydration of IDPs.

Myristoylation and intrinsically disordered proteins: Myristoylation is a co-translational or post-translational modification that involves the attachment of a myristoyl group, derived from myristic acid, to the N-terminus of a protein. This modification occurs through the action of the enzyme N-myristoyltransferase (NMT). Myristoylation serves as a lipid anchor, facilitating the association of proteins with cellular membranes. While myristoylation has been extensively studied in structured proteins, its effects on IDPs are relatively less understood.

Structural changes in myristoylated IDPs: IDPs lack a defined structure but exhibit conformational heterogeneity and flexibility. Myristoylation can induce structural changes in IDPs by promoting transient secondary structure elements or modulating local folding propensity. For example, myristoylation of the IDP MARCKS (Myristoylated Alanine-Rich C Kinase Substrate) induces the formation of an amphipathic α-helix upon binding to membranes. The myristoyl group can embed within the lipid bilayer, influencing the orientation and folding of the IDP. Additionally, myristoylation can promote the formation of protein-protein complexes through specific binding interactions, leading to changes in the IDP's overall structure [2].

Hydration changes in myristoylated IDPs: Hydration plays a vital role in protein stability and function. Myristoylation can modulate the hydration properties of IDPs by affecting their interaction with water molecules. Experimental studies have shown that myristoylated IDPs exhibit altered hydration dynamics compared to their non-myristoylated counterparts. The presence of the myristoyl group can shield specific regions of the protein from solvent exposure [3], leading to reduced local hydration. Conversely, myristoylation can enhance the hydration of other regions, potentially promoting the interaction of IDPs with partner proteins or membranes.

Biological implications and functional significance: The structural changes and altered hydration properties induced by myristoylation in IDPs have significant biological implications. Myristoylated IDPs are often involved in membrane targeting and protein-protein interactions critical for cellular signaling pathways. The myristoyl group can serve as a membrane anchor, facilitating the recruitment of IDPs to specific subcellular compartments. Moreover, the conformational changes and modulation of hydration can impact the IDP's binding affinity and specificity for partner proteins, influencing downstream signaling events.

Method

To investigate the changes in structure and hydration of proteins that have been myristoylated and are intrinsically disordered, a combination

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of experimental and computational methods can be employed. The following methods outline an approach to studying these changes:

Protein Expression and Purification:

a. Expression of the target protein, both myristoylated and non-myristoylated forms, using recombinant DNA techniques in a suitable expression system (e.g., Escherichia coli).

b. Purification of the expressed protein using affinity chromatography or other appropriate purification methods to obtain highly pure samples.

Circular dichroism (cd) spectroscopy:

a. CD spectroscopy can be utilized to assess changes in secondary structure induced by myristoylation. CD spectra can provide information about the presence of α-helices, β-sheets, and random coil conformations.

b. Comparisons can be made between the CD spectra of myristoylated and non-myristoylated forms of the protein to identify changes in secondary structure content.

Nuclear magnetic resonance (nmr) spectroscopy:

a. NMR spectroscopy is a powerful tool for studying the conformational dynamics and flexibility of proteins, including intrinsically disordered proteins.

b. 2D-NMR techniques, such as ^1H-^15N HSQC (heteronuclear single-quantum coherence) spectroscopy, can provide information about chemical shift perturbations and peak broadening, indicating changes in local or global conformation upon myristoylation.

Hydrogen-deuterium exchange mass spectrometry (hdx-ms):

a. HDX-MS can assess changes in protein hydration dynamics. It provides information about the accessibility of protein backbone amide hydrogens to solvent exchange.

b. By comparing the HDX profiles of myristoylated and non-myristoylated forms, differences in hydration patterns can be identified, indicating changes in local or global dynamics.

Molecular dynamics (md) simulations:

a. Computational MD simulations can complement experimental techniques to investigate the conformational changes induced by myristoylation in intrinsically disordered proteins.

b. Simulations can provide insights into the dynamic behavior, structural ensembles, and hydration properties of myristoylated and non-myristoylated proteins under different conditions.

Protein-protein interaction studies:

a. Techniques such as co-immunoprecipitation, surface plasmon resonance (SPR), or isothermal titration calorimetry (ITC) can be employed to assess the effects of myristoylation on protein-protein interactions involving intrinsically disordered proteins.

b. These studies can help elucidate the influence of myristoylation on the binding affinity, specificity, and dynamics of interactions with partner proteins [3, 4, 5].

Results

The myristoylation of intrinsically disordered proteins (IDPs) can induce significant changes in their structure and hydration properties. Here are some potential findings based on previous studies:

Structural changes: Myristoylation can promote the formation of transient secondary structure elements in IDPs. For example, the attachment of a myristoyl group to the N-terminus of an IDP may induce the adoption of an amphipathic α-helix upon binding to membranes. Local folding propensity within the IDP can be modulated by myristoylation, leading to the formation of specific structural motifs or enhanced conformational stability. Myristoylation can also influence the overall conformational ensemble of the IDP, potentially promoting the formation of protein-protein complexes or altering the IDP's intramolecular interactions.

Hydration changes: Myristoylation can impact the hydration dynamics of IDPs by altering their interaction with water molecules. The myristoyl group's presence can shield specific regions of the protein from solvent exposure, resulting in reduced local hydration. Conversely, myristoylation can enhance the hydration of other regions, potentially facilitating the interaction of IDPs with partner proteins or membranes. Changes in hydration patterns may influence the flexibility, stability, and binding properties of myristoylated IDPs [6, 7, 8]. It is important to note that the specific structural and hydration changes induced by myristoylation can vary depending on the IDP and the context of its interactions. Different IDPs may exhibit distinct responses to myristoylation, and the effects may be influenced by factors such as the length of the myristoyl group, membrane composition, and the presence of other post-translational modifications. Understanding these changes in structure and hydration is crucial for elucidating the functional implications of myristoylation in IDPs. These modifications can regulate membrane targeting, protein-protein interactions, and signaling events, contributing to various cellular processes and potentially impacting disease mechanisms.

Discussion

Proteins that have been myristoylated and are intrinsically disordered exhibit intriguing changes in structure and hydration, which have significant implications for their cellular functions and interactions. The findings discussed above highlight the impact of myristoylation on the conformational dynamics and hydration properties of these proteins [9]. Here, we delve into the broader implications and potential functional significance of these changes. One of the notable structural changes induced by myristoylation in intrinsically disordered proteins (IDPs) is the promotion of transient secondary structure elements. This alteration can lead to the formation of amphipathic α-helices, which play crucial roles in membrane targeting and binding. The myristoyl group serves as a lipid anchor, facilitating the recruitment of myristoylated IDPs to specific subcellular compartments, such as the plasma membrane or membrane-bound organelles. The induction of secondary structure elements by myristoylation may provide a means of regulating protein-membrane interactions and influencing membrane-associated processes. Furthermore, myristoylation can modulate the overall conformational ensemble of IDPs. This can influence the binding affinity and specificity of myristoylated IDPs for partner proteins, as well as their capacity to undergo intramolecular interactions. By altering the structural landscape of IDPs, myristoylation may facilitate or inhibit protein-protein interactions critical for signal transduction, protein assembly [10, 11], or enzymatic activities. The dynamic nature of IDPs, combined with myristoylation-induced structural changes, expands their functional repertoire and enables versatile regulatory mechanisms within cellular signaling networks.

Hydration changes in myristoylated IDPs also play a significant role

in their function. The myristoyl group can shield certain regions of the protein from solvent exposure, resulting in reduced local hydration. This reduced hydration may confer increased stability and protection to specific protein regions or facilitate the formation of hydrophobic interactions. On the other hand, myristoylation can enhance the hydration of other regions, potentially promoting solvation and facilitating protein-protein interactions. These hydration changes can influence the flexibility, folding propensity, and binding properties of myristoylated IDPs [12, 13].

The interplay between structural changes and altered hydration dynamics induced by myristoylation contributes to the precise spatiotemporal regulation of IDP function. By modulating the structural ensemble and hydration properties, myristoylation enables IDPs to respond dynamically to cellular cues, such as changes in membrane composition or signaling events. These changes provide a mechanism for IDPs to finely tune their interactions with binding partners, allowing for specific and efficient cellular responses.

Understanding the structural and hydration changes in myristoylated IDPs is crucial for deciphering the underlying mechanisms of cellular processes and disease pathways [14, 15]. Dysregulation of myristoylation or alterations in the structural and hydration properties of IDPs can have profound consequences, leading to disruptions in signaling pathways and cellular homeostasis. Therefore, further research into the specific molecular mechanisms governing the effects of myristoylation on IDPs is necessary to deepen our understanding of protein regulation and function.

Conclusion

The interplay between structural changes and altered hydration dynamics induced by myristoylation contributes to the precise spatiotemporal regulation of IDP function. By modulating the structural ensemble and hydration properties, myristoylation enables IDPs to respond dynamically to cellular cues, such as changes in membrane composition or signaling events. These changes provide a mechanism for IDPs to finely tune their interactions with binding partners, allowing for specific and efficient cellular responses. Understanding the structural and hydration changes in myristoylated IDPs is crucial for deciphering the underlying mechanisms of cellular processes and disease pathways. Dysregulation of myristoylation or alterations in the structural and hydration properties of IDPs can have profound consequences, leading to disruptions in signaling pathways and cellular homeostasis. Therefore, further research into the specific molecular mechanisms governing the effects of myristoylation on IDPs is necessary to deepen our understanding of protein regulation and function; myristoylation-induced changes in structure and hydration expand the functional repertoire of intrinsically disordered proteins. These modifications influence membrane targeting, protein-protein interactions, and cellular signaling processes. By combining experimental and computational approaches, we can continue to unravel the intricate interplay between myristoylation, structure, and hydration in IDPs, shedding light on their vital roles in cellular biology.

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Conflict of Interest

None

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