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Perspective

Advanced Developments in In-Cell NMR for Studying Biomolecules in the Native Environments

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DESCRIPTION

Nuclear Magnetic Resonance (NMR) spectroscopy is a powerful tool for elucidating the structures and dynamics of biomolecules. Traditionally, NMR studies have been conducted on purified proteins in vitro, providing detailed atomic-level. However, in recent years, the development of in-cell NMR has enabled scientists to study biomolecules within living cells, capturing their behavior in a native and physiologically relevant environment. This approach has opened new avenues for understanding biological processes and molecular interactions as they occur naturally.

The concept of In-cell NMR

In-cell NMR involves introducing isotopically labeled biomolecules into living cells and recording NMR spectra directly from these cells. This technique allows researchers to observe proteins, nucleic acids, and other biomolecules in the complex milieu of the cell, where they interact with other molecules and are subjected to cellular processes such as post-translational modifications, molecular crowding, and dynamic interactions.

Advances in isotopic labeling

The aspect of in-cell NMR is the ability to isotopically label the biomolecules of interest. Advances in labeling techniques have made it possible to selectively label proteins with NMR-active isotopes, such as 13C and 15N, without disrupting cellular function. These isotopically labeled proteins can be expressed directly in cells or introduced into cells through methods like microinjection or electroporation. Recent developments in metabolic labeling have further enhanced the ability to incorporate labeled amino acids into proteins within living cells.

Sensitivity and resolution enhancements

One of the significant challenges of in-cell NMR is the relatively low sensitivity and resolution due to the complex cellular environment and the presence of numerous background signals. Recent advancements in NMR hardware, such as high-field magnets and cryogenic probes, have significantly improved sensitivity. Additionally, techniques like non-uniform sampling and fast-pulsing methods have enhanced the resolution of in-cell NMR spectra, enabling the detection of signals from biomolecules at physiological concentrations.

Applications in protein-protein interactions

In-cell NMR has been particularly valuable for studying protein-protein interactions in their native context. By observing proteins within the cellular environment, researchers can gain into the transient and dynamic interactions that are often difficult to capture in vitro. For example, in-cell NMR has been used to study the interaction between tumor suppressor proteins and their binding partners, shedding light on the mechanisms underlying cellular signaling pathways and disease processes.

Protein folding and misfolding

Protein folding and misfolding are fundamental processes that can lead to various diseases, including neurodegenerative disorders. In-cell NMR provides a unique opportunity to study these processes in living cells, where chaperones and other cellular factors influence protein behavior. Recent studies have used in-cell NMR to monitor the folding pathways of proteins and to investigate the formation of amyloid aggregates, contributing to our understanding of protein homeostasis and the pathogenesis of misfolding diseases.

Challenges

Despite its advancements, in-cell NMR faces several challenges, including the limited size of biomolecules that can be studied

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due to spectral complexity and the difficulty of achieving uniform labeling in complex cellular environments. However, ongoing developments in NMR technology, such as the use of Dynamic Nuclear Polarization (DNP) to enhance sensitivity and the integration of NMR with other imaging techniques.

CONCLUSION

In-cell NMR has revolutionized the field of structural biology by enabling the study of biomolecules in their native cellular environment. Advances in isotopic labeling, sensitivity, and resolution have made it possible to observe protein dynamics, interactions, and folding processes within living cells. As the technology continues to evolve, in-cell NMR will undoubtedly provide deeper into the complex molecular machinery of life, advancing our understanding of biology and disease at an unprecedented level.