P-2.189

Intrinsically Disordered Regions as Key Modulators of Katp Channel Activity

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Proteins and disordered regions of proteins (IDPs/IDRs) have long been neglected in scientific research due to challenges in their experimental and computational analysis. Although recent advances in experimental and numerical methods have sparked increased interest in their functional roles,IDRs remain a significant challenge, often revealing their structure only in the presence of binding partners, as observed by cryoEM.

In ATP-sensitive potassium channels (KATP), which regulate insulin secretion and cardiovascular function, IDRs constitute approximately 15% of the system. Despite their seemingly small contribution, growing evidence suggests that neglecting IDRs prevents a complete understanding of channel mechanisms.

In this study, we investigate the role of IDRs in KATP channels using multiscale molecular dynamics simulations (atomistic and coarse-grained) and integrate experimental data to uncover interactions of previously unresolved regulatory regions. Our results indicate that IDRs modulate channel responses to ATP concentration and membrane potential changes, and ensure smooth system operation. Our work highlights the critical role of IDRs in channel function and provides a framework for studying IDRs in other complex biological systems. Understanding how "invisible" regions regulate KATP's dynamics have potential implications for treating diabetes and hypertension.