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Title: Intrinsic Disorder in the BK Channel and Its Interactome

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Abstract: The large-conductance Ca2+-activated K+ (BK) channel is broadly expressed in various mammalian cells and tissues such as neurons, skeletal and smooth muscles, exocrine cells, and sensory cells of the inner ear. Previous studies suggest that BK channels are promiscuous binders involved in a multitude of protein-protein interactions. To gain a better understanding of the potential mechanisms underlying BK interactions, we analyzed the abundance, distribution, and potential mechanisms of intrinsic disorder in 27 BK channel variants from mouse cochlea, 104 previously reported BK-associated proteins (BKAPS) from cytoplasmic and membrane/cytoskeletal regions, plus BK beta- and gamma-subunits. Disorder was evaluated using the MFDp algorithm, which is a consensus-based predictor that provides a strong and competitive predictive quality and PONDR, which can determine long intrinsically disordered regions (IDRs). Disorder-based binding sites or molecular recognition features (MoRFs) were found using MoRFpred and ANCHOR. BKAP functions were categorized based on Gene Ontology (GO) terms. The analyses revealed that the BK variants contain a number of IDRs. Intrinsic disorder is also common in BKAPs, of which similar to 5% are completely disordered. However, intrinsic disorder is very differently distributed within BK and its partners. Approximately 65% of the disordered segments in BK channels are long (IDRs) (>50 residues), whereas >60% of the disordered segments in BKAPs are short IDRs that range in length from 4 to 30 residues. Both alpha and gamma subunits showed various amounts of disorder as did hub proteins of the BK interactome. Our analyses suggest that intrinsic disorder is important for the function of BK and its BKAPs. Long IDRs in BK are engaged in protein-protein and protein-ligand interactions, contain multiple post-translational modification sites, and are subjected to alternative splicing. The disordered structure of BK and its BKAPs suggests one of the underlying mechanisms of their interaction.

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