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Intrinsically disordered protein, alternative splicing, and post-translational modification: A toolkit for developmental biology

Intrinsically disordered proteins and regions (IDPs and IDRs) lack well-defined tertiary structures, yet carry out various important cellular functions, especially those associated with cell signaling and regulation. In eukaryotes, IDPs and IDRs contain the preferred loci for both alternative splicing (AS) and many post-translational modifications (PTMs). Furthermore, AS and/or PTMs at these loci generally alter the signaling outcomes associated with these IDPs or IDRs. However, the prevalence of such functional modulations remains unknown. Also, the signal-altering mechanisms by which AS, and PTMs modulate function and the extent to which AS and PTMs collaborate in their signaling modulations have not been well defined for particular protein examples. Here, we focus on three important signaling and regulatory IDR-containing protein families in humans, namely G-protein coupled receptors (GPCRs), which are transmembrane proteins, the nuclear factors of activated T-cells (NFATs), which are transcription factors (TFs), and the Src family kinases (SFKs), which are signaling enzymes. The goal here is to determine how AS and PTMs individually alter the outcomes of the signaling carried out by the various IDRs and to determine whether AS and PTMs work together to bring about differential cellular responses. We also present data indicating that a wide range of other signaling IDPs or IDRs undergo both AS- and PTM-based modifications, suggesting that they, too, likely take advantage of signal outcome modulations that result from collaboration between these two events. Hence, we propose that the widespread cooperation of IDPs, AS and/or PTMs substantially contributes to the vast complexity of eukaryotic cell signaling systems.

Biography

A Keith Dunker switched his focus to intrinsically disordered proteins (IDPs) on November 15, 1995, following a seminar by Charles Kissinger on the structure and function of calcineurin (CaN), After studying virus and phage structure and function for more than 25 years. This serine/threomine phosphatase has a long IDP region that contains both an auto-inhibitory domain and a calcium-calmodulin (Ca-CaM) binding site. This long CaN IDP region functions as a Ca-CaM-regulated on-off switch for CaN's phosphatase activity, thus connecting Ca-CaM and phosphorylation/dephosphorylation signaling pathways. By now, he and his collaborators have coauthored over 200 papers on IDPs and their functions. In 2014/2015/2016 and 2017 he has been recognized as a Highly Cited Researcher by Clarviate Analytics.

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