“Dueling Activation and Repression in the Disorder Mediated Allostery Glucocorticoid Receptor”

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Intrinsically disordered protein (IDP) regions, such as the N-terminal domain of glucocorticoid receptor (GR), present a functional paradox because they lack stable tertiary structure, but nonetheless play a central role in signaling, utilizing a process known as allostery. Allostery in structured proteins has historically been interpreted in terms of propagated structural changes that are induced by effector binding. As such, it is not clear how IDPs, lacking such well-defined structures, can allosterically affect function. Here we show mechanistically how IDPs transmit signals through a probabilistic process originating from the simultaneous tuning of both activating and repressing ensembles of the protein. We demonstrate that human GR modulates this signaling *in vivo* by producing translational isoforms with variable disordered regions. We expect this ensemble model of allostery will be important in explaining signaling in other IDPs.