Abstract:

Multiple essential processes, including those associated with signaling, cell division, and cellular differentiation, are regulated by post-translational modification and alternative splicing of proteins. The addition or deletion of linear recognition motifs and structural changes induced by post-translational modifications promote or diminish interactions with partner proteins and consequently alter the behavior of entire biological interaction networks. The molecular bases for these effects, especially those involving intrinsically disordered proteins (IDPs), are poorly understood. Here we focus on intrinsic disorder in the regulation of an essential system, dynein, in which phosphorylation and alternative splicing in one subunit modulate multiple functions of the larger complex. Dynactin subunit p150\textsuperscript{Glu} and NudE share a common binding site on dynein and are both essential proteins, raising the question of the molecular basis of selective binding of one protein over another when both are present in the same cellular compartment. Using multidimensional NMR, isothermal titration calorimetry, and various other biophysical techniques, we present a novel mechanism for posttranslational modification and alternative splicing in regulation of dynein/dynactin interaction. Studies here provide a novel example wherein phosphorylation is not accompanied by a change in secondary structure either at the phosphorylation site or the partner-binding site but by promoting a conformation that blocks access of the partner to the binding site.

Other efforts of the Barbar lab that are focused on elucidating molecular processes that regulate dynamic protein networks involving the hub protein LC8 will also be presented. Most notably will be the role of LC8 in regulating its own transcription and in rabies virus replication.

Relevant reading: