Invited Lecture

Cancer: when the delicate balance of oncogenes and their suppressors get out of control by polymerization

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While the elucidation of regulatory mechanisms of folded proteins is facilitated due to their amenability to high-resolution structural characterization, investigation of these mechanisms in disordered proteins is more challenging due to their structural heterogeneity, which can be captured by a variety of biophysical approaches. Here, we used the transcriptional master corepressor CtBP, which binds the putative metastasis suppressor RAI2 through repetitive SLiMs, as a model system. Using cryo-electron microscopy embedded in an integrative structural biology approach, we show that RAI2 unexpectedly induces CtBP polymerization through filaments of stacked tetrameric CtBP layers. These filaments lead to RAI2-mediated CtBP nuclear foci and relieve its corepressor function in RAI2-expressing cancer cells. The impact of RAI2-mediated CtBP loss-of-function is illustrated by the analysis of a diverse cohort of prostate cancer patients, which reveals a substantial decrease in RAI2 in advanced treatment-resistant cancer subtypes. As RAI2-like SLiM motifs are found in a wide range of organisms, including pathogenic viruses, our findings serve as a paradigm for diverse functional effects through multivalent interaction-mediated polymerization by disordered proteins in healthy and diseased conditions. The specific properties of these repeated interactions open up new therapeutic opportunities.