Mitochondrial membrane remodelling by Bcl-2 family members to control apoptosis

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This talk will cover work in my laboratory over the past decade on the molecular design of genetically encoded stimulus responsive elastin-like polypeptides (ELPs). Below a characteristic inverse transition temperature (Tt), ELPs –peptide polymers composed of VPGXG repeats– are soluble in aqueous solution, but when the temperature is raised above their Tt, they desolvate and undergo phase separation. We have exploited ELPs to create stimulus responsive nanostructures via three approaches. In the first approach, we have designed diblock ELPs with two ELP blocks with different hydrophobicity's that self-assemble into spherical micelles with an increase in temperature above the critical micellization temperature of the diblock polymer. Building on this architecture, we have incorporated histidine residues in the hydrophobic block to create a diblock ELP that self-assembles into spherical micelles with an increase in temperature, while a small drop in pH from 7.4 to 6.4 leads to micelle disassembly. In a second –chemical attachment triggered self-assembly– approach, we have shown that the attachment of multiple copies of small molecule hydrophobes to the multiple cysteine (C) residues of an ELP with the sequence (VPGXG)n(CGG)8 can drive their self-assembly into spherical micelles. In a third approach, we replace the Cys (C) with W, Y, or F, and find that oddly, this leads to the formation of stimulus responsive worms and vesicles depending on the specific residue. These are the first examples of stimulus responsive worms and vesicles in peptide polymers. These results pose the following question: what are the molecular and environmental determinants that drive self-assembly of these peptide polymers into a specific morphology? Answering this question will require theory and simulation to help unravel the molecular origins of these phenomena.