Title:

What Role Does the Polymer Backbone Play in the Bioactivity of Peptide Brush Polymers

Body:

Oligomerization of peptides enhances their functional diversity. This evolutionary mechanism produces proteins with conserved supersecondary structures, creating functionalities ranging from elasticity to specific binding. Similarly, we polymerize peptide macromonomers to generate systems with emergent properties. These globular peptide brush polymers are named “Protein-like Polymers” (PLPs). Unlike free peptides, PLPs exhibit extended metabolic activity, cellular penetration, and vastly improved binding affinities. While the PLP platform can accommodate nearly any peptide, the influence of the synthetic backbone on bioactivity remains underexplored. We hypothesize that the therapeutic outcomes of PLPs are sensitive to changes in backbone chemistry in the same way that a single mutation may affect protein structure and function. Herein, we synthesized PLPs to inhibit an intracellular protein involved in neurodegenerative diseases. Three macromonomers, norbornene-dicarboximide (NIm), norbornene-carboxamide (NAm), and methacrylamide (MAm) were polymerized using one of three strategies: stereoselective ring-opening metathesis polymerization (ROMP), ring-expansion metathesis polymerization (REMP), or reverse-addition fragmentation chain-transfer polymerization (RAFT). Non-selective ROMP generated E/Z poly(NIm) and E/Z poly(NAm) with a nearly equal mixture of *E* and *Z* alkenes. A *Z*-selective ruthenium initiator generated *Z*-enriched PLPs named Z poly(NIm) and Z poly(NAm). REMP yielded cyclized versions of E/Z poly(NIm) and E/Z poly(NAm). Finally, poly(MAm) was synthesized via RAFT. Characterization via small-angle neutron scattering (SANS) revealed polymer flexibility, while hydrophobicity was assessed through Nile Red binding. Findings suggest that rod-like poly(NAm) penetrates bilayers most effectively while Z isomers best bind the target protein. Comparatively, poly(MAm) performs poorly in each context, likely due to its hydrophilicity.