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FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

Excretory-guided supramolecular assembly of a synthetic extracellular matrix

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The cellular interface is a critical nexus for therapeutic intervention, yet direct engineering of the pericellular space remains challenging due to the fragility of the plasma membrane and the dynamic complexity of the native extracellular matrix (ECM). Intracellular peptide self-assembly has emerged as a promising strategy to engineer both the extracellular microenvironment and cell behavior. However, the intracellular self-assembly pathways of peptides in living cells remain poorly understood, limiting the rational control of their biological functions.

Here, we combine sequence-programmed bio-responsive peptides with phasor fluorescence lifetime imaging (Phasor-FLIM), which has been well practiced in our group, to track intracellular dynamic self-assembly processes and investigate how distinct intracellular assembly pathways influence different biological outcomes. [1,2]

A glutathione-sensitive peptide bearing slow self-assembly kinetics is delivered intracellularly via TAT-mediated endocytosis and activated by reductive cleavage. This delayed assembly promotes trafficking into secretory vesicles, enabling vesicle-mediated excretion and extracellular fibril formation. The resulting synthetic extracellular matrix (syn-ECM) integrates seamlessly with the native ECM and presents orthogonal handles for chemical modification via click chemistry. High-density syn-ECM formation inhibits angiogenic signaling and suppresses cancer cell proliferation.

To further explore how intracellular assembly pathways influence biological functions, sequence-programmed bio-responsive peptides with distinct molecular architectures were designed to generate different intracellular assembly dynamics. These programmed assembly pathways finally lead to diverse biological outcomes.

Together, these studies demonstrate that programming intracellular peptide self-assembly provides a versatile strategy for engineering both extracellular matrices and cell behaviors, offering new opportunities for biomaterials, therapeutic intervention, and mechanistic studies of cell–material interactions.

References:

[1] S. Wu, *et al*., *Nature Synthesis.* Under revision (2026).
[2] Y. Ren, *et al*., *Nature Synthesis.* **4**, 673–683 (2025).