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FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

Metabolite-Driven Engineering of Dynamic Tumor Microenvironments Across Multiple Length Scales

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The extracellular matrix (ECM) and the pericellular interface provide essential biochemical and mechanical cues that regulate cellular behavior and integrate adhesion, migration, and metabolic signaling pathways.[1] In tumor microenvironments (TMEs), altered cancer cell metabolism strongly influences these reciprocal interactions, offering opportunities to develop dynamic biomaterials that respond directly to endogenous cellular signals.2 Here, we present two complementary strategies that exploit tumor-derived lactate as a metabolic trigger for engineering functional extracellular environments.

A chemically defined, self-assembling peptide (SAP) platform was developed to generate modular extracellular nanofiber scaffolds directly on living cancer cell surfaces without genetic modification. Screening pyrene-capped amphiphilic peptides differing by a single N-terminal amino acid identified Py-IH as the unique variant capable of forming stable fibrillar structures on A549 lung cancer cells while maintaining 94% cell viability. The Py-IH scaffold enabled non-covalent recruitment of structural and enzymatically active proteins, including lactate oxidase (LOx), achieving up to 40% immobilization efficiency while preserving catalytic activity. Localized lactate oxidation by scaffold-bound LOx generated hydrogen peroxide at the cell surface, inducing hallmarks of regulated cell death, including nuclear condensation, mitochondrial fragmentation, and membrane disruption. Substitution of isoleucine by valine or phenylalanine abolished cell-surface assembly despite comparable fiber formation in solution, demonstrating that subtle changes in interfacial hydrophobicity regulate membrane anchoring.3,4 Furthermore, co-assembly with an azide-functionalized Py-IH analogue enabled bioorthogonal conjugation of small-molecule cargo without affecting nanofiber morphology.

In parallel, a metabolite-responsive hydrogel system based on tyramine-functionalized alginate (Alg-TA) was developed to enable cell-instructed extracellular matrix formation. Alg-TA remains soluble until tumor-derived lactate is converted by LOx into hydrogen peroxide, which drives horseradish peroxidase-mediated covalent crosslinking of phenol groups. This mechanism enables rapid hydrogel formation within minutes with tunable mechanical properties ranging from 10 Pa to 5 kPa. In tumor spheroid models, including patient-derived glioblastoma spheroids, endogenous lactate production generated spatially confined gelation zones extending up to 1 mm from the tumor surface. Nanoindentation and fluorescence correlation spectroscopy revealed radial gradients in matrix stiffness and polymer density, while proteomic profiling indicated altered signaling pathways associated with proliferation, migration, and matrix remodeling.

Together, these approaches demonstrate how endogenous tumor metabolism can be harnessed as an instructive signal to drive extracellular material assembly across different length scales. By translating cellular metabolic activity into engineered biochemical and mechanical cues, these platforms provide versatile tools for investigating cell–matrix reciprocity and designing adaptive biomaterials for tumor microenvironment engineering.

(1) Hastings, J. F. et al. *British Journal of Pharmacology*. **176**, 82 (2019).
(2) H. Choi, et al., *J Nanobiotechnology*. **21**, 5 (2023).
(3) Wimley, W. C. and White, S. H. *Nat Struct Mol Biol*. **3**, 842 (1996).
(4) Saint Jean, K. D. et al. *Probiotics & Antimicro. Prot*. **10**, 408 (2018).