Facile Formation and Dissolution of Extracellular Matrix Gels on Demand

Technology #17184

Applications

Extracellular matrix (ECM) gels that can be formed and dissolved on demand by using methods accessible to the general cell biology community could be used *in vitro* to model complex human physiology in cell culture for biomedical research. Fast dissociation of the ECM is especially important when measuring and interpreting fast-changing cell signaling networks.

Problem Addressed

Scientists have traditionally used animal models for modeling human disease and predicting human responses to therapeutics. Recently, efforts to model human physiology has led to the development of new biomaterials and devices that foster the formation of human-like 3D tissues and organ subsystems, including natural ECM gels, such as collagen and Matrigel®, that provide a scaffold for cell growth. Natural ECM gels, while useful, have biophysical and compositional properties that are difficult to tune. They also require long incubations in protease solutions or thermal, chemical, or ionic shifts to dissolve, which are either limited to applications in thin tissues or can perturb the very cell signaling and transcriptomics that are under investigation. An ECM gel that can undergo rapid non-proteolytic breakdown would provide an elegant solution to this problem.

Technology

This invention uses crosslinking, modification, and dissolution of prototypical polyethylene glycol (PEG) hydrogels by engineered mutants of Staphylococcus aureus Sortase A (SrtA), which catalyze a reversible peptide exchange process of the general form: (R)-LPXTG + GGG-(R) = (R)-LPXTGGG-(R) + G. This reaction may be driven in the reverse direction by the addition of the small peptide GGG. The mutant SrtA enzymes are engineered to have 100x greater catalytic efficiencies and tailored substrate affinities compared to wild type enzymes, to have good diffusion rates compared to other larger crosslinking enzymes, and can be produced recombinantly with high yields. In preliminary findings, mechanically-robust PEG hydrogels could be formed and dissolved in minutes while preserving encapsulated cell viability that is similar to other gel types, thus opening up the possibility that a single relatively low-cost, broadly accessible reagent can be exploited to create and break down highly tailored synthetic ECM. In particular, the dissolution approaches can be carried out on gels produced by a wide spectrum of already-established crosslinking processes by simply including the SrtA ligation sequence LPRTG within the crosslink bridge. Further, the reversible SrtA reaction can be used to release on command gel-embedded protein ligands, such as growth factors. In general, this method is much simpler, less expensive, and more broadly accessible to the cell biology community than existing methods, and enables greater functionality to be built in to synthetic gels.

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Advantages

- Fast dissociation of ECM gel in minutes
- High cell viability comparable to other gel types
- Non-proteolytic synthesis and breakdown
- Crosslinking enzyme with high catalytic efficiency and tailored substrate specificity
- Versatility in incorporating large proteins such as growth factors into ECM gel
- Mechanically robust
- Inexpensive and broadly accessible methods

Categories For This Invention:

Life Sciences
Biomaterials
Research Tools
Cell Line
Other (Research Tools)
Protein & Protein Chemistry
Reagent

Intellectual Property:

Hydrogel comprising a scaffold macromer crosslinked with a peptide and a recognition motif
US Patent Pending
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Publications:

On-demand Dissolution of Modular, Synthetic Extracellular Matrix Reveals Local Epithelial-stromal Communication Networks
Biomaterials
2017
On-demand Dissolution of Modular, Synthetic Extracellular Matrix Reveals Local Epithelial-stromal Communication Networks
Elsevier
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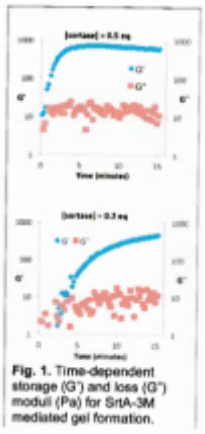

Fig. 1. Time-dependent storage (G') and loss (G") moduli (Pa) for SrtA-3M mediated gel formation.

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