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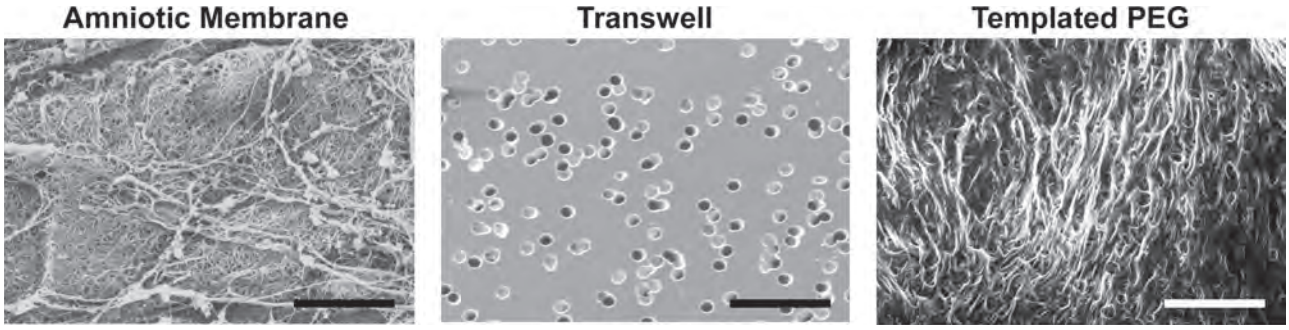
PRESS RELEASE

Chemically- and mechanically-tunable porated polyethylene glycol gels for leukocyte integrin independent and dependent chemotaxis

June 1, 2014 — Urea crystal templating of polyethylene glycol hydrogels enables complex mechanistic investigations into the chemical and mechanical features that guide three-dimensional leukocyte migration.



Chemically- & mechanically-tunable porated polyethylene glycol gels for leukocyte integrin independent and dependent chemotaxis. SEM images of human amniotic membrane (left), polycarbonate transwells (3 micron pore; center) and crystal templated PEG gels (10 kDa PEG with 40% urea; right) demonstrate the similar complexity of human tissue and the crystal templated PEG hydrogel. All scale bars are 20 microns.

In human inflammation, extracellular matrix (ECM) proteins, signaling molecules and mechanical signals are sensed by and regulate migrating leukocytes. The mechanisms by which these mechanical and biochemical signals govern leukocyte migration are not well understood. Elucidating these signals could lead to a better understanding of, and treatment for, chronic inflammatory diseases. Yale University researchers directed by Dr. Anjelica Gonzalez, assistant professor of biomedical engineering, have presented a novel *in vitro* hydrogel model for human ECM that facilitates mechanistic investigations into the ECM's regulation of inflammation. This work is presented in the June issue of the journal TECHNOLOGY.

"The tools previously available for investigating leukocyte migration were limited in their relevance to human tissue or their ability to be controllably manipulated for mechanistic studies," says Gonzalez. "Our model provides a useful tool to present human proteins, integrin binding sites, mechanical cues, and other regulatory aspects of an *in vivo* system, but in a controlled *in vitro* setting."

The model modifies polyethylene glycol (PEG), a bioinert polymer that is commonly used in biomaterials. Although PEG is useful in two-dimensional migration assays because it is easily modified biochemically and mechanically, its small pores prevent it from being used for three-dimensional assays. Gonzalez's team used urea crystal templating to reliably and controllably create complex pore networks throughout the gels. The pore sizes and densities were controlled via the conditions of crystal templating to enable three-dimensional leukocyte migration studies.

The group recapitulated four features of human ECM *in vitro* with the templated PEG hydrogels: bulk elasticity (as determined by the Young's modulus), local elasticity (as determined by the molecular weight of the PEG backbone), peptide and protein presentation, and pore architecture (size and density). Comparison of the templated PEG hydrogels to human amniotic membranes, one human ECM commonly used *in vitro*, and polycarbonate transwells, one commercial *in vitro* substrate, confirmed that PEG gels more accurately replicated the complex environment of human tissue.

"With PEG, in contrast to other three-dimensional substrates, not only are we able to replicate healthy tissue, but we can independently control structural, mechanical, and biochemical signals presented to migrating neutrophils to replicate diseased tissue and to gain insight into how inflammation is affected by disease," says Holly Lauridsen, one of the papers co-first authors along with Bryan Walker.

Functionally, Gonzalez's team determined that within the physiological range for healthy soft tissues (<5 kPa) less stiff and more locally elastic membranes are increasingly permissible to neutrophil migration. Further, small pores, high pore densities, and whole proteins will further promote chemotaxis.

Moving forward, Gonzalez and her team plan to advance this model even further by incorporating more complex proteins and biochemical signals from different pathological tissues. "Countless conjugation schemes to include various peptides and proteins in PEG hydrogels already exist. Using crystal templating opens the door to apply these protocols to immunological investigations," says Bryan Walker.

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