Dynamic degradation of biocompatible hydrogels measured using passive microrheology

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Synthetic hydrogel scaffold are designed for a broad array of applications, including wound healing, tissue regeneration and 3D stem cell culture platforms. The lack of knowledge of the material microstructure and its effect on the performance of the scaffold is a growing challenge especially in complex matrices. We will discuss the characterization of two poly(ethylene glycol) (PEG) based hydrogel systems, a covalently adaptable (CA) hydrogel and an enzymatically degradable PEG-peptide scaffold. In this work, we use multiple particle tracking microrheology (MPT) to measure dynamic material properties during scaffold degradation. MPT measures the thermal motion of embedded probe particles to extract rheological properties using the Generalized Stokes-Einstein Relation. CA hydrogels mimic the native extracellular matrix that cells experience *in vivo* due to their ability to physically adapt to their environment. The CA hydrogel system we are studying is made from multi-arm PEG molecules that form reversible bis-aliphatic hydrazone bonds. This unique chemistry creates a material that yields when a stress is applied or is pushed out of equilibrium by a change in pH and reforms covalent bonds once the stress is released. MPT determines that pushing the scaffold out of equilibrium with one change in pH causes the bonds in the scaffold to degrade and reform several times before undergoing hydrolysis and transitioning to a sol. To further our understanding of how cells interact with synthetic scaffolds, we characterize a PEG-peptide hydrogel. To understand the dynamic rheology during cellular remodeling, we use microrheology to characterize a matrix metalloproteinase (MMP) degradable hydrogel both temporally and spatially during 3D human mesenchymal stem cell (hMSC) encapsulation focusing on the region directly around the cell, the pericellular region, during migration. We measure that hMSCs degrade a gradient into the material with the largest degradation furthest from the cell. For motility hMSCs must adhere to the network and use cytoskeletal tension to move. We measure cellular adhesion to the material directly under the cell prior to motility while MMPs are secreted to degrade the scaffold enabling facile motility. This work provides a foundation to quantitatively understand dynamic environments during scaffold remodeling due to external stimuli and cell reengineering enabling the design of tunable synthetic materials to enhance and direct cellular processes during wound healing and tissue regeneration.