Enhancing the Programmability of Engineered Extracellular Matrices with Sequence Specific Peptoids

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Hydrogel substrates have garnered intense interest as engineered extracellular matrices due to their tailorable mechanics and degradability. These substrates can be composed of naturally derived materials (e.g., collagen) or synthetic materials (e.g., poly(ethylene glycol). Synthetic materials are attractive due to their known chemical compositions and scalability, but the challenge with their use lies in the lack of complexity as compared to biological systems, especially with regard to sequence-specific bioactivity. Hence, our work aims to enhance the programmability of synthetic hydrogel biomaterials by using precise polymer architectures, specifically with a class of materials called peptoids. Here, we describe our efforts to control two key properties of hydrogel substrates with peptoid functionality: 1) bulk mechanics and 2) enzymatic degradability. Tailoring these features is essential for regulating the interface of hydrogel substrates with adhered cells for efficacious cell manufacturing and tissue engineering platforms.

Drawing inspiration from semiflexible biopolymers, we achieved control over the mechanics of hydrogel substrates by controlling chain structure with peptoid cross-linker sequence. Specifically, helical peptoids increased the shear moduli of hydrogels due to increased chain stiffness as compared to non-helical peptoids, while keeping all other hydrogel parameters fixed. This strategy decoupled bulk mechanics of the substrate from the network connectivity, allowing for investigation of mechanical effects on adhered mesenchymal stromal cell (MSC) behavior. We found that MSCs adhered on soft substrates secreted higher levels of indoleamine 2,3-dioxygenase (IDO), an immunomodulatory enzyme necessary for enhanced cell performance. Furthermore, we examined the ability of peptoids to tune hydrogel degradability via proteolysis. We substituted peptoids into key sites of proteolytically degradable substrates, enabling a tailored material response to matrix metalloproteinases secreted by cells. Overall, our results suggest that sequence control of synthetic peptoids may provide effective strategies for expanding the functionality of biomaterial scaffolds for tissue engineering and regenerative medicine, particularly with respect to mechanics and degradation in complex biological environments.