Biomimetic Hydrogels for Supporting Cell Fate Processes

Hydrogels prepared from natural materials (e.g., collagen, gelatin, hyaluronic acid, etc.) inherently contain bioactive motifs that can support certain aspects of cell fate processes. While not containing cell-signaling motifs, hydrogels prepared from purely synthetic polymers (e.g., PEG, PVA, etc.) can sometimes support the survival and even proliferation of certain cells (Lin et al. 2011). These passive matrices do not interact with the cells, necessitating the incorporation of artificial bioactive motifs for supporting complex cell fate processes. Much of the knowledge regarding biomimetic motifs comes from our ever-increasing understanding of the compositions of extracellular matrix proteins (Lutolf and Hubbell 2005; Martino et al. 2014). The presentations of ECM proteins/signals in a cell's native microenvironment are far from static because ECM proteins (e.g., fibrin, fibronectin, laminin, collagen, etc.) are secreted by cells residing within the regenerating niche or recruited from neighboring tissue. The arrival of different types of cells at different time scales during tissue morphogenesis or regeneration explains the dynamic nature of these cell-secreted ECM motifs.

To mimic a natural cell niche, it has become a common practice to tether individual biomimetic motifs into synthetic hydrogels. This approach allows for studying receptor-mediated intracellular signaling. Since most of the cell fate processes are elicited by receptor-mediated intracellular signaling events, hydrogels contain ECM motifs are useful in not only providing a 3D culture context, but also in studying ligand-mediated receptor activation. In addition to full-length ECM proteins, integrin receptor activation can also be induced by short peptides derived from ECM proteins. The most ubiquitous integrin-binding peptide is the tri-peptide RGD, which represent the smallest peptide sequence for activating integrins. Although RGD was first discovered from fibronectin, it is also found in the peptide sequence of numerous matrix proteins, including fibrin, osteopontin, TGFβ-latent protein. Other receptor binding peptides/proteins (e.g., laminin-derived peptides (Raza et al. 2013; Bal et al. 2014; Lam et al. 2015), stromal cell derived factor 1 (SDF-1) (Cuchiara et al. 2013), Notch ligands (Dishowitz et al. 2014), etc.) have also been increasingly used to study stem cell differentiation, and for promoting tissue regeneration.

In addition to mimicking cell-matrix interactions through conjugating matrix proteins or peptides in the crosslinked hydrogels, increasing efforts have been devoted to recapitulating aspects of cell-cell interactions in biomimetic matrices. For example, Lin and Anseth identified cell density as a crucial factor governing pancreatic β-cell survival and function in chain-polymerized PEGDA hydrogels (Lin and Anseth 2011). They further integrated cell-cell communication mimicry motifs in the cell-laden hydrogels through co-polymerizing thiolated recombinant Ephrin and Eph, a pair of cell surface receptor/ligand important in regulating β-cell viability and insulin secretion. The immobilized Ephrin/Eph motifs provided additional cell-signaling motifs in the otherwise inert PEG gel network to support the survival and function of MIN6 β-cell even when they were encapsulated at low cell density.

The development of biomimetic hydrogels for 3D cell culture has also benefited significantly from recent development in advanced biofabrication, such as 3D