Physical hydrogels composed of macromolecular self-assembly

Entropy-driven hydrophobic interaction is an effective way of creating stable bonds linking polymer chains into crosslinked hydrogels. A variety of hydrophobic interactions, such as coiled-coil peptides and amphiphilic block copolymers, have been explored in cell-compatible hydrogel fabrication (Banta et al. 2010; Woolfson 2010). The coiled-coil domain is a left-handed superhelix composed of two or more right-handed α-helices. Its signature amino acid sequence typically contains repeat units of (*abcdefg*) with *a* and *d* being hydrophobic residues and the rest are polar residues. The hydrophobic residues are line up to form the hydrophobic core, which undergoes conformational changes upon applying external stimuli (e.g., temperature, pH, ionic strength, etc.). When the coiled-coil domain is incorporated in hydrogel design, external stimuli cause microscopic protein conformational changes that also lead to changes in macroscopic material properties. For example, Wang et al. combined the coiled-coil protein domains and metal ion chelation to synthesize thermal-responsive hydrogels (Wang et al. 1999). Genetically engineered coiled-coil proteins with a hexa-histidine (6xHis) tag are assembled on a linear copolymer composed of N-(2-hydroxypropyl)-methacrylamide (HPMA) and metal-chelaing (N',N'-dicarboxymethylaminopropyl)-methacrylamide (DAMA), the later serves as a pendant metal-chelating ligand (i.e., iminodiacetate, IDA) for chelating with Ni^{2+} and the His-tagged coiled-coil protein. Due to temperature-induced cooperative conformational transition in the coiled-coil protein domain, these hybrid hydrogels collapse (i.e., decreased swelling) at an elevated temperature (mid-point transition temperature of 39°C).

While the aforementioned coiled-coil protein hydrogel was not used in cell encapsulation or cell culture, it paved the way for later studies in such endeavor. In one recent example, coiled-coil domains with free terminal cysteine were engineered and used to form self-assembled multifunctional thiols, which react with vinylsulfone-conjugated PEG through Michael-addition (Liu et al. 2011). The resulting hydrogels are composed of both physical coiled-coil association and chemical thiol-vinylsulfone crosslinks. The system is compatible for cell encapsulation and the dynamic nature of the coiled-coil association is believed to serve as open paths for cell migration and higher order morphogenesis (e.g., epithelial cyst formation) in 3D. Similar coiled-coil protein domains have also being conjugated to synthetic polymers for forming shear-thinning and temperature-responsive hydrogels (Glassman et al. 2013).

Physical hydrogels formed by host-guest interactions

Supramolecular 'host-guest' interactions have been exploited to form hydrogels capable of 'self-healing' due to their reversible binding nature (Webber et al. 2015). However, most of the early work on host-guest hydrogels employed organic solvents for dissolution of the hydrophobic macromers. Recently, researchers have begun to design host-guest hydrogels suitable for cell encapsulation. Host and guest molecules that non-covalently interact with each other are separately conjugated to multi-functional polymers (e.g., polyvinyl alcohol, hyaluronan, gelatin, etc.) and are assembled into gels upon mixing the host macromers with multifunctional guest crosslinkers (Highley et al. 2015; Mealy et al. 2015; Rodell et al. 2015a; Rodell et al. 2015b). Many of these