Chemoselectively Crosslinked Hydrogels for Cell Delivery

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Hydrogels are three-dimensional networks composed of hydrated polymer chains and have been a material of choice for many biomedical applications such as drug delivery, biosensing, and tissue engineering due to their unique biocompatibility, tunable physical characteristics, flexible methods of synthesis, and range of constituents. In many cases, methods for crosslinking polymer precursors to form hydrogels would benefit from being highly selective in order to avoid cross-reactivity with components of biological systems leading to adverse effects. This presentation reports the use of a chemoselective native chemical ligation (NCL) reaction to form hydrogels by covalently cross-linking water-soluble macromonomers consisting of a multi-armed poly(ethylene glycol) core with ends functionalized with thioester and N-terminal cysteine. Upon mixing aqueous solutions of the macromonomers, rigid hydrogels formed within minutes. Effects of buffer, pH, polymer concentration and reaction temperature on the gelation kinetics and the viscoelastic behavior were studied by oscillatory rheology. In addition to the rapid gel formation under physiological conditions, a useful feature of this crosslinking strategy is the regeneration of thiol functional groups as a result of the NCL reaction, thereby allowing functionalization of the polymer hydrogel for various applications. This was shown by conjugation of maleimide-terminating peptides to an NCL hydrogel through a Michael-addition, permitting the attachment of human mesenchymal stem cells on the gel surface presenting the sequence GRGDSPG-NH₂. Incorporation of bioactive components into the 3D hydrogel network was demonstrated by including a maleimide-terminating anti-inflammatory peptide, an inhibitor of IL-1α receptor, in the solutions of macromonomers during the gelation. Such gel was able to maintain the viability of encapsulated islet beta cells up to three weeks. Modification of the NCL reaction through replacement of the thioester with the N-hydroxysuccinimide ester and physical crosslinking facilitators were utilized to tune the properties of NCL hydrogels at a wider scale. Due to the mild reaction conditions, chemoselectivity, and the flexibility for biological functionalization, the NCL-crosslinked hydrogels may prove useful for many biomedical applications.