Molecular Modeling to Predict Peptide Accessibility for Peptide-functionalized Hydrogels

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Statement of Purpose: Peptide-functionalized (PF) hydrogels are being widely investigated by the tissue engineering and regenerative medicine communities for a broad range of applications because of their unique potential to mimic the natural extracellular matrix and promote tissue regeneration. In order for these complex material systems to perform their intended bioactive function (e.g., cell signaling), the peptides that are tethered to the hydrogel matrix must be accessible at the hydrogel surface for cell-receptor binding. The design parameters from surface chemistry perspective influencing the surface accessibility of the tethered peptide include the length of the tethers and the loading (i.e., concentration) of the peptide. The purpose of this work is to develop coarse-grained (CG) molecular models for a type of poly(ethylene glycol) (PEG)-based PF hydrogel and to conduct molecular simulations to investigate the distribution of the peptides within the hydrogel and their surface accessibility as a function of tether length and peptide concentrations.

Methods: All simulations were conducted using a three-step multiscale modeling toolset developed in house. In a coarse graining process, several atoms are grouped together and represented by a super bead with the mapping point being taken as the center of mass of each group of atoms. Fig. 1 illustrates the strategy used to coarse grain the two types of crosslinkers (PEGDA and MethG_mRGDSP) and the copolymer network formed by them. The water molecules were also represented by a CG scheme, in which four water molecules represented by atomic model are represented by one single CG bead. In this work, nine peptide loadings (concentrations) from 1.7 to 15.3 mM and three tether lengths (MethG_mRGDSP with m = 2, 4 and 6) were considered.

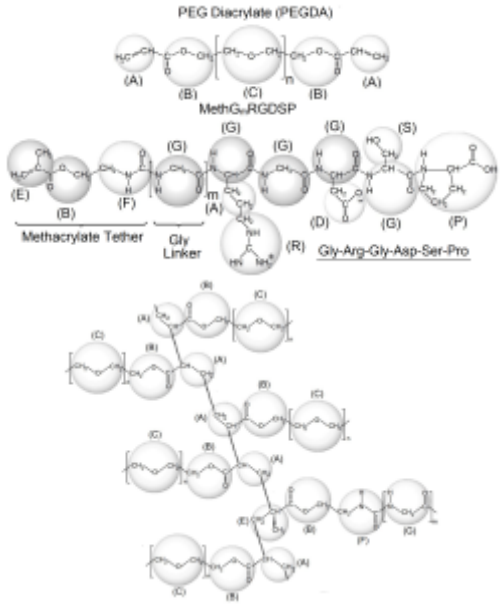

Figure 1. Coarse gaining strategy for MethG_mRGDSP (m = 2, 4 and 6) and PEGDA (n = 12) crosslinkers and the network formed by them.

Results: CG model results of chain conformation characterized by end-to-end distance and radius of gyration were found to agree closely with corresponding atomic model results. The simulation results revealed that, as the peptide loading or the tether length increases, the tethered peptide has a tendency to phase separate from the hydrogel matrix and be preferentially concentrated at the hydrogel-water interface. Fig.2 combines the cell adhesion number obtained from experiments and the peptide surface concentrations obtained from simulation. As clearly shown from this plot, the G_4 and G_6 tether lengths provide substantially greater cell adhesion than the G_2 tether length at a given peptide surface concentration, thus this result indicates that the longer tether lengths present the peptide in a manner that is more conducive to cell adhesion. Fig. 2 demonstrates an example of how the results from the molecular simulations provide insights into the molecular behaviors of the PF-hydrogels that influence their bioactivity but cannot be obtained by the experimental studies alone.

Conclusions: A multiscale modeling toolset developed in our series of studies has been successfully applied to characterize the properties of a specific type of PF-hydrogel. The toolset is able to efficiently and accurately predict the structures and bioactivities of the PF-hydrogel. We propose that the developed method has the potential to provide a powerful new tool for hydrogel design for tissue engineering and regenerative medicine to optimize cellular response.

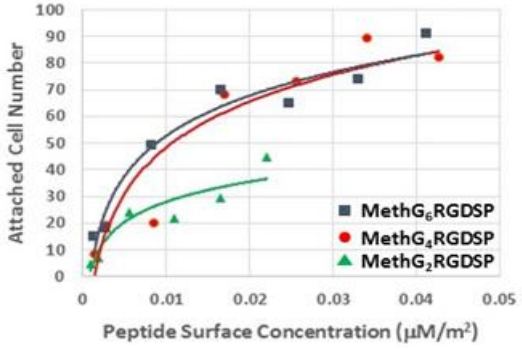

Figure 2. Cell adhesion number obtained from experiment vs. the peptide surface concentration density obtained from simulation for each peptide loading and tether length in the hydrogel.

Acknowledgements: This work was supported by "RESBIO—The National Resource for Polymeric Biomaterials" funded under NIH Grant No. P41 EB001046-01A1.