

# Self-Assembly of Peptides into Hydrogel

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Self-assembly is a process that allows the formation of micro- or nanoscale structures from simple building blocks. Among them, self-assembled materials from natural organic molecules such as nucleotides, saccharides, phospholipids, or amino acids have attracted significant attentions because of their unique and tunable nanostructures changing amino acid sequences or properties of peptides [1]. For self-assembly, a delicate balance must be reached between the attractive and repulsive non-covalent interactions, which is essential to drive the self-assembly process.

Typical interactions include H-bonding, ionic interactions,  $\pi$ - $\pi$  interactions, van der Waals interactions, and hydrophobic interactions. The resulted balance precisely controls the assembly process, and optimized molecular conformations and higher order structures are formed spontaneously. Hydrogen bonding occurs between hydrogen attached to atoms with a greater electronegativity and atoms with a free lone pair of electrons. The strength depends on the dipole moment between the bond of the hydrogen donor atoms and the lone pair on the proton acceptor.  $\pi$ - $\pi$  interaction makes another crucial force in the self-assembly of supramolecular structures, which forms between the  $\pi$ -orbitals of aromatic rings and an electropositive s/p orbitals. The hydrophobic interaction tends to drive minimally charged organic molecules together in an aqueous environment to develop a dehydrated core.

Nanomaterials assembled from organic molecules have been widely applied in various research fields such as biomedical diagnostics, drug delivery, tissue engineering, optoelectronic, solar cells and so forth [2-5]. The highly defined nanostructure of the hydrogel is of particular interest due to its applications in the field of material science for membrane, separation technology, catalysis, crystal engineering, and fuel engineering [6,7]. They provide physically-rigid, three-dimensional, and cross-linked networks and retain a high water content. Meanwhile, pore size, morphology, and mechanical properties of hydrogels are easily controllable. Compared with hydrogels made from amphiphilic molecules or synthetic copolymers, peptide-based hydrogel has special advantages in tissue engineering as well as drug delivery because of its excellent biocompatibility and is generally recognized as safe (GRAS) [8]. Aside from that, peptide-based hydrogel has suitable mechanical properties as a result of a combination of strong secondary intermolecular interactions such as  $\beta$ -sheet or  $\alpha$ -helical coiled coil.

Zhang et al. reported the self-assembly of polypeptides with alternating hydrophilic and hydrophobic amino acids, which formed the hydrogel at neutral pH but no gelation at neither low pH (due to charged lysines) nor high pH (due to glutamic acids) [9]. Schneider et al. have investigated lysine-rich  $\beta$ -hairpin peptides controlled by pH and ionic strength. No gelation was observed at neutral pH and low ionic strength, but screening of the charged lysine side chains triggered by increased ionic strength allowed self-assembly and gelation [10].

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Coumarins are one of the simplest heterocyclic structures that are frequently found in nature and exhibited very broad scope of biological activities such as anticoagulation, antibiotic, antioxidant, antibacterial, antiviral, antifungal, antipsoriasis, cytotoxic, anti-HIV, anti-inflammatory. In addition to their therapeutic properties, coumarins are widely used as fluorescent probes in biology and medicine since coumarins are relatively photostable, show low cytotoxicity, possess high fluorescence ability compared to fluorescence of cellular components, tissues, and biological fluids. Kim et al. reported a cross-linked self-assembled-dipeptide hydrogel [11]. Self-assembly of  $\beta$ -sheet nanofibers effectively leads to hydrogel formation in aqueous media. The mechanical properties of hydrogels are strongly dependent on their aqueous environment, suggesting an additional means to tune their physical properties. Irradiation at 365 nm crosslinks the coumarin moieties and retains the nanofiber structure. The cross-linked nanostructure remains intact in TFE, a potentially denaturing solvent, which dissolves the non-cross-linked material.

Fluorescence imaging has been used as a powerful tool in biological *in vitro* cell imaging research [12]. Particularly, nano-sized fluorescence materials have been studied extensively for their improved circulation time in the blood compartments and efficient accumulation at sites like tumor and arthritis [13,14]. Combining these features, it can be expected that nanoprobe from peptide-hydrogel will find greater applications for biomedicine shortly.

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