Molecular-level Bioinspired Engineering

Design and Preparation of New Synthetic Biomaterials for Regenerative Medicine

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Natural evolutionary processes have produced structural proteins that can surpass the performance of man-made materials (e.g., mammalian elastin in the cardiovascular system that lasts half a century without loss of function and spider webs composed of silk threads that are tougher than any synthetic fiber). These biological polypeptides are all complex, multifunctional copolymers that derive their phenomenal properties from precisely controlled sequences and compositions of the constituent amino-acid monomers, which, in turn, lead to precisely controlled self-assembled nanostructures. Recently, there has been interest in developing synthetic routes for preparation of mimics of these natural polymers as well as wholly artificial polypeptide sequences for applications in regenerative medicine.

There has been an abundance of research in recent years on development of polymeric materials as scaffolds for tissue engineering. Current challenges in this area include incorporation of multiple levels of functionality into these materials for cell binding, controlled degradation, cell signaling, as well as tuning of physical properties such as rigidity and porosity. Addition of functionality has been challenging since many polymeric materials have limited capability for modification, and once functionalized, physical properties may be significantly altered or impaired. For these reasons, there is a need for new materials that can be prepared using a versatile method that allows fine tuning of chemical composition and structure, and uses building blocks that are biocompatible and easily functionalized, mimicking natural materials. Our group has been working on biomimetic polypeptide based materials since these are reproducibly prepared pyrogen free in large quantities, chain lengths and compositions are easily modified, they allow facile incorporation of bioactive functionality by use of amino acid monomers, and their chain conformations can be used to guide physical properties independent of many other parameters. The versatility of polypeptides gives them tremendous potential as multifunctional carriers that can be used overcome the many hurdles encountered in regenerative medicine. Here, I will discuss a class of polypeptide amphiphiles that contain an unprecedented amount of structural and functional programming to guide assembly into hydrogel structures for use as scaffolds in regenerative medicine.

Amphiphilic diblock copolypeptide hydrogels (DCH) are synthetic materials with many features that make them attractive as tissue engineering candidates for applications that are likely to require progressive adjustment and fine-tuning of material properties. We have used a combination of chemical synthesis and structural characterization to establish a detailed understanding of DCH structure-property relationships that allows a high level of control over gel strength, gel porosity, gel functionality and media stability; and many of these properties can be adjusted independently of each other. DCH are physically associated gels that can be deformed and thinned by stress and injected through small-bore cannulae, after which they rapidly re-assemble into rigid gel networks. These properties provide DCH with the potential for facile and minimally invasive delivery *in vivo*. DCH form elastic gels with fibril-like nanostructures and porous microstructures theoretically suitable for integration with host cells. The polypeptide backbone of DCH allows straightforward incorporation of peptidic functionality that can impart cell adhesion, molecular signaling or enzymatic degradability, either by direct incorporation of desired amino acids into the primary polypeptide chain, or by attaching sequence specific peptides at defined locations on the chains so that bioactive groups can be linked to the polypeptide chains with

controlled density and spatial resolution. In addition, DCH can easily and reproducibly be produced in large quantities of high purity with complete removal of chemicals employed during synthesis; and the samples are free from pyrogens or biological contaminants and are easily sterilized by autoclave.

Overall, I will give a brief overview of the role played by synthetic biomaterials in improving medicine and healthcare. I will summarize the positive attributes and limitations of current materials and the qualities desired for the future to address challenges in regenerative medicine. This will lead to some discussion on how synthetic biomaterials must be designed and prepared with molecular level control, and I will outline some targets/strategies in this area, exemplified by some work from my lab on the preparation of materials for tissue regeneration, with a key point of emphasis on how molecular level features influence their performance. I will also stress how the future synthetic biomaterials must be multifunctional to accomplish their goals, and the challenges and strategies to achieve this, namely how to design biomaterials with control over both structure and functionality, over multiple length scales. The relation between molecular design and properties/uses will be strongly emphasized.