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Silk - Based Drug Delivery Systems

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Silks are biodegradable, biocompatible, self-assembling proteins that can also be tailored via genetic engineering to contain specific chemical features, offering utility for drug and gene delivery. Silkworm silk has been used in biomedical sutures for decades and has recently achieved Food and Drug Administration approval for expanded biomaterials device utility. With the diversity and control of size, structure and chemistry, modified or recombinant silk proteins can be designed and utilized in various biomedical application, such as for the delivery of bioactive molecules. Silk proteins have been used successfully in the biomedical field as sutures for decades, and also explored as biomaterials for cell culture and tissue engineering,achieving Food and Drug Administration approval for such expanded utility because of their excellent mechanical properties, versatility in processing and biocompatibility.This topic focuses on the biosynthesis and applications of silk- based multi-block copolymer systems and related silk protein drug delivery systems.

Keyword: -Silk Base Drug Delivery System, Bioactive Molecules, Self-Assembling Proteins, Biomaterials.

INTRODUCTION: Despite the multitude of applications, no system currently exists for controllable, sustained, long-term drug delivery via fully degradable implants. To address this need, polymeric systems have been studied and while there are a number of biomaterials available for drug delivery devices, purified silk fibroin protein is a unique material particularly well suited to controlled release applications. Implants derived from silk exhibit the requisite biocompatibility and degradation profile for implantable applications, but also possess the necessary material properties to provide a sufficient diffusion barriers (even for small molecule drugs) and highly-controllable material features that can in turn be used to precisely tailor drug release behavior. Studies have suggested that a particular desired release profile adapted to the target drug delivery application can be obtained by varying polymer coating formulation and processing parameters, but the systematic characterization of these effects necessary to achieve tight control has never been undertaken. Release of the small molecule adenosine from a variety of silk-based drug delivery systems was examined to correlate fundamental relationships between material features (e.g., processing conditions, crystallinity, degumming time, layer thickness, etc.) and resulting release kinetics. Characterizing and modeling these effects led to development of an integrated model that incorporated multiple control points that could be

modulated to achieve specific target release profiles. The predictive accuracy of the model was confirmed by comparing theoretical release predictions to experimental release behavior. Degradation also played a role in drug release both in cases of freely diffusible drugs and for drugs bound to the silk matrix. Degumming time, film fabrication process and coating thickness impacted degradation of the silk carriers and release kinetics. Strategies to control local proteolytic degradation via proteinase inhibitors and proteolytic enzymes were demonstrated. Silk drug delivery implants have significant potential clinical applications due to the features above, including treatment of neurological disorders, stabilization and delivery of antibiotics and incorporation of signaling molecules into tissue engineering scaffolds. These fundamental and application-driven in vitro and in vivo studies showed that hydrophobic, hydrophilic, small and large molecule drugs can be entrapped and released from silk-based devices with tight control of the release kinetics through manipulation of the implant processing and material properties. The unique mechanical properties of silks together with their excellent biocompatibility have recently sparked interest of this protein polymer class for medical applications. This study details the possibilities and limitations for silk-based biomaterials as carriers for controlled drug delivery.

SILK- BASED BIOMATERIALS FOR DRUG DELIVERY[1,3,5]

Silk fibroin is one of the promising biomaterials for medical applications. Its unique mechanical properties and biocompatibility make the silk fibers an attractive material and scaffold for tissue engineering. As a result of biodegradability, silk has been recently explored in the field of drug delivery. Silk fibroin has been suggested as a platform for drug delivery in the form of films, hydrogels and porous 3D scaffolds. Design of such drug delivery system is based onthe ability of silk fibroin to undergo conformational transition from a random coil to a sheet form to produce an interpenetrating network. Possibility to fine tune the release kinetics by controlling the secondary structure of silk fibroin was demonstrated. Control over crystallinity and structure as well as design of the silk - based delivery system in general represent important variables in tailoring the release kinetics of the active compounds. Several advanced strategies of using silk in drug delivery will be presented. Silk based delivery systems deals with the use of silk protein as a polymer for various drug delivery systems. Silks are biodegradable, biocompatible, self-assembling proteins that can be tailored via genetic engineering to contain specific chemical features, offering its utility for drug and gene delivery. This topic focuses on the biosynthesis of silk-based polymer systems and related silk protein drug delivery. Silk-based biomaterials are used to deliver bioactive molecules, such as small drugs, proteins, genes. They show remarkable mechanical properties, versatile processing in an aqueous environment, biocompatibility, and controlled degradation suggest silks as attractive biomaterials for controlled and sustained release, stabilization and delivery of bioactive molecules. Silk solutions can be morphed into a variety of biomaterial formats, including films, 3D porous scaffolds, hydrogels , micro- and nano -spheres, nanofibres and coatings. Targeted delivery can be achieved Hybrid or composite silk-based materials containing other biopolymers, have not been extensively studied, yet should provide applicable mechanical, thermal, and biological properties for not only drug/gene delivery but also for tissue engineering, medical imaging, and regenerative medicine.

SILK FIBROIN AS A VEHICLE FOR DRUG DELIVERY APPLICATIONS[6,7,8,10]

Silk fibroin (SF), a naturally occurring protein polymer, has several unique properties making it a favorable matrix for the incorporation and delivery of a range of therapeutic agents. SF is biocompatible, slowly biodegradable, and endowed with excellent mechanical properties and processability. Novel manufacturing techniques including mild all-aqueous processes have expanded its range of application even to sensitive protein and nucleic acid therapeutics. SF

matrices were demonstrated to successfully deliver protein drugs and preserve their potency. Adjustments in SF crystallinity, concentration and structure, the design of the delivery systems as well as the molecular weight and structure of the embedded agents represent important variables when it comes to precisely tailor the release kinetics of SF matrices. Other strategies to fine-tune the release from SF matrices comprise the embedment of drug loaded micro- or nanoparticles or the coating of micro- or nanoparticles with SF films. So far, the main focus of SF drug delivery systems has been on tissue regeneration applications. For instance, growth factor loaded SF scaffolds were suggested for the tissue engineering of bone and cartilage, as well as for vascular and nerve regeneration devices and wound healing products. Moreover, SF matrices were proposed for oral, transmucosal and ocular drug delivery. This article reviews SF properties and fabrication processes that affect the release from SF drug delivery systems. For illustration, we discuss a variety of examples for the incorporation of drugs into SF systems and their release

SILK FIBROIN BIOMATERIALS FOR CONTROLLED RELEASE DRUG DELIVERY

Given the benefits of polymer drug delivery implants over traditional periodic systemic administration, the development of biomaterial systems with the necessary properties (biocompatibility, degradation, stabilization, controllability) is paramount. Silk fibroin represents a promising, naturally derived polymer for local, controlled, sustained drug release from fully degrading implants and the polymer can be processed into a broad array of material formats. This review provides an overview of silk biomaterials for drug delivery, especially those that can function as long-term depots. Fundamentals of structure and assembly, processing options, control points and specific examples of implantable silk drug delivery systems (sponges, films) and injectable systems (microspheres, hydrogels) from the 1990s and onwards are reviewed. Owing to its unique material properties, stabilization effects and tight controllability, silk fibroin is a promising biomaterial for implantable and injectable drug delivery applications. Many promising control points have been identified, and characterization of the relationships between silk processing and/or material properties and the resulting drug loading and release kinetics will ultimately enhance the overall utility of this unique biomaterial. The ever-expanding biomaterial 'tool kit' that silk provides will eventually allow the simultaneous optimization of implant structure, material properties and drug release behavior that is needed to maximize the cost-efficiency, convenience, efficacy and safety of.

NONMULBERRY SILK BIOPOLYMERS [2,4,5,6,28]

The silk produced by silkworms are biopolymers and can be classified into two types--mulberry and nonmulberry. Mulberry silk of silkworm Bombyx mori has been extensively explored and used for century old textiles and sutures. But for the last few decades it is being extensively exploited for biomedical applications. However, the transformation of nonmulberry silk from being a textile commodity to biomaterials is relatively new. Within a very short period of time, the combination of load bearing capability and tensile strength of nonmulberry silk has been equally envisioned for bone, cartilage, adipose, and other tissue regeneration. Adding to its advantage is its diverse morphology, including macro to nano architectures with controllable degradation and biocompatibility yields novel natural material systems in vitro. Its follow on applications involve sustained release of model compounds and anticancer drugs. Its 3D cancer models provide compatible microenvironment systems for better understanding of the cancer progression mechanism and screening of anticancer compounds. Diversely designed nonmulberry matrices thus provide an array of new cutting age technologies, which is unattainable with the current synthetic materials that lack biodegradability and biocompatibility. Scientific exploration of nonmulberry silk in tissue engineering, regenerative medicine, and

biotechnological applications promises advancement of sericulture industries in India and China, largest nonmulberry silk producers of the world. This review discusses the prospective biomedical applications of nonmulberry silk proteins as natural biomaterials.

SILK-BASED BIOMATERIALS[6,7,25,29]

Silk from the silkworm, Bombyx mori, has been used as biomedical suture material for centuries. The unique mechanical properties of these fibers provided important clinical repair options for many applications. During the past 20 years, some biocompatibility problems have been reported for silkworm silk; however, contamination from residual sericin (glue-like proteins) was the likely cause. More recent studies with well-defined silkworm silk fibers and films suggest that the core silk fibroin fibers exhibit comparable biocompatibility in vitro and in vivo with other commonly used biomaterials such as polylactic acid and collagen. Furthermore, the unique mechanical properties of the silk fibers, the diversity of side chain chemistries for 'decoration' with growth and adhesion factors, and the ability to genetically tailor the protein provide additional rationale for the exploration of this family of fibrous proteins for biomaterial applications. For example, in designing scaffolds for tissue engineering these properties are particularly relevant and recent results with bone and ligament formation in vitro support the potential role for this biomaterial in future applications. To date, studies with silks to address biomaterial and matrix scaffold needs have focused on silkworm silk. With the diversity of silk-like fibrous proteins from spiders and insects, a range of native or bioengineered variants can be expected for application to a diverse set of clinical needs

FUTURE PERSPECTIVES[8,9,13,16,20]

Silk-based biomaterials to deliver bioactive molecules, such as small drugs, proteins, and genes, are described in this review. The remarkable mechanical properties, versatile processing in an aqueous environment, biocompatibility, and controlled degradation suggest silks (both native as well as recombinant) are attractive biomaterials for controlled and sustained release, stabilization and delivery of bioactive molecules. Silk solutions can be morphed into a variety of biomaterial formats, including films, 3D porous scaffolds, hydrogels, micro- and nano-spheres, nanofibers, and coatings. The degradation rate of these biomaterials can be also controlled during processing, by the secondary structures. In addition to these useful properties, silk proteins derived from recombinant DNA technology can be bioengineered for highly tailored chemistries, greatly expanding the suite of options for targeted delivery. Targeted-delivery function is a significant factors in drug delivery, hence, these silk proteins can be prepared with functional sequences to hone to specific cells, tissues or organs, as a useful strategy for silk-based delivery systems with bioactive molecules. When combined with the novel features of the silk proteins themselves, including self-assembly, robust mechanical properties, water-based processing, controlled biodegradation and biocompatibility, silks offer a unique and versatile delivery platform for small molecules, large proteins, DNA and RNA. Hybrid or composite silk-based materials containing other biopolymers, have not been extensively studied, yet should provide applicable mechanical, thermal, and biological properties for not only drug/gene delivery but also for tissue engineering, medical imaging, and regenerative medicine.

SILK DELIVERS DRUGS WITHOUT THE PAIN[11,12,13,16,19]

US researchers have developed a new microneedle drug delivery system using silk. The team says that its multifunctional properties could offer a safe and pain-free way to administer drugs and vaccines, as well as store drugs without the need for refrigeration. Microneedles have gained a lot of interest in recent years as a safe, pain-free alternative to hypodermic needles. As a patch, they can be placed onto the skin like a plaster allowing for self-administration, and as they can't reach pain receptors under the skin they don't hurt. But while some microneedle systems have

shown promise, the materials they have been made from - namely sugars, cellulose-based materials and synthetic polymers - have had limitations, such as the inability to precisely control drug release and to prevent the onset of local infections. Now, David Kaplan and Fiorenzo Omenetto and colleagues at Tufts University have developed high-aspect-ratio microneedles with silk fibroin - a protein found in silk - that presents a multifunctional solution to overcome previous limitations. The team demonstrated that their silk microneedle is biocompatible and degradable, can incorporate, store and controllably release sensitive drugs, and can even include antibiotics to prevent skin infections'We are certainly enthusiastic about the potential for this technology in many areas of medicine,' says Kaplan. 'The drugs can be entrapped in the silk and become stabilized - even at higher temperatures - thus allowing processing from water into delivery systems that can be used like a band aid, carried in your pocket and shipped around the world without refrigeration.' The silk microneedles were made by first creating an elastomer-based negative mould of a microneedle array using polydimethylsiloxane (PDMS). A silk fibroin solution obtained from silk worm cocoons was then drug loaded and cast over the PDMS template and left to dry. By adjusting the hydration state of the silk, and thus the secondary protein structure, the team could modify degradation and diffusion properties of the silk microneedles. 'The structure of the silk used in the microneedles determines the release kinetics of the drugs entrapped in the microneedles,' says Kaplan. 'The microneedles pierce only the outer layer of the skin thus it does not hurt, and then the drug will diffuse from the needles into the tissue at a rate that is programmable in the materials.' To test out the release kinetics, the team applied the microneedles to *in vitro*hydrogel skin models. They also created microneedles loaded with an antibiotic and observed a 10-fold reduction in bacterial density when applied to a cell culture, which could help avoid skin infections associated with other microneedle systems.

CONCLUSION:

The biomedical application of silk fibroin (SF) was evaluated and the research was conducted to develop a novel silk-based platform for the controlled drug delivery. The SF containing matrixes were prepared by spray-drying and film casting, and the release profile of the model drugs was evaluated. SF containing matrixes and microparticles were prepared from aqueous solutions of the fibroin protein polymer. Crystallinity was induced and controlled by treatment with different solvents and by spray-drying, resulting in a formation of a fine interpenetrating network (IPN) of SF. In this study, we selected several model drugs and prepared SF matrixes. The in vitro release assays have shown that the increase in crystallinity resulted in sustained release of the model drugs from the dehydrated SF containing matrix, proving SF is an interesting polymer for drug delivery of bioactive compounds, particularly for colonic drug delivery. Silk based nanoparticles from silk fibroin solutions were stable, spherical, negatively charged, 150-170nm in average diameter and showed no toxicity. g. Hydrogels : Hydrogels of silk fibroin are formed via sol-gel transitions by sonication , vortexing , or the presence of acid and /or ions. h. Coatings: Silk fibroin solution was applied as coating over the delivery systems like microspheres, nano - particles or directly on the drug surface in order to get a sustained release of the drug. The thickness of one layer was reported to be around 10nm when deposited from a 1mg/ml silk aqueous solution. Release from these coatings can be controlled via layer thickness, number of layers and secondary structure of the fibroin layer.

REFERENCES:

1. Guziewicz N, Best A, Perez-Ramirez B, and Kaplan DL. "Lyophilized silk fibroin hydrogels for the sustained local delivery of therapeutic monoclonal antibodies." Biomaterials 2011; 32: 2642-2650.

2. Rockwood DN, Preda RC, Yücel T, Wang X, Lovett ML, and Kaplan DL. "Materials

fabrication from Bombyx mori silk fibroin." Nature Protocols 2011; 6: 1612-1631.

3. Wang X, Yücel T, Lu Q, Hu X, and Kaplan DL. "Silk nanospheres and microspheres from silk/PVA blend films for drug delivery." Biomaterials 2010; 31: 1025–1035.

4. Yücel T, Kojic N, Leisk GG, Lo TJ, and Kaplan DL. "Non-equilibrium silk fibroin adhesives." Journal of Structural Biology 2010; 170: 406-412.

5. Yücel T, Cebe P, and Kaplan DL. "Vortex-induced injectable silk fibroin hydrogels." Biophysical Journal 2009; 97: 2044-2050.

6. Numata K, Subramanian B, Currie HA, and Kaplan DL. "Bioengineered silk protein-based gene delivery systems." Biomaterials 2009; 30: 5775–5784.

7. Wang X, Kluge JA, Leisk GG, and Kaplan DL. "Sonication-induced gelation of silk fibroin for cell encapsulation." Biomaterials 2008; 29: 1054-1064.

8. Lovett ML, Cannizzaro CM, Vunjak-Novakovic G, and Kaplan DL. "Gel spinning of silk tubes for tissue engineering." Biomaterials 2008; 29: 4650-4657.

9. Wang X, Wenk E, Matsumoto A, Meinel L, Li C, and Kaplan DL. "Silk microspheres for encapsulation and controlled release." Journal of Controlled Release 2007; 117: 360–370.

10. Charman W.N., Chan H.-K., Finnin B.C. and Charman S.A., "Drug Delivery: A Key Factor in Realising the Full Therapeutic Potential of Drugs", Drug Development Research, 46, 316-27, 1999.
11. Santini Jr, J.T., Richards A.C., Scheidt R., Cima M.J. and Langer R., "Microchips as Controlled Drug-Delivery Devices", Angew. Chem. Int. Ed., 39, 2396-407, 2000.
12. Kopecek J., "Smart and genetically engineered biomaterials and drug delivery systems", European Journal of Pharmaceutical Sciences, 20, 1-16, 2003.

13. Torchilin V.P., "Structure and design of polymeric surfactant-based drug delivery systems", Journal of Controlled Release, 73, 137-72, 2001.

14. Muller-Goymann C.C., "Physicochemical characterization of colloidal drug delivery systems such as reverse micelles, vesicles, liquid crystals and nanoparticles for topical administration", European Journal of Pharmaceutics and Biopharmaceutics, 58, 343-56, 2004.

15. Haag R., "Supramolecular Drug-Delivery Systems based on Polymeric Core-Shell Architectures", Angew. Chem. Int. Ed., 43, 278-82, 2004.

16. Bae Y., Fukushima S., Harada A. and Kataoka K., "Design of Environment-Sensitive Supramolecular Assemblies for Intracellular Drug Delivery: Polymeric Micelles that are Responsive to Intracellular pH Change", Angew. Chem. Int. Ed., 42, 4640-43, 2003.

17. Soppimath K.S., Aminabhavi T.M., Kulkarni A.R., Rudzinski W.E., "Biodegradable polymeric nanoparticles as drug delivery devices", Journal of Controlled Release, 70, 1-20, 2001.

18. Packhaeuser C.B., Schnieders J., Oster C.G., Kissel T., "In situ forming parenteral drug delivery systems: an overview", European Journal of Pharmaceutics and Biopharmaceutics, 58, 445-55, 2004.

19. Agnihotri S.A., Mallikarjuna N.N., Aminabhavi T.M., "Recent advances on chitosan-based micro- and nanoparticles in drug delivery", Journal of Controlled Release, 100, 5-28, 2004.

20. Sood A. and Panchagnula R., "Peroral Route: An Opportunity for Protein and Peptide Drug Delivery", Chemical Reviews, 101, 3275-303, 2000.

21. Niculescu-Duvaz I., Springer C.J., "Andibody-directed enzyme prodrug therapy (ADEPT): a review", Advanced Drug Delivery Reviews, 26, 151-72, 1997.

22. Manabe T., Okino H., Maeyama R., Mizumoto K., Nagai E., Tanaka M., Matsuda T., "Novel strategic therapeutic approaches for prevention of local recurrence of pancreatic cancer after resection: trans-tissue, sustained local drug-delivery systems", Journal of Controlled Release, 100, 317-30, 2004.

23. Ziaie B., Baldi A., Lei M., Gu Y., Siegel R.A., "Hard and Soft Micromachining for BioMEMS: Review

of Techniques and Examples of Applications in Microfluidics and Drug Delivery", Advanced Drug Delivery Reviews, 56, 145-72, 2004.

24. Byrne M. E., Park K., Peppas N., "Molecular imprinting within hydrogels", Advanced Drug Delivery Reviews, 54, 149-61, 2002.

25. Vandermeulen G. W. M., Klok H-A., "Peptide/Protein Hybrid Material: Enhanced Control of Sructure nad Improved Performance through Conjugation of Biological and Synthetic Polymers", Macromolecular Bioscience, 4, 383-98, 2003.

26. Rosler A., Vandermeulen G. W. M., Klok H.-A., "Advanced drug delivery devices via self-assemply of amphiphilic block copolymers", Advanced Drug Delivery Reviews, 53, 95-108, 2001.
27. Alvarez-Lorenzo C., Concheiro A., "Molecular imprinted polymers for drug delivery", Journal of Chromatography B, 804, 231-45, 2004.

28. Vasir J. K., Tambwekar K., Garg S., "Bioadhesive microspheres as a controlled drug delivery system", International Journal of Pharmaceutics, 255, 13-32, 2003.

29. Winterhalter M., Hilty C., Bezrukov S. M., Nardin C., Meier W., Fournier D., "Controlling membrane permeability with bacterial porins: applications to encapsulated enzymes", Talanta, 55, 965-71, 2001.