Sustained Protein Delivery from Coated Surgical Sutures

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Statement of Purpose: Therapeutic proteins including cytokines, enzymes and growth factors play a pivotal role in tissue regeneration by actively directing tissue growth toward complete functional restoration. A great deal of strategies have been proposed to deliver therapeutic proteins at healing sites, and protein release can be achieved in a controllable manner. However, existing approaches are often incompatible with standard surgical procedures, limiting their translation to clinical practice. Inspired by the widespread use of sutures in surgical procedures coupled with their proximity to healing tissue, we propose an approach for controlled protein delivery from sutures. Our strategy includes the formation of a resorbable hydroxyapatite (HAP) coating on sutures to mediate protein binding and release, since HAP materials have unique advantages as carriers for controlled protein delivery. We hypothesized that HAP-coated surgical sutures could serve as a platform to deliver therapeutic proteins to healing tissue in a controlled manner.

Methods: Orthocord (USP No. 2; DePuy Mitek, Raynham, MA) sutures were hydrolyzed and subsequently incubated in modified simulated body fluid (mSBF) to create HAP coatings on the suture surface. The resulting HAP coatings were analyzed using scanning electron microscopy (SEM), energy dispersive X-ray spectroscopy (EDS), Fourier transform infrared (FT-IR) spectroscopy, and X-ray diffractometry (XRD). Protein binding and release experiments were done with bovine albumin serum and lysozyme as models for acid and basic proteins, and with basic fibroblast growth factor (bFGF) as a therapeutic growth factor. The amount of protein was quantified by a microBCA protein assay (Pierce, Rockford, IL) and normalized to suture length. We examined the coating stability by comparing HAP coating coverage and remaining protein (^{125}I-labeled bFGF) or rhodamine-labeled lysozyme) on suture before and after passing the HAP-coated and protein-bound sutures through cadaver sheep infraspinatus tissue.

Results: The mSBF incubation of pre-hydrolyzed Orthocord resulted in the formation of nano-porous HAP coatings, which continuously covered the entire surface (Figure 1a). The ratio of calcium to phosphorous (inset of Figure 1a), characteristic peaks of FT-IR (Figure 1b) and XRD spectrum (Figure 1c) confirms that the coating created on Orthocord was mainly composed of carbonate-substituted HAP. The amount of protein bound to HAP-coated Orthocord increased proportionally with the protein concentration in the binding medium (Figure 2a). Protein binding capability was notably enhanced by the presence of HAP coating. Lysozyme was released in a sustained manner over 30 days at pH 7.4, and release was completed in 20 days at pH 4.0 (Figure 2b). In both cases, lower-level sustained release was commonly found after initial burst release. This sustained release can be attributed to reversible adsorption-desorption of protein within the HAP coating, which likely occurs repeatedly until the protein molecules diffuse out of nano-porous HAP coating. Over 75 % of bFGF initially loaded was retained on the HAP-coated suture after five passages through the sheep infraspinatus tendon (Figure 3a), and bFGF release in vivo led to enhanced tissue formation in a sheep rotator cuff model (data not shown). It is also visually evident that a substantial amount of HAP coatings and rhodamine-lysozyme remained on HAP-coated Orthocord after multiple passages through infraspinatus tissue (Figure 3b-c). We confirmed that the HAP coating did not deteriorate suture handling properties, such as flexibility, knottability and knot retention (Figure 3d).

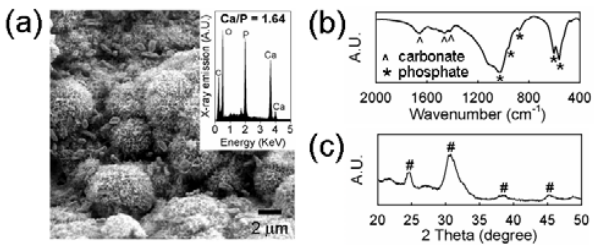

Figure 1. (a) SEM micrograph and EDS spectrum (inset), (b) FT-IR spectrum and (c) XRD spectrum of HAP coating created on Orthocord suture.

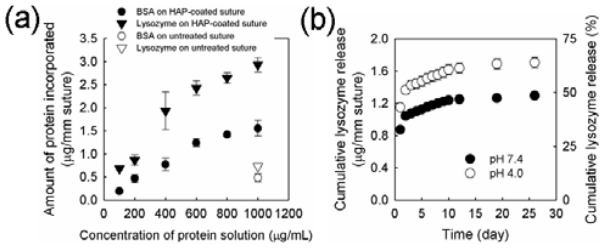

Figure 2. (a) Binding profile of lysozyme and BSA on HAP-coated Orthocord suture. (b) Cumulative lysozyme release from HAP-coated Orthocord suture.

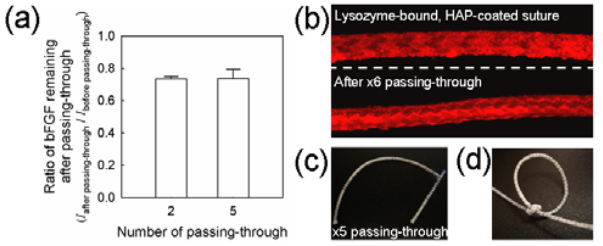

Figure 3. (a-c) HAP coating stability was examined by passing through cadaver sheep infraspinatus tissue; (a) ratio of bFGF remaining on HAP-coated and bFGF-loaded Orthocord; (b) fluorescence micrographs of HAP-coated Orthocord loaded with rhodamine-labeled lysozyme; (c) photographs of HAP-coated suture. (d) Photograph of knotted HAP-coated Orthocord suture.

Conclusions: Commercially available surgical sutures coated with HAP can be used as a carrier for controlled protein delivery without the sacrifice of their inherent properties. Considering the ubiquity of sutures and their locations adjacent to healing tissue, the approach described here may find the utility as an efficient, site-specific way to guide new tissue formation.