Preparation and Characterization of Hyaluronic Acid Derivatives for DDS and Tissue Engineering Applications

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Hyaluronic acid (HA) is biodegradable, biocompatible, non-toxic, non-immunogenic and linear polysaccharide.[1] HA has distinctive biological functions to control tissue hydration, and to play pivotal roles in wound healing and in promoting cell motility. Because of various functions and physicochemical properties, HA and modified HA have been widely used for arthritis treatment, ophthalmic surgery, drug delivery, and tissue engineering. In this work, preparation and characterization of HA and its derivatives for drug delivery and tissue engineering applications will be presented.

A novel sustained release formulation of human growth hormone (SR-hGH) for once-a-week injection has been developed incorporating hGH into sodium hyaluronate microparticles.[2,3] The spray dried solid microparticle of sodium hyaluronate with a high molecular weight worked as an excellent protein drug reservoir. A single administration of SR-hGH to beagle dogs resulted in sustained release of hGH up to 72 hrs and induced continuous elevation of serum IGF-I for a week, which supported the possibility of SR-hGH as a once-a-week injection formulation of hGH. SR-hGH using sodium hyaluronate is unique in safety issues and easy to be scaled-up due to the simple production process. For longer sustained release of protein and peptide drugs, various HA derivatives were synthesized and used for the preparation of selectively crosslinked HA hydrogels.[4] Erythropoietin (EPO) was *in situ* loaded during HA hydrogel with crosslinking agents. According to *in vivo* release test of EPO from HA hydrogels in rats, elevated EPO concentration above base line level could be maintained from 7 days up to 18 days depending on the preparation methods of HA hydrogels. No adverse effect was observed in both cases during and after the *in vivo* tests.

In order for tissue engineering applications, HA hydrogels were prepared through var-

ious crosslinking reactions. At first, two different types of HA hydrogels were synthesized with divinyl sulfone and poly(ethylene glycol)-divinyl sulfone, and assessed for the delivery of vitamin E succinate (VES), an anti-inflammatory drug.[5] The released VES reduced the expression and secretion of tumor necrosis factor-α (TNF-α) from activated macrophages significantly. Monocyte adherence on the different HA hydrogel surface was poor, as expected for a highly hydrated, "non-fouling" surface. This anti-inflammatory effect of the released VES suggests that HA hydrogels containing anti-inflammatory drugs may be promising for use as coatings of biomedical implants or tissue engineering scaffold components. Secondly, surface modification of glutaraldehyde fixed bovine pericardium (GFBP) was carried out using chemically modified HA with adipic dihydrazide (ADH).[6,7] HA-ADH was grafted to the free aldehyde groups on the GFBP, which was finally coated with HA-ADH hydrogels crosslinked with PEG-succinimidyl-derivatives of butanoic acid. Following a two-week subcutaneous implantation in osteopontin-null mice, the calcification of HA-modified bovine pericardium was drastically reduced. In case of the positive controls, however, clinically significant levels of calcification were observed. The anti-calcification effect of HA surface modification was also confirmed by microscopic analysis of explanted tissue stained with Alizarin Red S for calcium. Finally, a biocompatible polyelectrolyte complex multilayer (PECML) film consisting of poly-L-lysine (PLL) as a polycation and HA as a polyanion was developed to test its use for surface modification to prevent cell attachment and protein drug delivery.[8] The surface modification with PECML of PLL and HA resulted in drastically reduced peripheral blood mononuclear cell attachment. Concerned with its use for protein drug delivery, we confirmed that bovine serum albumin as a model protein could be incorporated into the PECML and its release might be triggered by the degradation of HA with hyaluronidase.

References

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