Acta Biomaterialia 8 (2012) 2529–2537

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Synthesis and characterization of poly(antioxidant β-amino esters) for controlled release of polyphenolic antioxidants

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ARTICLE INFO

Article history:
Received 28 November 2011
Received in revised form 9 February 2012
Accepted 9 March 2012
Available online 16 March 2012

Keywords:
Antioxidant polymers
Polyphenols
Oxidative stress
Curcumin
Biocompatibility

ABSTRACT

Attenuation of cellular oxidative stress, which plays a central role in biomaterial-induced inflammation, provides an exciting opportunity to control the host tissue response to biomaterials. In the case of biodegradable polymers, biomaterial-induced inflammation is often a result of local accumulation of polymer degradation products, hence there is a need for new biomaterials that can inhibit this response. Antioxidant polymers, which have antioxidants incorporated into the polymer backbone, are a class of biomaterials that, upon degradation, release active antioxidants, which can scavenge free radicals and attenuate oxidative stress, resulting in improved material biocompatibility. In this work, we have synthesized poly(antioxidant β-amino ester) (PAβAE) biodegradable hydrogels of two polyphenolic antioxidants, quercetin and curcumin. The degradation characteristics of PAβAE hydrogels and the antioxidant activity of PAβAE degradation products were studied. Treatment of endothelial cells with PAβAE degradation products protected cells from hydrogen-peroxide-induced oxidative stress.

1. Introduction

The biomaterial-induced inflammatory response is inextricably linked to cellular oxidative stress, where inflammatory cells like macrophages release a plethora of inflammatory cytokines and generate reactive oxygen and nitrogen species (ROS and RNS) [1–3]. Indeed, the detection of ROS is currently being used to characterize the inflammatory host tissue response to the biomaterial, in both in vitro and in vivo models [4,5]. In the case of biodegradable polymers, this inflammatory response is often a result of the local accumulation of polymer degradation products [6–8]. Strategies that can suppress this localized toxicity can theoretically extend the biocompatibility window for a variety of degradable materials. The conjugation of antioxidants to polymers is one such attempt that has been demonstrated to suppress biomaterial-induced inflammation and oxidative stress [2,9–12]. Some of the examples of antioxidant polymers include the conjugation of small molecule antioxidants like superoxide dismutase mimetics, vitamin E, gallic acid, catechin, vitamin C and glutathione to ultrahigh molecular weight poly(ethylene), poly(acrylic acid), gelatin, poly(methyl methacrylate) and poly(ethylene glycol), respectively. Conjugation of antioxidants to a polymer provides improved localization of effect and an avenue of long-term controlled release.

Recently, our laboratory has developed a polyester polymer composed entirely of the antioxidant (i.e. trolox, a water-soluble analogue of tocopherol) with 100% antioxidant content [13,14]. While this material has been shown to effectively inhibit oxidative stress induced by metal nanoparticles (e.g. nanocobalt), poly(trolox ester) degradation is slow, and there is very little or no control over its degradation rate. As the field of antioxidant polymers emerges, important questions, like the choice of antioxidant and the rate at which antioxidants should be released from the polymer, still need to be addressed. The answers to these questions will likely depend on the settings where antioxidant polymers are intended to be applied and will determine the success of antioxidant therapy. In order to address these questions, there is a strong need for a flexible polymer chemistry platform that can allow the study of the biological response to a biomaterial based upon the type of antioxidant, the release rate, and method of exposure (e.g. coating, nanoparticle, implant).

In this work, a modified step-growth polymerization poly(antioxidant β-amino ester) (PβAE) chemistry [15] is presented as a platform to synthesize antioxidant polymers with tunable properties. Using a Michael addition reaction between diacrylates and primary diamines, this method allows taking advantage of the vast libraries of acrylate and amine monomers that have been studied to tune PBAE properties [16,17]. Another important advantage of this PBAE chemistry is that it can be extended to all polyphenolic antioxidants. Naturally derived antioxidant polyphenols quercetin and curcumin (Fig. 1) were selected as the test compounds for

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http://dx.doi.org/10.1016/j.actbio.2012.03.022