Acta Biomaterialia 8 (2012) 4253–4259

Contents lists available at SciVerse ScienceDirect

Acta Biomaterialia

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

Pro-angiogenic CD14^{++} CD16^{+} CD163^{+} monocytes accelerate the in vitro endothelialization of soft hydrophobic poly(*n*-butyl acrylate) networks ☆

Anke Mayer, Toralf Roch, Karl Kratz, Andreas Lendlein *, Friedrich Jung

Center for Biomaterial Development and Berlin-Brandenburg Centre for Regenerative Therapies, Institute of Polymer Research, Helmholtz-Zentrum Geesthacht, Teltow, Germany

ARTICLE INFO

Article history:
Available online 16 August 2012

Keywords:
Multifunctional biomaterial
Endothelialization
Monocytes
Co-culture
Cellular cytokine release system

ABSTRACT

As the majority of the polymers used as cardiovascular grafts so far do not match the elasticity of human arteries (100–1000 kPa) and the required endothelialization, a multifunctional material approach is needed to allow the adjustment of the mechanical properties while at the same time exhibiting a haemocompatible surface. Recently soft poly(*n*-butyl acrylate) networks (cP*n*BA) with adjustable mechanical properties were introduced as candidate materials with a surface that can be endothelialized. In this study, angiogenically stimulated intermediate CD163^{+} monocytes/macrophages (aMO2) were utilized as a cellular cytokine release system to realize the functional endothelialization of the hydrophobic cP*n*BA surface. We investigated the influence of co-cultured aMO2 on the morphology, density and cytokine secretion of human umbilical venous endothelial cells (HUVEC) seeded on cP*n*BA with an elastic modulus of around 250 kPa (cP*n*BA0250). A functional confluent HUVEC monolayer could be developed in the co-culture within 3 days. In contrast, the HUVEC in the monoculture exhibited stress fibres, broadened marginal filament bands and significantly more and larger cell-free areas in the monolayer, indicating incomplete cell–substrate binding. Remarkably, a functional confluent monolayer formation could only be achieved in co-cultures; it did not develop with the sole supplementation of recombinant VEGF-A_{165} to the HUVEC monocultures (unpublished data). The study demonstrated the multifunctional potential of cP*n*BA in combination with aMO2 as a cellular cytokine release system, adapting their secretion to the demand of HUVEC. In this way, a functional confluent monolayer could be generated within 3 days.

© 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Arteriosclerosis is the leading cause of death worldwide. Blood vessel bypassing remains the standard treatment, especially for end-stage vascular disease. Unfortunately, 40% of patients do not have suitable autologous replacement material [1]. Therefore there is an increasing need for synthetic vascular grafts and their tissue engineering [2]. At present, the grafts of choice are made of either polyethylene (PET) or expanded polytetrafluoroethylene (ePTFE), both of which exhibit a satisfying long-term patency rate for large-calibre grafts (≥8 mm) but fail as small-calibre grafts (<6 mm) due to their thrombogenicity and intimal hyperplasia [3]. Also, the mechanical properties of these polymers do not match with the elastic modulus of healthy human arteries, which is considered to be involved in the occlusion process of small-diameter vascular grafts [4]. Therefore, soft polymer networks with adjustable elastic properties, such as covalently crosslinked poly(*n*-butyl acrylate) networks (cP*n*BA), have recently been introduced as candidate materials for cardiovascular grafts [5]. The elastic modulus of cP*n*BA can be tailored to the elasticity of human arteries, which varies in the range between 100 kPa [6] and 1,000 kPa [7], by variation of the crosslink density.

The most effective approach to render polymers haemocompatible is endothelialization of the surface. In a previous study we showed that endothelial cells are able to adhere, migrate and proliferate on cP*n*BA and that larger amounts of the vascular endothelial growth factor VEGF-A_{165} was adsorbed on the softer polymer (cP*n*BA with a Young's modulus of 250 kPa; cP*n*BA0250) than on their stiffer counterparts with a Young's modulus of 1100 kPa [8].

The formation of a functional confluent endothelium is described as being dependent on the cytokine milieu of the surrounding environment, and especially on pro-angiogenic growth factors like VEGF-A_{165} [9]. The covalent binding of growth factors on the material [10,11], the short half-life of growth factors in blood [12] or the dose-dependency of cellular responses [13] might hinder endothelial cell proliferation.

As a new strategy to achieve haemocompatibility of cardiovascular implants, a specific subset of monocytes (called MO2) [14] could be useful in accelerating the establishment of a functional

☆ Part of the Special Issue "Advanced Functional Polymers in Medicine (AFPM)", guest editors: Professors Luigi Ambrosio, Dirk W. Grijpma and Andreas Lendlein.

* Corresponding author. Tel.: +49 3328 352 450; fax: +49 3328 352 452.
E-mail address: andreas.lendlein@hzg.de (A. Lendlein).

1742-7061/$ - see front matter © 2012 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.actbio.2012.08.011