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Synergistic effect of defined artificial extracellular matrices and pulsed electric fields on osteogenic differentiation of human MSCs

Ricarda Hess [a,*], Anna Jaeschke [a,1], Holger Neubert [b,2], Vera Hintze [a,1], Stephanie Moeller [c,3], Matthias Schnabelrauch [c,4], Hans-Peter Wiesmann [a,5], David A. Hart [d,6], Dieter Scharnweber [a,7]

[a] Max Bergmann Center of Biomaterials, Technische Universität Dresden, Budapester Straße 27, 01069 Dresden, Germany
[b] Institute of Electromechanical and Electronic Design, Technische Universität Dresden, Helmholtzstraße 10, 01069 Dresden, Germany
[c] Biomaterials Department, INNOVENT e.V., Prüssingstrasse 27 B, 07745 Jena, Germany
[d] McCaig Institute of Bone and Joint Health, University of Calgary, 3280 Hospital Drive NW, Calgary, AB T2N 1N4, Canada

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ABSTRACT

In vivo, bone formation is a complex, tightly regulated process, influenced by multiple biochemical and physical factors. To develop a vital bone tissue engineering construct, all of these individual components have to be considered and integrated to gain an *in vivo*-like stimulation of target cells. The purpose of the present studies was to investigate the synergistic role of defined biochemical and physical microenvironments with respect to osteogenic differentiation of human mesenchymal stem cells (MSCs). Biochemical microenvironments have been designed using artificial extracellular matrices (aECMs), containing collagen I (coll) and glycosaminoglycans (GAGs) like chondroitin sulfate (CS), or a high-sulfated hyaluronan derivative (sHya), formulated as coatings on three-dimensional poly(caprolactone-*co*-lactide) (PCL) scaffolds. As part of the physical microenvironment, cells were exposed to pulsed electric fields via transformer-like coupling (TC). Results showed that aECM containing sHya enhanced osteogenic differentiation represented by increases in ALP activity and gene-expression (RT-qPCR) of several bone-related proteins (RUNX-2, ALP, OPN). Electric field stimulation alone did not influence cell proliferation, but osteogenic differentiation was enhanced if osteogenic supplements were provided, showing synergistic effects by the combination of sHya and electric fields. These results will improve the understanding of bone regeneration processes and support the development of effective tissue engineered bone constructs.

1. Introduction

Bone is a dynamic, highly vascularized tissue with the ability to repair itself without scarring [1]. However, bone defects resulting from accidents, infections or tumor ablations can become so large that the body's own regenerative capacity is not sufficient to close such gaps [2]. The treatment of so-called critical size defects is a great challenge for reconstructive surgery [3,4]. Up to now, autologous bone grafts from the iliac crest represent the 'gold standard' [4]. However, the amount of suitable bone is limited and its collection is painful associated with the risk of infection [5]. In addition, other clinically accepted reconstructive strategies (i.e. autografts, allografts, xenografts, and bone graft substitutes) do not always yield satisfying results because of numerous limitations [6]. In an attempt to overcome the shortcomings of tissue replacements, the use of tissue engineered bone substitutes provides a therapeutically option using the combination of living cells and biocompatible scaffolds to generate a biologic substitute capable of sustaining itself and integrating with functional host native tissue [7]. *In vivo*, bone formation is a complex, tightly regulated process, controlled by multiple interconnecting factors such as (i) cell–cell communication; (ii) cell–matrix interactions; (iii) soluble

* Corresponding author. Tel.: +49 351 463 39376; fax: +49 351 463 39401.
E-mail addresses: ricarda.hess@tu-dresden.de (R. Hess), anna.jaeschke1@mailbox.tu-dresden.de (A. Jaeschke), holger.neubert@tu-dresden.de (H. Neubert), vera.hintze@tu-dresden.de (V. Hintze), sm@innovent-jena.de (S. Moeller), ms@innovent-jena.de (M. Schnabelrauch), hans-peter.wiesmann@tu-dresden.de (H.-P. Wiesmann), hartd@ucalgary.ca (D.A. Hart), dieter.scharnweber@tu-dresden.de (D. Scharnweber).
[1] Tel.: +49 351 463 39376; fax: +49 351 463 39401.
[2] Tel.: +49 351 463 35250; fax: +49 351 463 37183.
[3] Tel.: +49 3641 282555; fax: +49 3641 282530.
[4] Tel.: +49 3641 282512; fax: +49 3641 282530.
[5] Tel.: +49 351 463 39400; fax: +49 351 463 39401.
[6] Tel.: +1 403 220 4571; fax: +1 403 270 2772.
[7] Tel.: +49 351 463 39379; fax: +49 351 463 39401.

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