Self-organizing systems in Regenerative Medicine

Charles James Kirkpatrick [1,2,3]

[1] Emeritus Professor of Pathology, Johannes Gutenberg University, Mainz,
[2] Department of Biomaterials, Sahlgrenska Academy, University of Gothenburg, Sweden
[3] Clinic for Maxillofacial Surgery, Johann Wolfgang Goethe University, Frankfurt

Healing processes are a highly regulated series of biological activities in the so-called "regenerative niche" to restore structural and functional integrity, and involve the coordinated and sequential release of numerous biological signals from various cell types. Understanding these processes is a pre-requisite for regenerative medicine. However, studying tissue reactions at the interface with biomaterials is complex and requires relevant cellular models. Our model systems, which represent co-culture models with self-organizing ability, have concentrated on an essential component of healing, namely vascularization. Thus, in studying bone regeneration, human osteoblasts or mesenchymal stromal cells differentiated along the osteogenic lineage demonstrate characteristic molecular interactions in co-culture with human microvascular or progenitor endothelial cells, and yield microvascular structures as a result of mutual stimulation [1,2]. The latter can also be formed on a 3D biomaterial scaffold *in vitro*, the resulting microvessels being rapidly integrated on implantation *in vivo* [3]. More recent research involves the role of the initial inflammatory reaction, indicating that pro-inflammatory macrophages, can accelerate this vascularization process [4]. Preliminary *in vivo* studies confirm that, for example, macrophages pre-cultivated on ceramics can stimulate the vascularization response following implantation.

Further co-culture models have been established for the respiratory tract, e.g. the air-blood barrier [5,6], which is of interest for nanomedicine applications in which nanoparticles could be transported into the body by an inhalational route [7-9]. The most complex of these air-blood barrier models involves the incorporation of macrophages, as these cells are also present in the alveoli [10]. In addition, co-cultures of respiratory basal epithelial progenitor cells with lung fibroblasts have been established as a model of upper respiratory tract regeneration and demonstrate formation of an intact, functional respiratory mucosa [11-12]. These interactions could be used for cellular colonization of decellularized upper airways [13]. Other co-culture models have been developed to simulate the blood-brain and skin barriers.

Supported by the EU Institute of Excellence, EXPERTISSUES, and research grants from the DFG, BMBF & the German-Israeli Foundation (GIF).

1. Kirkpatrick CJ, Fuchs S, Unger RE. Adv Drug Deliv Rev 2011; 63: 291-299
2. Kirkpatrick CJ. Tissue Engineering Part A 2014; 20: 1355-1357
3. Ghanaati S et al. J Tissue Eng Reg Med 2011; 5/6: e136-143
4. Dohle E et al. E Cells & Mater J 2014; 27:149-164
5. Hermanns MI et al. Lab Invest 2004; 84, 736-752
6. Hermanns MI et al. J R Soc Interface 2010; 7, S41-S54
7. Kasper J et al. Part Fibre Toxicol 2011; 8: 6
8. Kasper J et al. Eur J Pharm Biopharm 2013; 84: 275-287
9. Kasper J et al. Beilstein J Nanotechnol 2015; 6: 517-528
10. Kasper J et al. JTERM 2015 ; doi: 10.1002/term.2032
11. Pohl C et al. Eur J Pharm Biopharm 2009; 72: 339-349
12. Pohl C et al. J Biotechnol 2010; 148: 31-37
13. Melo E et al. Tissue Engineering Part C 2015; 21: 909-921