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REPORT

Interface Biology of Implants

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Abstract To successfully apply implant materials for regenerative processes in the body, understanding the mechanisms at the interface between cells or tissues and the artificial material is of critical importance. This topic is becoming increasing relevant for clinical applications. For the fourth time, around 200 scientists met in Rostock, Germany for the international symposium "Interface Biology of Implants". The aim of the symposium is to promote interdisciplinary dialogue between scientists from different disciplines. The symposium also emphasizes the need of this applied scientific field for permanent input from basic sciences.

When we started with the first symposium in 2003, the idea was to discuss basic questions regarding the generation of implant materials that function not only as mechanical support for cells and tissue, but provide a matrix to control molecular mechanisms responsible for the regeneration of tissues. Since then, significant advances have been made in our understanding both of the cellular mechanisms and the generation of bioactive material surfaces, which makes the application of tissue engineering approaches using implant materials more attractive. On the other hand, the progress in research again provoked new questions on a higher level of discussion. The fourth "Interface Biology of Implants" symposium in Rostock (Germany) in May 2012 again provided an excellent platform to discuss this topic within a multi-disciplinary community of around 200 scientists (Fig. 1). Traditionally, the first evening of the symposium starts with a keynote lecture, which this time was presented by Paolo Bianco (Rome, Italy). Bianco is an expert in the field of mesenchymal stem cells related to bone regeneration. He pointed to some aspects of this field which have changed since the beginning of the explosion in stem cell research 10 years ago. Today we know that skeletal stem cells reside in bone marrow sinusoids and novel markers have been identified for their isolation. On the other hand, non-stringent in vitro assays are routinely employed, which results in the failure of a common experimental standard. Applications are proposed in the clinical area that diverge from the original paradigm of regenerative medicine and range from proper to odd. The field of stem cells in medicine is exciting and is also driven by the interplay of business and technology development.

The 2-day symposium was composed of four sessions covering the interdisciplinary research in the field. The first session was focused on different aspects of the generation of materials that control cells and tissue. M. Textor (Zurich) demonstrated techniques to fabricate ECM functionalized cell-culture platforms on the basis of PDMS or PEG hydrogels including 3D structures, which enable a tunable stiffness, ligand density, or cell adhesion area. The approaches are aimed to mimic the vivo microenvironment, which is also important for the in vitro screening of extrinsic parameters on the effects of cancer drugs [1]. The group of P. Thomsen (Gothenburg) is interested in the analyses of biological parameters directly at the interface between implant materials and the tissue in vivo (Fig. 2). Site-specific determination of gene expression by quantitative RT-PCR was realized using a section instrument with a femtosecond laser to retrieve bone micro-sections at different distances from the implant [2]. The session revealed that implants can be generated to stimulate specific biological responses. J. Groll (Würzburg) fabricated

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Fig. 1 An interesting audience during the sessions

Fig. 2 Peter Thomsen (Gothenburg) is presenting his talk

polymers of PLGA that affected macrophages differently. Flat substrates stimulated the release of pro-inflammatory cytokines by macrophages, whereas 3D nanofibers provoked the induction of pro-angiogenic factors such as VEGF, which supported tissue healing. Also, in a short talk J. Kajahn (Leipzig) presented evidence that an artificial extracellular matrix which contained high sulphated hyaluronan was able to control the release of cytokines by macrophages. Because the humoral response of macrophages has become a key factor in controlling progenitor cells in regenerative processes [3], the specific stimulation of immune cells to promote tissue regeneration by characteristics of implant materials will become a new challenge in implant technology. A number of presentations during the symposium focused on the fabrication and evaluation of antibacterial material surfaces, stressing the need for implants that prevent infections. H. J. Griesser (Mawson Lakes) reported on his experiences with different approaches to prevent bacterial adhesion to biomaterials. He

Fig. 3 The exhibition provided a platform for contacts between scientists and the industry

favours plasma polymers with chemically reactive groups to immobilize antibiotics or Ag^{+} ions. These materials reduced adhesion of bacteria up to 99 % [4].

The interdisciplinary field of the interface between material and biological systems requires permanent stimulation from basic sciences, notably from cell biology (Fig. 3). Mechanisms of cell adhesion which control signal transduction to induce a biological response in cells play a key role. Recent data concerning the mechanisms of the interaction of cells with the extracellular matrix were presented in session 2 of the symposium. P. Friedl (Nijmegen) presented new insights into the mechanisms of cell migration in vivo [5]. Applying intravital multiphoton microscopy, he was able to show fascinating images of the dynamic behaviour of cells in vivo. Friedl demonstrated how cell migration is a plastic and adaptive process, governed by the structural and signaling determinants of transmigrated tissue structures. Cell migration may occur as single-cell or collective migration mode in response to changes of the physicochemical signatures of either cell or encountered tissue. A key determinant of how cells move is whether cell–cell junctions are retained or not. R. Zaidel-Bar (Singapore) reported on recent data concerning the regulation of cadherin-mediated cell–cell adhesions. He was able to present the Cadhesome network, with 140 proteins and over 400 interactions, and an analysis of its organization and regulatory circuitry. The research of A. Bershadsky (Rehovot) is focused on cellular mechanisms that regulate adhesion and migration in vitro (Fig. 4). He demonstrated how radial and tangential actomyosin stress fibers are involved in the regulation of cell polarization. Fibroblast polarization and formation of stress fiber arrays depend on the mechanosensitivity of focal adhesions. A. J. Garcia (Atlanta) demonstrated how the engineering of controlled densities of integrin ligands on a biomaterial enhances implant osseointegration and bone repair. In addition, he was able to synthesize hydrogels presenting defined densities of adhesive ligands, vasculogenic growth

Fig. 4 P. Bianco (Rome) and A. Bershadsky (Rehovot) in discussion

factors, and protease degradable sequences that direct vascular growth in vivo. Because the extracellular matrix not only provides ligands for cell adhesion, but functions as a presenter of growth factors, van der Smissen (Leipzig) presented data on how the introduction of sulphated glycosaminoglycans to bind TGFβ modulated the differentiation of dermal fibroblasts.

Session 3 of the symposium focussed on material induced biological responses. To study and manipulate stem cells in vitro, M. Lutolf (Lausanne) developed a biomaterial-based approach to display and deliver stem cell regulatory signals in a precise and near-physiological fashion which serves as an artificial microenvironment. He demonstrated that 2D and 3D microarrayed artificial niches based on hydrogels can be used as a platform to study the complexity of the biochemical characteristics of a stem cell niche. For the systematic deconstruction of a stem cell niche into a smaller number of distinct signalling interactions, Lutolf applies high-throughput screening systems [6]. This systematic screening of the physiological complexity is aimed at defining and reconstructing artificial niches for the transition of stem cell biology into the clinic. Because regenerative processes depend on the interaction of different cell types, C. J. Kirkpatrick (Mainz) asked how biomaterials control the biological response in co-culture systems in vitro. His special interest is in the stimulation of endothelial cell differentiation by osteoblasts to promote vascularisation. On a polymer a co-culture of endothelial progenitor cells with osteoblasts stimulated the formation of lumen-containing microvessel-like structures [7]. Determining how changes of the chemical composition of a scaffold and the introduction of a further cell type into the co-culture influence vessel formation is a current research topic. The group of M. Riehle (Glasgow) is interested in the development of a three-dimensional scaffold which allows the control of cells of the nervous system. The construct consists of rolled up nano/microstructured sheets, and individual aspects of the material, such as porosity, topography, stiffness, and geometry, can be tuned. Optimized scaffolds induced a myelination of neuronal long-term cultures. Materials can control the biology of cells, such as differentiation and proliferation, via regulating the cell shape. K. Anselme (Mulhouse) is interested in topographically-induced changes in the shape of the cell nucleus which might be of physiological relevance. She found that nuclei in living cells can be severely deformed and adopt the surface topography of the underlying material without consequences in differentiation or proliferation.

Since the finding of Discher's group that the stiffness of the substrate for cell adhesion determines the direction of stem cell differentiation [8], cell mechanics has also attracted the attention of researchers in the field of tissue engineering. In session 4 of the symposium, talks presented basic insights into mechanically induced mechanisms as well as material-related aspects of cell mechanics. The work of V. Vogel (Zurich) has significantly contributed to our understanding of how cells sense and transform mechanical signals into biochemical signals to regulate cell function. Her talk focused on the mechanical aspects of bacterial adhesion. The adhesin of *Escherichia coli* forms a catch bond with surface-exposed mannose which is regulated by mechanical forces. These structures are also used by macrophages to remove *E. coli* from their surface. Investigations with *Staphylococcus aureus* revealed that the bacterial adhesins can distinguish physically stretched from relaxed fibronectin fibers [9]. Two short talks presented evidence for the role of the focal adhesion protein vinculin in force transmission by the cells. V. Auernheimer (Erlangen) demonstrated that vinculin binding to actin, to the src-substrate p130cas and its phosphorylation on position Y1065, is required to transmit mechanical forces. Using vinculin-deficient fibroblasts, I. Thievessen (Erlangen) presented data which show that vinculin mediates the actin retrograde flow to focal adhesions in migrating cells. For tissue engineering approaches, it is important to predict how the interaction between cells, biomaterial and external stimuli, which include mechanical forces, induce healing of tissue. D. Lacroix (Sheffield) has developed a computational model in which he simulates cell seeding, proliferation, and differentiation to optimize cell seeding as a function of cell density, pore shape and pore size in a scaffold [10]. The model involves the calculation of local mechanical stimuli, and it is believed that such an approach will provide a rationale for the design of tissue engineering scaffolds.

In conclusion, the symposium is becoming a tradition, and scientists who attended it for the first time will become permanent attendees. The meeting is attractive, both for

registered participants and internationally renowned invited speakers. This is for several reasons: the topic is of increasing relevance for clinical applications; the conference is strongly focused on the interface of medical implants; and the conference brings together various disciplines and receives input from basic sciences. The rather small audience and having no sessions in parallel stimulate a fruitful communication between scientists.

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