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EDITORIAL

Endogenous musculoskeletal tissue regeneration

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Damaged musculoskeletal tissues collectively represent the most common cause of pain and functional disability worldwide (Mason 2007). Clinical efforts to restore structural integrity and function to non-healing musculoskeletal tissues are often complicated by challenging biomechanical conditions, advanced age, adjacent tissue trauma, infection risks, ischemia conditions, or the general disease status of the patient (Lysaght et al. 2008). With this special issue, we aim at reviewing recent scientific developments in the field of musculoskeletal regeneration and at identifying clinical challenges associated with augmenting or stimulating endogenous repair processes and restoring function to musculoskeletal tissues.

In parallel with discussions among the authors of this special issue, an International Workshop on Endogenous Musculoskeletal Tissue Regeneration was held on March 16, 2011 in Hilton Head, South Carolina, USA. Contributors to the special issue were invited to speak at the workshop and over 80 participants from North America, Europe and Asia were in attendance.

Several recurring concepts and unresolved questions emerged from the workshop presentations and discussion. There was a clear consensus that effective regenerative therapies must take into consideration the biological constraints specific to the individual patient and clinical problem. Advanced age, radiation therapy, composite tissue trauma, or accompanying diseases such as diabetes, for example, present special challenges in the functional regeneration of damaged tissues. For some of these clinical scenarios, the endogenous progenitor cell supply might be critically diminished. The creation of extracellular matrix niches either in vitro or in vivo appears as an emerging strategy to enhance the viability and function of exogenously delivered cells. As has become evident, the direct synthesis of extracellular matrix might be only one role that progenitor cells play in regeneration and other aspects such as paracrine effects on adjacent cells might also be relevant to enable endogenous regeneration cascades. The potential for delivered cells to be used as tissue-inductive drug-delivery vehicles needs further investigation, as does the potential effects of the local host cells and environment on delivered stromal cell function and survival.

Another important new strategy to promote endogenous regeneration is to increase the supply of circulating progenitor cells and their homing to sites of injury. Factors that stimulate the mobilization of stromal cells into the blood or provide signals to enhance site-specific recruitment could overcome the poor endogenous repair capacity in aged or otherwise impaired patients in order to heal challenging defects. A question that remains widely unanswered in regenerative medicine is whether healing deficits are a direct cause of a lack of responding progenitor cells or other factors. An alternative strategy to enhance regeneration

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might be to enable the blocking antagonists or counteracting cell compartments.

Considerable discussion ensued on the relevance of inflammation, fibrosis and scarring in blocking endogenous regeneration. The modulation of the invading macrophage phenotype from pro-inflammatory (M1) to pro-differentiation (M2) could be a powerful emerging paradigm that is relevant across tissue types in enhancing regenerative cascades.

In addition to the identification and delivery of key biologic signals, there is increasing recognition that the local mechanical environment is a critical factor regulating the pathway of tissue regeneration. The timing, mode and magnitude of local mechanical signals can have both negative and positive effects on the key processes of inflammation, vascular growth, cellular differentiation and tissue remodeling and thus requires substantial further attention.

The design of biomaterial scaffolds is also critical for optimizing endogenous healing responses. Novel scaffold fabrication methods are being developed to provide the right balance at a cellular and tissue level with regard to mechanical properties, degradation rate, biologic delivery kinetics and cellular/vascular invasion (Hutmacher and Dalton 2011).

Finally, a major concern was the appropriateness of most in vivo models that we employ to mimic the clinical situation and for the evaluation of repair strategies and technologies. To date, the regenerative medicine field has often employed, in young healthy animals, single tissue defect models that are just large enough not to heal without intervention. Unfortunately, such models do not typically simulate the biological constraints inherent to unmet clinical needs for regenerative therapies. They frequently lack an adequate immune status or age conditions mimicking clinical challenges. Moreover, although many animal models have been developed for the testing of tissue regeneration technologies, few studies have been designed to provide direct head-to-head comparisons of multiple regenerative strategies or to quantify efficacy relative to existing clinical standard treatments. The quantitative and competitive evaluation of regenerative therapies in compromised in vivo models represents a critical opportunity to facilitate the progression and translation of the most promising technologies into clinical use (Reichert et al. 2009).

This special issue compromises 27 articles that cover, in a comprehensive manner, the above-described topics. Several comprehensive reviews summarize key recent developments in the field. A review by Adam (2011) gives a focused perspective on endogenous musculoskeletal tissue engineering. The Mao laboratory (Nie et al. 2012) covers the field of musculoskeletal tissue engineering by endogenous progenitor cells, whereas Brehm et al. (2011) give an overview from a veterinary orthopedics perspective. The Badylak group (Turner and Badylak 2011) reviews the main points of the current muscle tissue engineering work in the field and Jakob et al. (2011) comprehensively summarize the emerging topic of in situ guided tissue regeneration in musculoskeletal diseases and aging.

Berner et al. (2011) address the important clinical application of long bone defects and non-unions, whereas the Duda group from Berlin complements the review of the field with a paper titled “Inflammatory phase of bone healing initiates the regenerative healing cascade” (Schmidt-Bleek et al. 2011) and the Knaus lab (Knaus et al. 2011) provides a view on molecular mechanisms underlying BMP action during musculoskeletal tissue formation.

Several original articles are based on novel bone tissue engineering concepts. Botchwey’s group (Huang et al. 2011) has studied the way that the local delivery of FTY720 accelerates cranial allograft incorporation and bone formation. Dupont et al. (2011) and Hutmacher et al. (2011) present two small-animal studies in which a critical-sized femur defect is treated with novel scaffold-based bone engineering concepts. The Schwarz laboratory (Takahata et al. 2011) presents a paper that demonstrates the manner in which parathyroid hormone treatment can enhance musculoskeletal tissue engineering.

Next to bone tissue engineering, cartilage tissue engineering plays a major role in this special issue. Ito’s group (Kock et al. 2011) gives an overview of the current status of tissue engineering of functional articular cartilage. Opinion papers by the Woodfield (Schon et al. 2011) and Doran (Doran et al. 2011) groups deal with most recent cartilage tissue engineering concepts and the high-through-put assembly of micropellets and application of decellularized cartilage particles, respectively.

Moving on to so-called bench-to-bedside concepts, a project for regenerating heart muscle is presented by Sekane et al. (2011), whereas a concept for adipose tissue engineering is presented in a small-animal study by Wiggenhauser et al. (2011).

Interesting in vitro studies are presented in the papers by two groups from Georgia Tech in Atlanta, namely the McDevitt group (Baraniak and McDevitt 2011) on osteogenic effects of mineral-coated microspheres incorporated within three-dimensional stem cell spheroids and by Seto et al. (2011) on the differentiation of mesenchymal stem cells in heparin-containing hydrogels via coculture with osteoblasts. The Klein laboratories (Schrobback et al. 2011) report an in vitro study on the way to manipulate osteoarthritic human articular chondrocytes in order to use them ultimately in a matrix-based system.

The Mauck group (Mauck et al. 2011) demonstrates the use of a novel scaffold design and fabrication technology platform in several soft tissue engineering applications. Last but not least, a group from Korea (Khang et al. 2011) have included a paper entitled “Neurogenesis of bone marrow-derived

mesenchymal stem cells onto β-mercaptoethanol-loaded PLGA film" and a group from India (Kundu et al. 2011) describes their innovative natural biomaterials work, which is directed towards skin tissue engineering in "Potential of 2D cross-linked sericin membranes with improved biostability for skin tissue engineering".

In conclusion, this special issue presents numerous rapid and exciting developments in the area of endogenous musculoskeletal tissue engineering. The scaffolds and matrices that are used in endogenous tissue engineering strategies are generally meant to act as provisional substitutes for an extracellular matrix, providing a temporary structural support combined with specific biochemical signals that encourage cells to create their own extracellular matrix environment. However, the extracellular matrix is much more than a static mechanical support for tissues. It supplies the physical microenvironment of a cell and is responsible for transmitting signals that initally interact with cell membrane receptors and that eventually reach the nucleus via intracellular signaling cascades. Cells are not only affected by molecular composition but also by the topography and mechanical properties of their surrounding extracellular matrix. Matrix-directed regulation of cell function, either for applications in tissue engineering or in regenerative medicine, thus requires a major improvement of our understanding the way that cells interact with their own matrices. Thus, the immediate focus of the research presented in this special issue is to elucidate the biology of the cell/extracellular matrix interface and the scaffold/ECM/cell interface. Cells exhibit a dynamic reciprocity with their extracellular environment: cells both organize their extracellular matrix environment and the extracellular matrix in turn provides signals that govern a host of cell functions that include proliferation, differentiation, migration and apoptosis. Thus, the work presented in this special issue demonstrates the importance of regulating the state of the extracellular matrix for the transmission of signals to host cells that control cell fate at the regeneration site.

We, the editors of this special issue, are sure that this collection of papers will be of interest to both young and senior scientists and to surgeons. Indeed, the workshop has already stimulated collaborations and interactions with our colleagues who participated.

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