Saving Faces - Tissue Repair and Regeneration

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Regenerative medicine (repair and regeneration of tissues and/or organs) is an emerging, but still poorly defined, field of biomedicine. The ongoing 'regenerative medicine revolution' is based on a series of new exciting breakthrough discoveries in the field of stem cell biology and developmental biology. The key issue in enhancing tissue and organ regeneration is how to mobilize circulating stem and progenitor cells and how to provide an appropriate environment ('niche') for their tissue and organo-specific recruitment, 'homing' and complete functional integration (Mironov et al, 2004).

Advances in cell, developmental and molecular biology, and the discovery of regeneration-competent cells in many non-regenerating mammalian tissues, have given impetus to systematic investigations that will enable us to regenerate these tissues by cell transplantation or the pharmaceutical induction of regeneration from the body's own tissues. A significant avenue of research is the identification of the soluble and insoluble signals and their transduction pathways that govern the proliferation and differentiation of regeneration-competent cells, and the signals that inhibit their activity after injury (Stocum, 2004).

Recent advances in stem cell biology may make possible new approaches for the treatment of a number of diseases including cardiovascular disease, neurodegenerative disease, musculoskeletal disease, diabetes and cancer. These approaches could involve cell replacement therapy and/or drug treatment to stimulate the body's own regenerative capabilities by promoting survival, migration/homing, proliferation, and differentiation of endogenous stem/progenitor cells. However, such approaches will require identification of renewable cell sources of engraftable functional cells, an improved ability to manipulate their proliferation and differentiation, as well as a better understanding of the signaling pathways that control their fate. Cell-based phenotypic and pathway-specific screens of synthetic small molecules and natural products have historically provided useful chemical ligands to modulate and/or study complex cellular processes, and recently provided a number of small molecules that can be used to selectively regulate stem cell fate and developmental signaling pathways. Such molecules are likely to provide new insights into stem cell biology, and may ultimately contribute to effective medicines for tissue repair and regeneration (Ding and Schultz, 2005).

Cell-based phenotypic and pathway-specific screens of natural products and synthetic compounds have recently provided a number of small molecules that can be used to selectively control stem cell proliferation and differentiation. Examples include the selective induction of neurogenesis and cardiomyogenesis in murine embryonic stem cells, osteogenesis in mesenchymal stem cells and dedifferentiation in skeletal muscle cells. Such molecules will likely provide new insights into stem cell biology, and may ultimately contribute to effective medicines for tissue repair and regeneration (Ding and Schultz, 2004).

Tissue engineering is a rapidly evolving discipline that seeks to repair, replace, or regenerate specific tissues or organs by translating fundamental knowledge in physics, chemistry, and biology into practical and effective materials, devices, systems, and clinical strategies. Stem cells and progenitors that are capable of forming new tissue with one or more connective tissue phenotypes are available from many adult tissues and are defined as connective tissue progenitors. Stem cell function is controlled by changes in stem cell activation and self-renewal or by changes in the proliferation, migration, differentiation, or survival of the progeny of stem cell activation, the downstream progenitor cells. Three-dimensional porous scaffolds promote new tissue formation by providing a surface and void volume that promotes the attachment, migration, proliferation, and desired differentiation of connective tissue progenitors throughout the region where new tissue is needed (Muschler et al, 2004).

The cellular component of the tissue engineering paradigm is arguably the most important piece of the complex task of regenerating or repairing damaged or diseased tissue. Critical to the development of clinical strategies is the need for reliable sources of multipotent cells that can be obtained with limited morbidity. The adult

stem cell population may be well suited for this task. The next several years will bring Phase I and II studies using adult stem cells as the cellular foundation for engineered tissue constructs. Future research should be directed toward better characterization of this cell population, including identifying unique markers and mapping out lineage development. For now, the ideal source of adult stem cells remains uncertain, but as questions are answered, adult stem cell biology will likely transition from bench top to clinical reality (Hedrick and Daniels, 2003).

This section on 'Tissue Repair and Regeneration' covers a variety of these topics ranging from the assessment of specific cytokines/factors and their role(s) as signaling factors (Nör, this issue) over the role of specific cells, progenitor and/or stem cells explored to see their role(s) in repair and regeneration (Smith, this issue; Grigoriadis, this issue) and their interactions in the process of wound healing (Paul Martin, University of Bristol, UK). Also the use of these multiple factors of cells, signals and scaffolds to explore the area of tissue engineering as a means of enhancing wound healing and assisting in regeneration and repair of soft tissues will be addressed (Feinberg, this issue). Finally, using the salivary gland as a model the nascent area of gene therapy and the development of new and novel vectors that might be the future of tissue regeneration and repair is outlined (Chiorini, this issue).

Anthony Smith focuses on 'Dentine Regeneration: Key Roles for Stem Cells and Molecular Signaling' and in particular discuss the regenerative potential of the dentine-pulp complex that is seen after injury. He will show the role of variations in stem / progenitor cells and the molecular signaling processes directing these regenerative responses. The ability to understand these regenerative processes, whether they be specifically dentinogenic or a less specific minieralized tissue response, will assist in the future development on novel clinical therapies.

Agamemnon Grigoriadis addresses 'Control of Bone Formation by AP-1 Transcription Factor and Rho GTPases: Implications for Bone Regeneration and Tissue Repair'. The repair and regeneration of bone tissue is extremely complex. Its development and function throughout life are dependent on multiple cell types which must communicate and function with extremely tight controls at the structural, hormonal, local and molecular concepts underlying tissue repair and tissue regeneration that touch on the areas of stem cell biology and biomaterials. He will review the basic features of bone cell biology and bone remodelling, and focus on two signalling pathways that control the growth and differentiation of osteoblast differentiation and bone formation, with particular implications for bone growth and repair.

Paul Martin is speaking on 'Wound Healing' (not published in this issue). His presentation will cover the fundamental understanding of wound-healing biology. It will show that it is based on the knowledge of the signals that trigger relatively sedentary cell lineages at the wound margin to proliferate, to become invasive, and then to lay down new matrix in the wound gap. Studies in the last decade have provided a list of the growth factors and matrix components that are available to provide these "start" signals, and one of the tasks now begun is to relate these factors specifically to the starting and stopping of each of the many cell activities by which the wound is healed.

John Chiorini takes a different approach to tissue repair and regeneration by addressing 'Future of Gene Transfer in Oral Biology'. In oral biology, vector–mediated gene transfer is a promising for the treatment of autoimmune disease- and irradiation-induced damage to the salivary glands, loss of bone as a result of trauma or osteoradionecrosis, or for the treatment of chronic pain. Dr. Chiorini will concentrate on major salivary glands as a target organ for gene transfer. Because of the salivary glands unique location, functions and activity as both an endocrine and exocrine organ, gene transfer to these glands possesses the potential to treat several genetic or acquired disease conditions. The salivary glands offer a number of advantages as a depot organ for therapeutic protein production initiated by the gene transfer and furthermore the efficiency and number of vectors available for this gene transfer, and the host's response to vector infusion, which is necessary prior to wide utilization of gene therapy will be discussed.

Stephen Feinberg focuses on 'Tissue Engineering of a Human Oral Mucosa for Tissue Repair and Regeneration'. Within the past decade a new field of 'tissue engineering' or 'regenerative medicine' has emerged that offers a new and exciting alternative for soft tissue reconstruction. The advantages and disadvantages of different approaches to development of an oral mucosa equivalent are discussed. Future research directions in this exciting area of repair and regeneration of oral mucosa are presented regarding stem cell isolation and gene therapy that will eventually lead to human clinical trials.

Jacques Nör addresses 'Activation of Latent TGF-β1 by Thrombospondin-1 is a Major Component of Wound Repair'. Thrombospondin 1 (TSP1) is a matrix glycoprotein that regulates cell adhesion, migration, and proliferation, and is a natural inhibitor of angiogenesis. Recent evidence suggests that TSP1 is a major physiologic activator of latent transforming growth factor-β1 (TGF-β1), and that TGF-β1 is important for wound healing. Dr. Nör will examine whether excisional wound healing in TSP1-deficient mice is compromised as a result of deficient TGF-β1 activation.

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