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INTRODUCTION

Form and function in regenerative medicine: introduction

The field of regenerative medicine aims to facilitate the repair or regrowth of damaged tissue or organs. Humans can naturally regenerate some tissues, including the liver, which if damaged due to disease or injury, can grow back to its original size and function, though not its original shape. Unfortunately, many other human tissues do not regenerate, and a goal in regenerative medicine is to find ways to promote tissue regeneration in the body, or to engineer replacement tissues using tissue engineering. The process has been recognised by scientists for the past 3 decades and was even described by the ancient Greeks, who depicted liver regeneration in the myth of Prometheus. Having stolen the secret of fire from the gods of Olympus, Zeus punished Prometheus by chaining him to Mount Caucasus with an eagle feasting on Prometheus' liver, which was renewed as fast as it was devoured (Taub, 2004). The clinical realisation of regenerative therapies is fast approaching with large-scale clinical trials showing positive outcomes. This will bring a paradigm shift in the way we currently treat degenerative diseases and will be an area of huge hope for patients.

A symposium was held in the Royal College of Surgeons in Ireland entitled 'Form and Function in Regenerative Medicine' and included speakers with expertise in stem cell biology, biomaterials and tissue engineering. During the course of the symposium, researchers discussed the importance of form and function in realising therapeutic success within the regenerative medicine field. This symposium issue captures important trends in regenerative medicine, particularly the need to consider final function of replacement tissues ahead of form when designing novel regenerative therapeutics.

The important trends discussed at the meeting include:

1. In-depth studies of the pathology of degenerative diseases are needed to optimise design criteria for successful therapeutic interventions. Walter et al. highlight the need for consensus on which histological stains offer the clearest visualisation of specific areas within the intervertebral disc (IVD) to better understand the degenerative changes in the IVD structure. The objective of this study using human samples was to compare multiple stains and evaluate their ability to highlight structural features to implement a scoring system for degeneration. This paper highlights how IVD degeneration is not a single disease but a composite of multiple processes such as ageing, injury, repair and disease that is unique to each individual. These results point toward the need to better understand the pathology underlying a disease state when developing optimal regenerative treatments; in some cases, these regenerative treatments may need to be on a patient-specific basis.
2. The source of stem cells used in regenerative medicine is critical and cells should understand, interact and integrate with their local environment once implanted. Steward and Kelly review the strides that have been made in elucidating how mesenchymal stem cells (MSCs), a leading regenerative medicine stem cell source, sense and respond to their mechanical environment in terms of both substrate mechanics and extrinsic mechanical cues. The authors address this area with a specific focus on orthopaedic applications including bone and cartilage. They also stress the importance of assessing multi-factors in unison, which can be complemented by computer-aided modeling approaches. The information provided, underscores the complex interactions MSCs have with their environment and a full understanding of this crosstalk will play an integral role in realising orthopaedic grafts and replacement tissues.
3. Material properties and composition of tissue-engineered replacement scaffolds can play an important part in driving function for specific disease applications. Ryan et al. demonstrate how tissue-engineered scaffolds that aim to provide an optimised environment to regenerate bone tissue, have to balance between mechanical properties and architecture known to be conducive to enable tissue regeneration. The authors improved the mechanical properties of a bone-specific extracellular matrix analogue by adding hydroxyapatite (HA) using various production methods into collagen scaffolds while maintaining the internal pore architecture, a known element in promoting enhanced bone formation. The authors found that the method of incorporation of varying sizes HA (micron to nano scale) had a profound effect on stem cell attachment and calcium production. The present findings will help guide future design considerations for composite scaffolds for orthopaedic regenerative medicine purposes.
4. Three-dimensional cell culture models allow interrogation of important aspects of tissue regeneration without the need for excessive *in vivo* assessment.

Knight and Przyborski discuss the importance of assessing cell interactions in tissue culture models that represent the three-dimensional (3D) environment of tissues in the human body. The authors emphasise that it is particularly important to recognise how the structure of a cell influences its function and how co-culture models can be used to represent more closely the structure of real tissue. This is important when interrogating cell phenotype and function in pathological or disease model settings, as two-dimensional (2D) cell culture plastic is not representative of the natural environment. This review points towards a need for consensus on the ideal requirements of 3D models. The authors conclude that such models will contribute to advancing basic research, increasing the predictive accuracy of compounds, and reducing animal usage in biomedical science.

5. The physiologic environment used for pre-implant culture is of key importance when generating tissue replacements for specific treatment applications. Two papers in this issue highlight the importance of the local conditions of the biochemical microenvironment, such as oxygen tension and glucose concentration, when studying regenerative processes and cell responses for tissue repair.

   Buckley and Naqvi highlight that bone marrow (BM) stem cells may be an ideal source of cells for intervertebral disc (IVD) regeneration; however, the harsh biochemical microenvironment of the IVD may significantly influence the biological and metabolic vitality of injected stem cells and impair their repair potential. This study investigated the viability and production of key matrix proteins by nucleus pulposus (NP) and BM stem cells cultured in the typical biochemical microenvironment of the IVD consisting of altered oxygen and glucose concentrations. The authors present results indicating that IVD-like concentrations of low glucose and low oxygen are critical and influential for the survival and biological behaviour of stem cells. Such findings may promote and accelerate the translational research of stem cells for the treatment of IVD degeneration, and demonstrate that an understanding of the final delivery conditions is a key aspect of successful outcomes.

   Lloyd-Griffith et al. discussed the need for new strategies to promote pre-vascularisation of tissue-engineered constructs for the treatment of ischaemic diseases, a large, unmet need. This study investigated the ability of amniotic fluid-derived stem cells (AFSCs) to differentiate down an endothelial lineage with the aim of producing an endothelial-like cell suitable for use in pre-vascularisation. As hypoxia and its associated pathways have been implicated in the induction of angiogenesis in a number of biological processes, it was hypothesised that culture in hypoxic conditions could enhance the endothelial differentiation of AFSCs. Overall, AFSCs subjected to hypoxic stimuli demonstrated a less mature endothelial profile and phenotype when compared with venous endothelial cells. However, this study is the first time that the positive effect of continuous hypoxic culture on endothelial differentiation in AFSCs has been demonstrated. This outcome highlights the need for further research into the ideal biochemical environment to produce a stem cell source with the key characteristics to promote vascularisation.

6. A holistic view of patient need should be at the centre of all future therapeutic interventions and lessons learned in leading areas of regenerative medicine can be applied to other less investigated areas. Schenke-Layland and Brucker finished the symposium issue by discussing the need to adapt current leading research for specific applications in women's health, particularly the need for tissue-engineered structures for genital reconstructive surgery including the vagina, uterus and cervix. The authors discuss current cell types of interest from both a pathological and regenerative standpoint and highlight in-depth studies on the local extracellular matrix of the endometrium and the application of this knowledge for new biomimetic tissue sources. Knowledge gained from the leading studies in relation to the importance of cell source, scaffold architecture, and final implant environment may potentiate success in women's health applications and offer hope to future patients where existing treatments are inadequate or non-existing.

Reference

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Fergal J. O'Brien[1,2,3] and Garry P. Duffy[1,2,3]
[1]Tissue Engineering Research Group, Department of Anatomy, Royal College of Surgeons in Ireland, Dublin, Ireland, [2]Trinity Centre for Bioengineering, Trinity College Dublin, Dublin, Ireland, [3]Advanced Materials and Bioengineering Research (AMBER) Centre, Royal College of Surgeons in Ireland and Trinity College Dublin, Dublin, Ireland