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Chew, Sing Yian

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Theme editor: Sing Yian CHEW, Ph.D.

Preface:

MicroRNA-based therapeutics have rapidly emerged in recent years as promising platforms for the treatment of genetic disorders and cancer. Perhaps less widely explored is the application of microRNAs to regenerative medicine and tissue engineering. However, microRNAs hold tremendous potential in these fields. This lack of advancement is probably triggered by the conventional mindset adopted in the field, which is to up-regulate factors in favor of regeneration as opposed to an atypical gene silencing approach. Compounded upon this may also be the fact that most studies on microRNAs have focused on the biological aspects of profiling and identifying microRNA involvement and signaling pathways. The translational use of this knowledge to engineering approaches is not directly straightforward in most cases. In this theme issue, we aim to highlight the potential of microRNA gene silencing in tissue engineering and regenerative medicine. The unique requirements of tissue regeneration prompt for special considerations in gene silencing. Most obvious may be the involvement of tissue scaffolds in regenerative medicine vs. typical systemic delivery of microRNAs for genetic disorders and cancer therapies.

MicroRNAs regulate biological processes. While the field has seen much advancement in the identification and profiling of microRNA expressions during tissue development, homeostasis and pathogenesis, the translational use of this knowledge to regenerative medicine remains limited. With this in mind, this theme

issue has been constructed to relate the roles of microRNAs in cellular responses that are critical to the regeneration process of major organs and tissues from a diseased or injured state. These include identifying potential candidates for directing stem cell differentiation and transdifferentiation (Wu, *et al.*), to regenerating specific organs like skin (Levinson, *et al.*), muscles (Sampaolesi, *et al.*), nerves (Chew, *et al.*), liver (Sauer, *et al.*) and blood vessels (Emanueli, *et al.*). In addition, most regenerative approaches require the reconstruction of tissue architecture, which are largely enabled by the implantation of scaffolding constructs. Hence, considerations of microRNA involvement in implant-revascularization (Emanueli, *et al.*) and host-implant integration (Wong, *et al.*) are also critical.

To begin with, Wu *et al.*, shares the relevance and importance of microRNAs in controlling the processes of self-renewal and differentiation in stem cells. The ability to control proliferation of stem cells is crucial in regenerative medicine in order to generate sufficient cell numbers for tissue reconstruction and transplantation therapy. Moving on to tissue regrowth, directed cell fate commitment is critical and microRNAs play significant roles in modulating these processes. In particular, microRNA involvement in cell fate commitment towards neurogenic, hematopoietic, osteo/chondro/adipogenic or cardiovascular lineages is discussed. Perhaps even more intriguing is the involvement of microRNA in cellular reprogramming to induced pluripotent stem cells and direct transdifferentiation to the desired lineages, bypassing the controversial pluripotent stage. In some cases, microRNAs enhanced reprogramming/transdifferentiation efficiency achievable by conventional transcription factor based methods; while in others, even transient

delivery of microRNAs alone appeared sufficient to achieve reprogramming *in vitro* and *in vivo.*

While obtaining the desired cell population is important, it is also vital to recognize that tissue organ formation also relies on the timely and accurate involvement of cell types that are native to the tissues/organs of interest. Most often than not, tissue/organ formation involves several cell types, the deposition of extracellular matrix and formation of appropriate structures. In these cases, the role of microRNAs is also significant. As revealed by articles in this theme issue, important construction steps and structures of various organs are first highlighted, to provide basic knowledge on the final structure of the organ of interest. Beginning with a detailed account of the skin regeneration process and the limitations of current wound healing approaches, Levinson *et al.*, sets a clear stage for skin tissue engineering. The multifaceted involvement of various cells types, ranging from basic skin-related cells (epithelial stem cells, keratinocytes, fibroblasts) to proper angiogenesis (endothelial cells), and aesthetic considerations (melanocytes for color, hair follicle cells for hair regrowth) are highlighted in detail. As revealed in the review, microRNAs are deeply involved in all of these processes, affecting cellular migration, proliferation, senescence, epithelial-mesenchymal transition and differentiation.

Along similar lines, the involvement of microRNAs in cardiac and skeletal muscle (Sampaolesi, *et al.*), nerves (Chew, *et al.*), liver (Sauer, *et al.*) and blood vessels (Emanueli, *et al*.) are also highlighted in this theme issue. Specifically, microRNA circuitry and signaling to engineer tissue structures or treat diseased

states are highlighted. Together, a potential regenerative regime may be speculated for efficient regrowth of tissues and for normalizing diseased conditions in a tissue specific manner.

For implant survival and integration, angiogenesis is crucial. In addition, host-implant integration must be considered. Focusing on the former, Emanueli *et al.*, reviews the involvement of microRNA expressions in vascular cell (endothelial cells, smooth muscle cells, pericytes) function and stem cell differentiation, highlighting microRNAs that directly target genes that regulate angiogenesis and facilitate the commitment of these cells to functional phenotypes for blood vessel formation. On the other hand, Wong *et al.*, focuses on the involvement of microRNAs in inflammatory response, attempting to provide speculations on novel factors that may be explored to decrease inflammatory response and implant fibrosis to enhance host-implant integration. The detailed descriptions of inflammatory response cascades and involvement of microRNAs will facilitate tissue engineers in considering the inclusion of microRNAs into future scaffold designs for enhanced tissue regeneration, with minimal adverse host response.

Any biomolecular therapy is effective only when coupled with the appropriate delivery platform/vehicle. In this respect, this theme issue ends with two critical reviews on methods to control microRNA expressions in order to translate microRNA technologies to regenerative medicine. These include methods aimed at increasing microRNA expression levels (reviewed by Leong *et al*.) and the delivery of microRNA inhibitory therapeutics (by Duvell *et al.*). Besides conventional

viral vectors and non-viral systemic delivery methods, of particular interest to regenerative medicine is the evolving area of scaffold-mediated transfection.

MicroRNAs holds wide potential as therapeutics. Through the articles in this theme issue, one will have a glimpse of the diverse advantages and targets that microRNAs hold as compared to other conventional biochemical therapeutics. The slow pick up rate in tissue engineering designs is perhaps due to the lack of a bridge that links microRNA profiling results, which are usually presented with a strong biological perspective, with practical, translational considerations that are necessary for engineering practical scaffold designs for regenerative medicine. The aim of this theme issue is to provide such a bridge and it is hoped that through this, tissue engineers will be inspired to venture into the amazing world of microRNAs to help realize the potential of these incredible molecules and provide more efficient treatments for patients.