Opinion

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3D Microfluidic Cell Culture Models for Potential Stem Cell Therapies

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Opinion

Over the last decades stem cell biology has fundamentally transformed our understanding of biological functions on a cellular and organism level and stem cell research has become ubiquitous in today's scientific world. Despite the wide spread use of stem cells in biomedical research, their clinical applications remain in certain situations constrained by potential ethical implications including informed consent, experimental intervention, and embryonic destruction as well as oversight of research [1]. Nevertheless, in recent years cell therapies have been recognized as an important alternative to conventional medical care to alleviate human diseases. Cell therapy, defined as the treatment in which cells are injected into a patient, can be divided into mesenchymal stem cell therapy, hematopoietic stem cell transplantation and allogeneic or autologous cell therapy [2]. Despite repeated success stories direct stem cell implantation for tissue engineering has not consistently yielded desired results. For instance, stem cells injected intraarticularly in medial menisectomized goats resulted in marked regeneration of the medial meniscus [3]; conversely, in an equine osteoarthritis model no significant long term differences in cartilage repair were identified between groups treated with stem cells in fibrin matrix versus those treated with only fibrin matrix [4]. Consequently, the generation of tissues in vitro for therapeutic purposes has been investigated using conventional cell culture techniques for many years. However, 3D-scaffolds, though promising for achieving tissue-like connectivity, are quite limited in controlling cell culture conditions including nutrient supply and waste removals. In turn, the combination of microfluidics with 3D cell culture systems has facilitated dynamic manipulation of culture conditions biochemically and biomechanically to provide a microenvironment that allows formation of artificial tissues from cultured cells.

Initially, microfluidic stem cell cultures have been used to investigate differentiation rates, cell-cell interaction, cell behavior in co-culture, as well as cell-matrix interactions. More recently, microfluidic stem cell culture systems have become popular avenues for modelling organs and/or native tissue in regenerative medicine applications, particularly in regard to screening possible novel cellular treatments. These homotypic and heterotypic tissue culture models are able to mimic the respective tissue closely both from a histologic as well as from a physiological and functional standpoint [5]. While microfluidics offer almost limitless environmental conditions, including mechanical stimulation, laminar fluid dynamics, control of gaseous permeability, live cell microscopy, and more, the latest advances in microfluidic technology for cell culture have shown to reflect in vivo tissue architecture by mimicking specific organic extracellular matrices with 3D cellular distribution. Extracellular matrices can be natural or synthetic, each with advantages and disadvantages pursuant to the experiment in which they are applied; these characteristics are extensively described elsewhere [5,6]. Microfluidic use of cells in 3D ECM accomplishes the micro environmental control required by tissue mimicry while substantially decreasing costs and material overhead, dramatically improving necessary experimental timeframes, and providing high throughput cellular as well as supernatant analyses. These benefits inherent to 3D microfluidic cell culture are therefore ideally suited for the creation of disease models used to identify regenerative therapies, while obviating to a large degree the need for research animal subjects as well as offering micro bioreactor production of cellular secretory products, identified with previously unrecognized importance exemplified by the paracrine influence of stem cells [7]. For example, in our lab we have recently established a 3D microfluidic chondrocyte culture in which biochemical injury simulates osteoarthritis. Once osteoarthritis is induced, degree of tissue regeneration after administration of variable stem cell and stem cell secretome can be assessed on chip, replacing countless animal models and considerably attenuating financial requirements. In the microfluidic device shown in Figure 1, re-differentiated chondrocyte morphology was maintained for greater than two weeks and used to assess phenotypic behavior of native-like chondrocytes in the presence of inflammatory environments. Moreover, our microfluidic system offers the opportunity to easily and efficiently compare the effects, not only of 2D stem cells vs 3D stem cells vs stem cell secretome, but also adult vs fetal stem cells and their respective secretomes. In particular the comparison between fetal and adult stem cell behavior using a physiologically relevant in vitro model is expected to yield deeper insights into differences in the response to injury of e.g. fetal ovine cartilage vs adult ovine cartilage. The study of fetal and adult stem cell behavior within microfluidic devices can therefore be used to address fundamental

questions in the role of stem cell aging on tissue repair and maintenance.

Another major benefit of microfluidics for stem cell therapy research is that micro devices can be designed in abundant fashions, thus providing the opportunity for custom-made tissue models even with increased complexity. Recent advances of micro fabrication technology have demonstrated simple, versatile and robust fabrication of multi-layered, membrane-integrated microfluidics that are ideally suited for customized tissue-, organ and body-on-a-chip systems capable of mimicking tissue interfaces and biological barriers [8]. Not only does microfluidics offer the possibility to analyze the effects of stem cells in simulated tissue regeneration without the use of animal models, microfluidics also offers experimentation with reduced requirements for expensive reagents as well as cellular numbers while maintaining sterility and live cell imaging with fluorescent cell trackers. Consequently, the automation and miniaturization of a reliable, robust and reproducible 3D-cell culture platform that features bioreactor capacities can improve cost-effectiveness by reducing expensive clinical grade reagents and hands-on labor costs. We believe that microfluidic 3D cell cultures will offer dramatically reduced costs, optimize time requirements, and significantly improve animal wastage in comparison to traditional research animal models. An added advantage in microfluidic research applications will be the ease of investigating the similarities and differences between primary cell types derived from a diverse patient population, thus providing the opportunity for individualized cell therapy applications. What remains to be seen is how science will harness such technology and whether a translation will become a competitive alternative to state-of-the-art 3D cell culture systems for cell-based products and therapeutics. Challenges that are already facing microfluidic 3D cell culture applications are substantial and include acceptance in the medical community, proof of in vivo relevance and regulatory approval. For instance, cross comparison between chip-based and clinical diagnostic readouts are difficult and histopathologic evidence remains one of the more important current limitations for validation of microfluidic 3D cell culture as an equal to traditional animal models. Finally, as outlined by the European Union Research Goals, we are already working in a world which, on one hand requires the use of animal trials in an effort to avoid complications in human lives, but on the other hand ethically begins to condemn the same practice for obvious reasons. Economical devices which can simulate native tissue and its respective diseases are not likely to fully alleviate this conundrum, although with today's microfluidic technology, one can begin to envision an era of stem cell research that is not only financially responsible, scientifically enabled, but also ethically responsible (**Figure 1**).

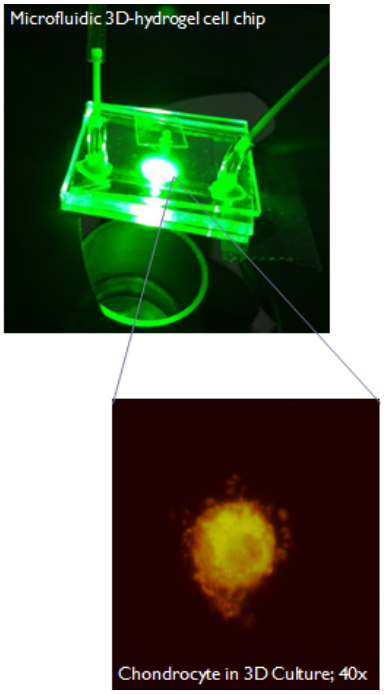

Figure 1 Picture of a microfluidic 3D-hydrogel cell chip containing a chondrocyte culture used to analyze effectiveness of stem cell therapy after biochemical injury (using TNFalpha+interleukin-1beta conditioned medium).

References

1. Lo B, Parham L (2009) Ethical Issues in Stem Cell Research. Endocr Rev 30: 204-213.
2. Wartmann D, Rothbauer M, Kuten O, Barresi C, Visus C, et al. (2015) Automated, miniaturized, and integrated quality control-on-chip (QC-on-a-chip) for cell-based cancer therapy applications. Front. Mater 2: 60.
3. Murphy JM, Fink DJ, Hunziker EB, Barry FP (2003) Stem cell therapy in a caprine model of osteoarthritis. Arthritis Rheum 48: 3464-3474.
4. Wilke MM, Nydam DV, Nixon AJ (2007) Enhanced early chondrogenesis in articular defects following arthroscopic mesenchymal stem cell implantation in an equine model J. Orthop Res 25: 913-925.
5. Rosser JM, Olmos I, Schlager M, Purtscher M, Ertl P (2015) Biologically Inspired Advances in 3D Microfluidic Hydrogel Cell Culture Systems. J Cell Biol Cell Metab 2:1.
6. Tibbit MW, Anseth KS (2009) Hydrogels as extracellular matrix mimics for 3D cell culture. Biotechnol Bioeng 103: 655-663.
7. Caplan AI, Dennis JE (2006) Mesenchymal stem cells as trophic mediators. J. Cell Biochem 98(5): 1076-84.
8. Sticker D, Rothbauer M, Lechner S, Hehenberger M, Ertl P (2015) Multi-layered, Membrane-integrated Microfluidics based on Replica Molding of a Thiol-ene Epoxy Thermoset for Organ-on-a-Chip Applications Lab Chip 15: 4542-4554.