

EDITORIAL

Closing the circle: from organoids back to development

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Organogenesis is an inherently fascinating developmental process. It requires the creation of complex form and function from a collection of distinct cell types, all of which come together without a template. To achieve this, cells within the developing organ undergo differentiation, migration, proliferation and appropriate growth and scaling in a spatially and temporally controlled manner. Moreover, many organs retain throughout life a capacity to regenerate or repair in response to injury in order to maintain function. Studies on both embryonic organogenesis and postnatal tissue homeostasis and repair have been essential foundations to the field of stem cell biology, as it is the stem/progenitor populations involved in these processes that are key. To date, our understanding of organogenesis, and to a lesser degree stem cell biology, has largely been based on animal models. The conservation of genes across organisms perhaps emboldened the view that we can infer knowledge of human development from animal models, but the lack of parallels shows that this is not the case. Instead, it is our capacity to examine stem cells from humans that is filling this gap. It is now possible to recreate miniature approximations of many human organs, referred to as organoids, entirely *in vitro*. Generated from either human pluripotent stem cells (PSCs) or human adult epithelial stem cells, organoids offer unprecedented insights into human developmental processes and can also be used to model postnatal repair and disease. As a result, organoid biology is at the forefront of our developmental studies in the human. For this reason, I am honoured to have been appointed Guest Editor at *Development*, with a particular focus on the emerging field of *in vitro* organogenesis, and with the aim of publishing a Special Issue on the topic (for more details, see below).

Two of the most seminal breakthroughs in recent decades have been the derivation of the first human embryonic stem cells (Thomson et al., 1998) and the reprogramming of human somatic cells to pluripotency (Takahashi et al., 2007). The development of protocols to direct the differentiation of human PSCs towards specific endpoints has resulted in the generation of derivatives of all three germ layers, including nerves, cardiac muscle, pancreatic beta-cells, hepatocytes and blood. Most of these studies have drawn heavily on our underlying knowledge of the morphogens involved in patterning the same cell types during embryogenesis. While initial focus was placed on generating specific target cell types, the cultures themselves began to reveal order amongst the complexity, with the formation of highly patterned multicellular structures *in vitro*. This occurred most notably when cultures were provided with some degree of three-dimensional space within which to interact; for example, as part of an embryoid body or with the support of an extracellular matrix such as Matrigel. The first study to recognise the emergence of a self-organising but recognisable tissue

from human PSCs was less than five years ago, with the generation of a patterned optic cup from the group of Yoshiki Sasai (Eiraku et al., 2011). What followed this seminal study was a growing number of reports describing organotypic morphogenesis as a result of the directed differentiation of human PSCs. Human PSC-derived organoids of the cerebral cortex, adenohypophysis, small intestine, stomach, lung, liver and kidney have now been reported (reviewed by Huch and Koo, 2015). In all cases, these organoids contain distinct cellular components patterned in a morphologically appropriate fashion – a level of cellular complexity previously thought unattainable *in vitro*.

These advances are exciting not only because they represent the long-term possibility of organ regeneration, but also because they provide a new approach to studying human morphogenesis and development. But the challenges here are immense. Are we sure that a cerebral organoid that appears to show evidence of an appropriate multicellular composition and gene expression profile is a sufficiently accurate model of human brain development? Can we reliably sustain such tissue long enough under appropriate conditions to allow it to mature as it would *in vivo*? If these questions are not appropriately addressed, there is a danger that the field will become absorbed by the characterisation of what are no more than *in vitro* dysmorphologies or models of abnormal patterning. This will require disciplined and thorough analyses that take into account what the stem cell field, particularly the induced PSC field, already appreciates is substantial experimental variability. Access to human fetal tissue signatures has been, and will continue to be, essential to ensure that we are on the right track. Indeed, single-cell profiling data comparing human cerebral organoids with developing human fetal brain show remarkable congruence, which is very encouraging (Camp et al., 2015). Based on the assumption that PSC-derived organoids do indeed represent a model of human development, we can be sure that their application will extend beyond developmental biology to personalised drug development, disease modelling, functional genomics and even bioengineering.

Organoids can also be generated from adult stem cells, such as those first reported by the group of Hans Clevers from the intestinal epithelium (Sato et al., 2009). This capitalises on the presence of an epithelial stem cell population in many postnatal organs. Organoids have now been derived from the epithelial stem cell populations of a wide variety of postnatal tissues, including lung, colon, prostate and liver (reviewed by Huch and Koo, 2015). In all instances, these organoids are composed exclusively of epithelial cell types supported by the provision of an extracellular matrix surrogate for surrounding mesenchymal tissues. Adult stem cell organoids have taught us much about the regenerative populations present in many postnatal tissues and the mechanisms by which these populations maintain homeostasis. Their applications in the understanding of disease and in personalised drug screening are now coming to the fore.

Organoids will not only advance our understanding of human development and tissue turnover, but also of morphogenetic

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principles. A major paradigm in morphogenesis has been the concept of positional information, initially described by Wolpert (1969). That concept proposed that morphogenesis during embryonic development results from the relative position of cells with respect to each other and the secreted morphogen gradients they experience. Revised views of this concept have taken into account a capacity for heterogeneous populations to create form without a predefined pattern – a phenomenon known as self-organisation. This has never been more evident than in what is now being observed in organoid studies, where complicated, multicellular form is created from a single starting cell type, and without the complete set of spatial cues normally present in an embryo. The robustness with which a complex structure can arise *in vitro* is surprising. More importantly, it provides the field with a capacity to re-evaluate the underlying principles governing morphogenesis and tissue homeostasis. Coupled with continuous advances in our capacity to image developing tissues at the resolution of individual cells across time and space, investigations into how organoids arise could well lead to rapid advances in our understanding of fundamental developmental principles.

The excitement of what organoid biology can add to our understanding of development has grown exponentially over the last few years, with several scientific meetings dedicated to discussing progress in this area. Development recognises that this is an exciting and rapidly expanding area, which is why we are announcing a Special Issue on organoids, to be published in early 2017. This will include Review articles from the pioneers and leaders of the field, as well as primary papers on topics ranging from methods and techniques for organoid formation to modelling developmental processes and diseases using organoids, in both human and non-human systems. As Development's Guest Editor, I will be taking a lead on coordinating this Special Issue, and invite interested readers to find out more about it – including further details on the issue's

scope and how to submit your work for consideration – on our website (<http://dev.biologists.org/content/special-issue-organoids>). We look forward to receiving your submissions.

In summary, the past decades have seen developmental biology guide us into stem cell biology, with developmental principles continuing to underpin this field. This is perhaps nowhere as compelling as in the generation of organoids. In turn, the generation of organoids is beginning to teach us not only about human development, but also about general developmental principles, helping to build an information flow in the reverse direction in a way that was previously impossible. The challenge now is to close the circle completely using organoid systems to reinforce the link between stem cells and developmental biology, which will bring these two fields closer together than ever before.

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