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EDITORIAL

3D cell biology – the expanding frontier

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I am very pleased to introduce this Special Issue. When Michael Way invited me to serve as the inaugural Guest Editor at Journal of Cell Science, we discussed how to capture our mutual excitement about current research in 3D cell biology. My own research seeks to elucidate how molecularly regulated changes in cell behavior drive alterations in the structure and function of mammalian organs. Specifically, how do cells integrate diverse chemical and mechanical signals, how do they compete and cooperate to change tissue form, and how does information propagate across groups of cells? A major barrier to answering these questions is that key mammalian developmental processes occur over days to months deep within the embryonic or postnatal animal. Accordingly, it is difficult to directly monitor cell and tissue dynamics in mammals by using optical microscopy. These issues have confounded the analysis of diverse processes in mammalian development and disease.

The cell biology field has historically taken three approaches to overcome this barrier. The first is to study small, transparent model organisms, in which genetic and imaging analyses can coincide in intact animals. The second approach is to use histology to compare different stages of development across different animals fixed at different times. Inferring cell and tissue dynamics in this fashion is especially challenging during processes that involve large changes in cell number and extensive cell migration. A third approach, however, is to develop 3D culture assays that enable key events in the *in vivo* process to be modeled in an experimentally convenient fashion. 3D culture is not a new invention. Embryonic tissues were explanted into culture starting in the early 1900s, cultures of whole mammalian organs were utilized in the 1950s, and diverse cells and tissues were explanted into extracellular matrix gels in the 1980s (Shamir and Ewald, 2014). The past five years have seen an explosion of interest in 3D culture, catalyzed by major innovations in induced pluripotent stem cells (iPS cells), organoid techniques, molecular imaging and higher-sensitivity approaches for molecular analysis of small samples. For this Special Issue we wrote a broad call for papers and received 70 submissions; the accepted papers reflect the fascinating diversity of research in 3D cell biology being conducted in the labs of JCS authors. It is our hope that – by bringing distinct methods, model systems and questions together – readers of the issue can learn new approaches and concepts that will benefit their own research.

As you will see, a few broad themes emerge from this Special Issue. The first is that model systems retain a central place in studies at the interface of cell and developmental biology. There are multiple strong studies in *Drosophila*, *Xenopus* and zebrafish that utilize sophisticated imaging methods to study cell migration and organ development *in vivo*. New techniques are reported advancing the sophistication of genetic interventions and molecular analyses in these systems. The second broad area consists of 3D culture assays, combining primary cells or immortalized cell lines with extracellular matrix gels to model simplified units of epithelial function, during both developmental and neoplastic processes. Technical advances enable these assays to focus on the transduction of mechanical signals, leverage recent advances in proteomics, systematically evaluate the influence of the 3D culture context on signaling networks, early steps in cancer invasion, and the interaction of different epithelial and stromal cell types. These 3D culture assays are also utilized to study mechanistic connections between adhesion, polarity, epithelial integrity and barrier function. The third broad group of papers leverages recent advances in electron microscopy to define 3D structure across a wide range of sizes and complexities, including viral replicase assembly, organelle and cytoskeletal dynamics, kidney morphology, and new structural connections between the membrane, cytoskeleton and nucleus within mammary tissues. These research articles are complemented by Tools and Techniques papers reporting exciting advances in ultrasound-based tissue patterning, mechanical analysis of 3D cultures, and correlative light and electron microscopy. Finally, biology-focused Commentaries discuss embryonic intercellular interactions, neuronal development and 3D cell migration, together with technology-focused Commentaries that discuss advances in optical, engineering and mechanical analysis.

It has been very rewarding to follow these papers throughout the submission and review process. They reflect the state of the art in the field and I believe they will be influential in driving further advances in our understanding of the cellular and molecular basis of organ function. We encourage regular submissions across these varied topics and in other emerging areas of 3D cell biology. In reflection of the multidisciplinary motivations and approaches being employed to advance this field, our sister journal, Development, has an upcoming Special Issue on Organoids. It is likely to be of great interest to the readers of Journal of Cell Science. I conclude by thanking the many authors and reviewers that made this issue possible.

Reference

Shamir, E. R. and Ewald, A. J. (2014). Three-dimensional organotypic culture: experimental models of mammalian biology and disease. *Nat. Rev. Mol. Cell Biol.* **15**, 647-664.