CellPress

Developmental Cell

Voices

What approaches are needed to understand human development and disease?

Researchers are leveraging what we have learned from model organisms to understand if the same principles arise in human physiology, development, and disease. In this collection of Voices, we asked researchers from different fields to discuss what tools and insights they are using to answer fundamental questions in human biology.

Berna Sozen
Yale University School of Medicine, New Haven, CT, USA

Seeing the unseen: Human embryogenesis *in vitro*

Human embryonic development is an intricate puzzle. Early disruptions can lead to a spectrum of developmental defects, long-term health complications, or outright embryonic lethality. However, our understanding of this process is hindered by limited accessibility and ethical concerns.

Recently, the field of developmental biology has witnessed a groundbreaking shift toward understanding human early development through *in vitro* stem-cell-based embryo models. Technological advances, such as pluripotent stem cells, advanced culture techniques, and bioengineering methods have been instrumental, providing ethical alternatives for studying human-specific aspects of early development that were previously insurmountable.

We are now able to investigate the molecular and cellular processes involved in implantation, gastrulation, early organogenesis, and other critical events, helping also understand the distinctions between human development and more commonly used mammalian models, like mouse.

Future progress relies on improving culture conditions; enhancing reproducibility; embracing single-cell-omics techniques; and leveraging bioengineering, gene editing tools, and organoid models. These innovations will help us reproduce the dynamic early embryonic environment more accurately and enable the study of how various factors, such as genetic mutations or environmental influences, impact the developing human embryo. As our understanding of human early development deepens, translating this knowledge into clinical applications for human health and reproduction becomes increasingly feasible.

Richard A. Flavell
Yale University, New Haven, CT, USA

Human language for cell communication in mice

Organs orchestrate countless functions. Thus, despite exposure to numerous inputs, the liver functions through division of labor between cell types and homeostatic regeneration. So far, *in vivo* studies are limited to animals. However, essential liver functions like drug detoxification, lipoprotein, cholesterol, and bile acid metabolism are fundamentally different in rodents and humans. Humanized mice enable the study of human cells in mice, but organs comprise numerous cell types, and mouse and human cells miscommunicate because many signals are species specific. By assembling human hepatocytes with other critical liver cells *in vivo*, we enabled human liver cells to speak in their own language within mice. From this model, we learnt more about human-specific communication between endothelial WNT2 and hepatocyte FZD5 receptor that instructs hepatocytes to synthesize molecules necessary for cholesterol uptake and bile acid conjugation.

Liver diseases affect millions of people. However, there are major differences in how human and rodent cells respond to liver damage. By using our above approach, in future we envisage being able to study human cell responses to liver damage in mice and to use this to discover better therapies for human liver diseases. And similar approaches enable study of other organs.

Dudley W. Lamming
University of Wisconsin-Madison, Madison, WI, USA

Moving beyond the calorie for healthy aging

The last decade has seen a revolution in our understanding of nutrition and an overturning of the long-held paradigm that ''a calorie is a calorie.'' It is now becoming clear that calories from different macronutrient sources or that are consumed at different times during the day have impacts on metabolic health and even aging that go far beyond their caloric value. This is particularly true with regards to protein; both the level of dietary protein and the amino acid composition of that protein regulates not only metabolic health but also healthy aging and even longevity in mice.

There is an emerging realization that work based on a single inbred sex and strain of mice—typically C57BL/6J males—may not apply to the genetically diverse human population. It is therefore vital that as research into how dietary composition regulates metabolism and healthy aging moves forward, scientists branch out and ensure their studies include multiple genetic backgrounds and both sexes of mice.

This research comes with challenges as well as opportunities—for instance, while appropriately powering these types of studies may require more resources, mapping the genetic loci associated with the response to dietary composition may help us to identify molecular mechanisms engaged by diet which regulate health, frailty, and lifespan. Identification of genetic variants that mediate responses to diet in mice may also help advance our understanding of how allelic variation contributes to the varied response of humans to different meals and diet plans. These studies will help guide us toward a future in which precision nutrigeroscience allows the optimal diet for healthy aging to be determined at the individual level by incorporating information about an individual's genotype.

Debra L. Silver
Duke University School of Medicine, Durham, NC, USA

The choreography of brain development

The brain controls diverse features that collectively define us as humans, including our advanced cognitive capacities. Brain development underlies these key functions and when perturbed causes disease. Studies in model organisms have generated foundational principles of brain development across anatomical, cellular, and molecular levels. New molecular atlases of the developing fetal brain now reveal unprecedented insights into unique aspects of human development.

But how does human-specific gene expression ultimately influence brain development? We can leverage epigenomic and genomic editing of iPSCs and organoids, derived from experimentally inaccessible species, to prioritize and investigate loci, tackling this challenging question of function. To gain a deeper understanding, *in vitro* studies must be accompanied by orthogonal investigations of fetal tissue, in which high-resolution imaging, lineage analysis, and functional interrogation are pursued.

We now have an emerging picture of human brain development at genomic, transcriptomic, and epigenetic levels. Gaps remain in our knowledge of post-transcriptional mechanisms of brain development; indeed, RNA and protein abundance likely tell different stories about cellular states, identity, and function. Continued advances in profiling diverse gene expression layers with single-cell and spatial resolution, and linking them to cell lineage and disease, will be invaluable for the field.

Simona Parrinello
UCL Cancer Institute, London, UK

Modeling cancer initiation in glioblastoma

Genome sequencing has revealed that phenotypically normal tissues bear a variety of driver mutations. This raises fundamental questions around cancer initiation: How do normal tissues silence potentially oncogenic mutations? What allows mutations to express their malignant properties at the onset of tumorigenesis? How do mutations sensitize cells to respond to tumor-promoting signals? Answering these questions holds enormous potential to improve outcomes for cancer patients through prevention and early detection.

Reconstructing the pathogenesis of cancer requires the systematic introduction of relevant mutations in cells of origin *in vivo*, which is only possible in animal models. Such models should faithfully recapitulate human disease mechanisms and be genetically tractable, ideally without the need for cumbersome and lengthy breeding of multiple transgenic lines. The advent of gene editing has greatly facilitated this, at least in tissues which are amenable to somatic transformation. The combination of Piggybac transposition and CRISPR/Cas9 technology allows generation of somatic glioblastoma mouse models through targeted delivery, via electroporation, of human driver mutations to neural stem cells within their native tissue microenvironment. Critically, these models "mimic" the histopathology, molecular features, and cellular states of the human disease. The system enables nearly unlimited functional studies through direct genetic engineering of the transposons, providing a powerful platform for discovery and translational research. An exciting future application of these models will be to unravel mechanisms of early recurrence by developing methods to mirror standard-of-care therapies.

Cory Abate-Shen
Columbia University Irving Medical Center, New York, NY, USA

At the crossroads of cancer and development

For several decades, my laboratory has been interested in understanding how normal developmental pathways go awry in cancer. We are studying prostate and bladder, which are ideal for comparative studies given the same embryological origin—endodermally derived urogenital sinus—but different features, as do their associated cancers. The bladder is an essential organ for both males and females, but cancers arise more often in men. The prostate is a male-specific organ that develops under the influence of androgens, which are required for prostate cancer. Bladder and prostate cancers are markedly different, particularly with respect to their histological features. Nonetheless, for both, the large majority are indolent, while only a handful become aggressive. So, it is important to understand what distinguishes these different forms of cancer so that we can intervene early and prevent cancer deaths. We believe the answer will arise from studying developmental pathways. To do so, we have developed a series of genetically engineered mouse models to study the range of cancers that arise from bladder and prostate. Advances in single-cell technologies have revolutionized our studies. However, what we learn from the mouse models and how well we can apply that to human cancer has been largely dependent on advances in systems biology, allowing us to extrapolate the information to human patients. In particular, working with "high-fidelity" mouse models that are faithful representatives of the cancers they are expected to emulate, we use gene regulatory networks to study the crosstalk between the mouse and human cancer to identify the key drivers—master regulators—that distinguish phenotypes. Since the conserved ones tend to be the most important, this approach has served us well.

Franziska Michor
Dana-Farber Cancer Institute and Harvard University, Boston, MA, USA

Cross-disciplinary insights may aid human health

Recent interdisciplinary trends have been instrumental in enhancing our understanding of human physiology and disease, bridging gaps between computer science and biology, technological advances and experimental innovations, and spanning time and length scales. A particularly fruitful interplay has emerged at the interface of developmental biology and oncology, both fields propelled by innovative experimental methodologies and computational insights. This synergy, while historically deep-rooted, continues to elucidate connections between developmental processes, such as wound healing and morphogenesis, and cellular phenotypes arising during tumorigenesis. For instance, our own research delineates striking similarities between mammalian embryogenesis and tumorigenesis, uncovering that the epigenetic landscapes established during early development—demarcating embryonic and extra-embryonic tissues—consistently differentiate various tumor types from their normal tissue counterparts. These findings imply that the evolutionary invention of placentation, despite its many adaptive advantages, may have inadvertently predisposed mammals to malignant cellular transformations. Such insights hold promise for groundbreaking applications, including non-invasive early cancer detection and novel therapeutic avenues. As we continue to weave together knowledge from disparate disciplines, we remain hopeful that this rich tapestry of interdisciplinary collaboration will yield vital breakthroughs with the potential to transform clinical practice.

Vijay G. Sankaran
Boston Children's Hospital and Harvard Medical School, Boston MA, USA

Getting blood from a (Rosetta) stone

As an MD-PhD student, I set out to define the mechanisms by which developmental hemoglobin switching occurred, with the hope that this would enable better treatments for sickle cell disease and other hemoglobin disorders. I started studying this process in mice, but after years of failure, I realized that we needed an alternative approach. Fortunately, advances in human genetics coupled with our functional follow-up studies revealed BCL11A as a key regulator of hemoglobin switching, leading to the development of potentially curative therapies for sickle cell disease and β-thalassemia. This experience has served as a North Star for all of our subsequent work, which seeks to continue unraveling new aspects of hematopoiesis by studying human genetic variation and defining its functional consequences. Advances in sequencing and computation have empowered increasingly larger studies that define how naturally occurring genetic variation impacts this process. Breakthroughs in single-cell genomics and genome engineering have enabled previously unimaginable mechanistic studies. As I reflect upon the exciting journey that began with these initial studies of hemoglobin switching, I am eager to see how further advances in our ability to read and write genomes in single cells will transform our understanding of human hematopoiesis in the coming years.

DECLARATION OF INTERESTS

V.G.S. serves as an advisor to and/or has equity in Branch Biosciences, Ensoma, and Cellarity, all unrelated to the present work. F.M. is a co-founder of and has equity in Harbinger Health, has equity in Zephyr AI, serves as a consultant for Harbinger Health and Zephyr AI, and is on the board of directors of Exscientia Plc.