Developmental Cell

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Voices

20 years of *Developmental Cell*: Looking back

In our 20th anniversary year, we reflect on how the cell and developmental biology fields have changed since the publication of *Developmental Cell*'s first few issues. In this collection of Voices, authors who published in our early issues discuss the advances that helped shape their field over the past two decades.

Joanne Chory
Salk Institute for Biological Studies

Eating humble pie

When asked to write about how my field has evolved over the past 20 years, I thought it would be a simple task. My field is signal transduction, and my organism is *Arabidopsis thaliana,* a model plant for all angiosperms. Twenty years ago, *Arabidopsis* had just entered the genomics era. Less than a handful of receptors were known from biochemical studies in plants, but with a genome sequence, one could predict the presence of more than 1,000 protein kinases, of which more than half were putative receptors. I thought the next decade would be one during which we would unravel the complex web of how information in the local light environment controls virtually all plant physiology as well as every developmental transition.

Boy, was I wrong! In my cockiness, I forgot that science is a search for the truth, which is sometimes complicated, and this takes perseverance, grit, and the development of new technologies. It took my lab almost 20 years to crack just a small part of the "light signaling" story. On our way there, a community formed and flourished, resources were shared, and important questions about the biology of plants were answered. Sometimes a good result is worth waiting for.

Eric N. Olson
University of Texas Southwestern Medical Center, Dallas

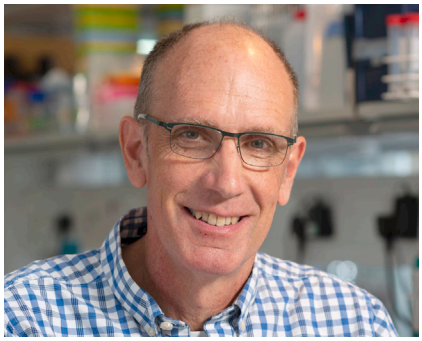
Insights from single cells and CRISPR

My lab seeks to understand the gene regulatory networks that control formation of diverse muscle tissues and to build upon this knowledge to devise innovative therapies for devastating muscle disorders. Over the past two decades, two technical advances transformed our field: single-cell sequencing technology and CRISPR gene editing. Whereas understanding of gene expression in embryos and complex tissues was previously restricted to bulk RNA sequencing, the advent of single-cell transcriptomics, including RNA sequencing and assay for transposase-accessible chromatin (ATAC) sequencing, enabled the exploration of gene expression at single-cell resolution. These technologies provided insights into cell lineage trajectories, cellular hierarchies, and cellular heterogeneity with unprecedented resolution, and they allowed for the establishment of transcriptional atlases of normal and diseased tissues and embryos at the cellular level. Prior analysis of gene functions via gene inactivation through homologous recombination, a foundation of developmental biology, was laborious and time-consuming. CRISPR gene editing transformed the field by enabling rapid and relatively simple genetic modifications in cells and tissues, as well as large-scale genetic screens and the creation of animal models of disease. The combination of single-cell technologies and CRISPR has enabled the manipulation of gene expression of individual cells and analysis of the consequences on large cell populations. The insights from these technologies have revealed fundamental insights into development and disease.

Lilianna Solnica-Krezel
Washington University School of Medicine in St. Louis

PCP as a cellular compass

Like origami, germ layers in vertebrate gastrulae fold into a 3D body with endoderm, mesoderm, and ectoderm layers that elongate from head to tail and narrow from back to belly. Ray Keller's pioneering work showed that simultaneous convergence and extension (CE) of germ layers is driven by intercalation of polarized cells between their anterior and posterior neighbors. A series of studies, including our paper in the second issue of *Developmental Cell,* implicated cytoskeletal control by a vertebrate equivalent of the *Drosophila* planar cell polarity (PCP) pathway in these polarized cell behaviors. Since then, new components of the vertebrate PCP pathway have been identified—raising the question of whether PCP signals via a single complex or multiple complexes with distinct upstream and downstream actors. As in *Drosophila*, vertebrate gastrula cells show asymmetric PCP component localization, and this implies that PCP acts as an anteroposterior cellular compass. The compass polarizes cells during CE, during neurulation, and in the left/right asymmetry organ. How does the PCP compass coordinate patterning and morphogenesis? In zebrafish, the dorsal to ventral BMP gradient that patterns germ layers also inhibits ventral expression of PCP components and CE. Although Nodal regulates anteroposterior patterning, in zebrafish, it polarizes CE behaviors both upstream and in parallel to PCP. How cells integrate the increasing number of signals that control their fate and movement to shape the body remains a fascinating area of study.



Sean Munro
Medical Research Council Laboratory of Molecular Biology

The pathways of life

The membrane trafficking pathways that allow cells to secrete and endocytose proteins have fascinated cell biologists since the early 1960s, when George Palade used electron microscopy to follow the secretion of zymogens from the pancreas (and in the process, finally convinced himself that the Golgi apparatus was not an artifact). By 2001, it had become clear that coat proteins form the transport vesicles, and SNARE proteins fuse them with their destinations, with a variety of Rab GTPases, "tethering" factors, and motor proteins doing something ill-defined in between. In the past 20 years, most of the remaining components have been characterized, allowing a better understanding of how cargo is sorted and vesicles are moved and then tethered prior to fusion to ensure specificity. The importance of contact sites between organelles has become clear, and this has revealed how lipids can hop around the cell without needing a ride in a vesicle. Likewise, mTOR signaling and autophagy have made lysosomes unexpectedly fashionable, and believers in phase separation have left membranes for the cytoplasm. New technologies have driven progress, with CRISPR bringing the rigor of genetics to cells, live cell imaging revealing dynamics, and a revival in electron microscopy delivering super-resolution imaging. However, looking to the future, real understanding of mechanism will require old-fashioned and unglamorous *in vitro* reconstitution, and understanding function will require studying cells in tissues.

Elaine Fuchs
The Rockefeller University, Howard Hughes Medical Institute

Stem cell niches grown up

In 2001, when *Developmental Cell* was in its infancy, I wrote a review article on the hair follicle, which was soon to emerge as an ideal model for studying how stem cells make and regenerate tissues. In 2001, we were pondering how stem cells might both self-renew and differentiate. We now know that factors such as cytoskeletal polarization, cell density, degree of adherence to the underlying basement membrane, and vacancies within the niche can influence whether a stem cell will divide symmetrically or asymmetrically and what fate will be the outcome.

Another paradigm-shifting finding was that tissue stem cells are architects of their own niche. We've learned that stem cells generate early progeny that signal to their stem cell parents to stimulate self-renewal and fuel tissue production, and they also generate differentiated progeny which feed back negatively. The field also has a good handle not only on the location of stem cells in tissues and their molecular properties but also on their amazingly diverse and complex niches.

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At the turn of this century, few developmental biologists foresaw the remarkable advances in high throughput technologies that would revolutionize our ability to probe stem cell characteristics. The past 20 years of stem cell research have revealed that tissue stem cells do not simply dance to the tune of their local progeny and short-range acting signals. Rather, through their interactions with niche components such as lymphatics, immune cells, and neurons, stem cells can also receive and transmit long-range signals, thereby integrating and coordinating tissue and body fitness.

Daniel St. Johnston
The Gurdon Institute, University of Cambridge

A phase change in developmental cell biology

When *Developmental Cell* started, most work in my field was based on analyzing mutant phenotypes from forward genetic screens, and I was skeptical about whether the vast resources being spent on genome projects would pay off. Twenty years later, it is obvious how wrong I was, as the genome sequence and genome-wide RNAi and CRISPR tools have made it possible to cheaply and efficiently analyze gene function. It would previously have taken years to go from a mutant to a cloned gene, but the dramatic drop in whole-genome sequencing costs has made forward genetics much easier, while CRISPR-mediated homologous recombination has hugely accelerated the testing of hypotheses about protein function. Imaging has also advanced quickly, including light sheet, super-resolution, and expansion microscopy, along with an explosion of new fluorescent proteins and sensors, and this has transformed phenotypic analysis. I also underestimated the power of self-organization in development and have been awed by the proliferation of organoid systems that recapitulate development in a dish. Besides these technological advances, the discovery that has most surprised me is that liquid/liquid phase separation underpins so many cell biological processes. My biggest disappointment is that transcriptional control is not solved despite a huge amount of effort, which is chastening for those of us who work on less tractable questions about how cells carry out processes that sustain life.

Véronique Lefebvre
The Children's Hospital of Philadelphia

A prosperous discovery growth plate

Twenty years have passed since my nascent research group published our very first article in *Developmental Cell*'s first issue. Through the generation and analysis of knockout mice, our paper revealed that the closely related SOX5 and SOX6 transcription factors are essential for cartilage formation. They powerfully enhance the ability of SOX9 to activate the chondrocyte differentiation program. They thereby form a master chondrogenic trio with their distant family member. This discovery, along with a myriad of other milestone studies published in *Developmental Cell* in the last two decades, has explored the fascination of scientists with the mysteries of development, fundamentally impacting the cartilage field and many others. Importantly, these studies have empowered discoveries about the underpinnings of developmental and adult diseases and searches for therapies. In skeletogenesis, breakthrough studies over the last 20 years have answered numerous questions, ranging from skeletal cell type diversity and stage-specific activities to functional interactions with other cells and regulation by various pathways. Like an ever-changing, multi-faceted growth plate cartilage tissue, studies in the developmental cell field have constantly diversified and adapted to new knowledge and technological progress. Like this pivotal template for skeletal growth and ossification, these studies have inspired countless scientists and have helped them grow and mature.

George Coupland
Max Planck Institute for Plant Breeding Research

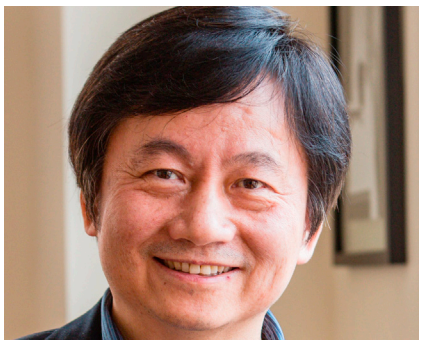
Signaling between plant cells and organs

The 20 years since the arrival of *Developmental Cell* have seen a transformation in our understanding of plant development. Notably, the diversity of mechanisms by which plant cells communicate to their neighbors or transmit signals systemically through the vascular system was unimaginable two decades ago. Intercellular signaling by the classical plant hormones was already described physiologically at the time, but now we also understand the molecular mechanisms by which each of them is perceived, and we recognize additional secondary metabolites, such as strigolactones, which also act as hormones. Perhaps more surprising was the demonstration that non-coding microRNAs, which were unknown in plants 20 years ago, also act as cell-to-cell and systemic signals in many developmental contexts. In my research area, the classical florigen systemic signal, which has long been known to be transported from leaves to the shoot meristem to induce floral development in response to changes in day length, was unexpectedly found to involve systemic movement of a small protein related to lipid binding proteins. This mobile protein, FT in *Arabidopsis*, acts at the shoot meristem to promote floral differentiation. Strikingly, it was found to act antagonistically to related anti-florigen proteins that are expressed in the meristem. The precise quantitative interplay between florigen and antflorigen contributes to the broad diversity of inflorescence architectures found among flowering plants. However, determining the molecular mechanisms underlying these quantitative interactions remains a challenge for the next decade.

Sarah E. Millar
Icahn School of Medicine at Mount Sinai

Getting under the skin

Classical recombination experiments showed that reciprocal epithelial-mesenchymal signals drive ectodermal appendage formation, but two decades ago their molecular identities were largely mysterious. It has been exciting to help unravel this mystery and uncover Wnt signaling as a key pathway initiating appendage development. One surprise was that Wnt activity directs morphogenesis of strikingly diverse structures such as hair follicles and taste papillae; another was that, as well as promoting epithelial stem cell proliferation, Wnt effectors drive specialized tongue and palmoplantar epithelial differentiation by cooperating with the suprabasal transcription factor KLF4. These studies have helped explain the variety of phenotypes in patients with WNT10A mutations and suggest potential therapeutic approaches. A further unexpected finding was that formation of hairless versus hairy skin results from spatially restricted expression of Wnt inhibitors. This provided a first clue into mechanisms that underly skin heterogeneity and may govern differential responses of diverse skin regions to skin and hair diseases. A current challenge is to translate this new information in order to engineer specific skin types for reparative grafting and to design effective drug or cell-based therapies for patients with genetic skin diseases. Raising great hope for the latter, a group in Italy recently used transgenic keratinocytes to successfully replace the epidermis of a child with a lethal blistering disease.



Haifan Lin
Yale University School of Medicine

Ushering in the birth of a new field

In the past 20 years, *Developmental Cell* has witnessed the birth and rapid growth of the PIWI-piRNA field. The *argonuate/piwi* gene family was first discovered in 1998 by my lab. Four years later, in 2002, *Developmental Cell* published the first report on the function of a mammalian *agonuate/piwi* gene, *miwi*. At that time, only a handful of papers were published on *piwi* genes. Another four years later, in 2006, the study of PIWI proteins led to the discovery of a new and enormous class of small noncoding RNAs, named Piwi-interacting RNAs (piRNAs), in the germline. This attracted many labs to join the race to decipher the functions of these mysterious proteins and RNAs. Subsequently, Piwi proteins and piRNAs have become widely recognized as the vanguard of genome defense, a guarantor of the germline fate and stemness, and, more recently, a likely culprit for malignancy in diverse somatic tissues. Today, the study of PIWI proteins and piRNAs continues to expand as an exciting field. How will it look in another 20 years? I believe the tens of millions of piRNAs, still largely untapped, will give us answers. These answers will reveal new territories of genome-wide gene regulation with medical implications, and, no doubt, many of these will be published in *Developmental Cell*!