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The Maturation of Development

David Bilder

Department of Molecular and Cell Biology, University of California-Berkeley

This issue celebrates the debut of *Developmental Cell* 15 years ago. The launch came in the midst of a Golden Age of developmental biology, when the insights of earlier observational and experimental embryologists became tied to concrete molecular functions. These ties, uncovered by many approaches, but in particular by molecular genetic analysis in model organisms, were nothing short of revolutionary. They not only unveiled the elegant logic by which a complex animal is constructed from a single cell; they also revealed that the astonishing diversity of metazoan life arises from a limited set of conserved molecular, as well as morphological, strategies. For those of us who trained during that period, it seemed that every week saw papers that uncovered new principles by which cells multiplied, diversified their fates, and organized themselves into the tissues that make up the earth's creatures. These were heady times, exemplified by the 1995 Nobel Prize awarded to Lewis, Nusslein-Volhard, and Wieschaus, and the pursuit of development's fundamental questions attracted many of the brightest and most active young scientists.

However, lately there has been a degree of soul-searching and reflection amongst developmental biologists. There is something of a perception outside (if not inside) the discipline that development is 'played-out', that the major principles have been uncovered, and that the triumphs of stem cell biology and its directed engineering of cell fates (which directly derive from hard-won developmental principles) has taken the glamour along with much of the funding and talent. There is a concern that the term 'development' itself has come to seem a bit old-fashioned, suggesting a bygone era whose practitioners persist as a legacy.

A reporter recently asked me to name my field within biology. I hesitated, but not out of any concern for affiliating with development. Instead, I found myself thinking that the term sounded too limiting. My own scientific trajectory has taken me from what Mike Levine called 'good old God-fearing developmental biology', to cloning new genes identified in large-scale screens, to probing resultant cell biological mechanisms, to our current work on biomechanics, epithelial homeostasis, and inter-tissue communication. Taken literally, development conveys a sense of working with embryos. Yet at the moment most of the work in my lab actually concerns adult animals. Was I no longer a developmental biologist, and if not, to what discipline did I now belong?

These questions prompted a reconsideration of what drew so many to study development in the Nineties. Surely each scientist had his or her own reasons, but in my case the motivation was to understand how animals, in their immense diversity, actually work. More pedantically, I wanted to uncover mechanisms that linked genotype to phenotype, at the level

of a living organism. Developmental biology offered a captivating approach to address this, relying on four key components.

The first component was genetics. Doing Mendelian genetics with well-defined alleles brought a logic and clarity to experimentation that was tremendously appealing. Moreover, the ability to carry out forward genetic screens, allowing unbiased identification of unanticipated connections, epitomized the scientific ideal of discovery. A second component was microscopy. Aside from the enchanting visual beauty of biological systems at any length scale, ‘just looking’ promoted a holistic view of an entire lifeform, rather than an isolated and extracted set of its elements. By capturing differences in space and time, microscopy also did justice to cells’ diversity and dynamics. The third component was working with a living organism. During brief forays into cell culture biochemistry, I would lie awake at night wondering what relation the day’s results actually bore to what was happening within the animals outside the window. By contrast, it was heartening to be certain of the physiological relevance of, say, a mutant phenotype, and to know that, however obscure its mechanism appeared at that moment, it would eventually reveal itself through either inspiration or dogged investigation. The fourth component was the level of analysis. Whereas cell biology had a tidy definition –what happens within the bounds of a single plasma membrane—development offered a messier, but also more expansive view. It inherently forced one to think about how the tiny piece under investigation works as part of a larger whole, integrating with the function of an entire organ and organism, shaped by evolution, and living in a particular ecosystem. Importantly, development included mechanistic investigations that went beyond classical molecular associations to address critical cellular and tissue-scale interactions as well.

At the time, these approaches were often best suited to embryos. Genetic clarity is maximized when using null alleles, and the consequence of losing a pleiotropic gene often first manifests during embryogenesis. For the beauty of microscopy, embryos offered a consistent, relatively thin and (if externally developing) conveniently accessible sample for imaging. And of course, one was working on real living animals, but at the beginning of their life when biology was particularly dynamic and fast-moving. Finally, embryos in all their complexity remained simple enough that basic experiments could nevertheless yield powerful inferences about the connections between individual molecular processes and their ultimate influence on the organism.

However, over the last 15 years, new techniques have allowed these approaches to move beyond embryos’ simple advantages. Tissue-specific knockouts, inducible overexpression and gene inhibition now allow routine generation of functionally mosaic animals at any stage, overcoming the barriers presented by pleiotropy. Advanced microscopy makes probing deeply into mature tissues as accessible as into transparent embryonic specimens, while live imaging and vital fluorescent probes capture the complex dynamic interactions between multiple cell types that occur therein. Overall, biological tools have become more sophisticated and biological analyses more quantitative: we can independently manipulate, measure, and model phenomena that involve diverse components, enabling dissection of what were formerly seen as hopelessly complex systems. This is to say nothing of the ‘omic’ revolutions, which now allow the molecular analysis of small cell populations within

heterogeneous tissue. Classical techniques of experimental embryology have been more difficult to adapt to mature stages, but the astonishing progress in organoid generation creates opportunity here as well.

Together, these approaches have opened up compelling new worlds of biological analysis, including those of adulthood. Many developmental biologists used to regard adulthood as the province simply of homeostasis, a somewhat dull and persistent stable state that was the worthy achievement of the embryo's manifold exertions. We now appreciate that this old dichotomy between development and homeostasis is based on a false premise; microperturbations constantly occur and growth, differentiation and related phenomenon do not stop after embryogenesis. This is true not only for morphological homeostasis; physiological homeostasis also involves a continuous and intricate network of active communication between organs – via cells, signaling peptides, small molecules and metabolites that move through the extracellular milieu.

Moreover, adult tissues are frequently challenged by injury, infection, disease, and degeneration. And how are these challenges met? By related but fascinatingly modified versions of the mechanisms first used during embryogenesis. Wound healing and regeneration, stem cell-based organ homeostasis and adaptive changes to the environment, tumor growth and age-related atrophy, metabolic and other physiological shifts: these all rely neither on 'new biology' nor on simple reiteration of developmental processes, but instead on parallel strategies that are adapted to the context of a mature organism. In understanding how these strategies fail during disease and aging, fluency in the developmental perspective can provide critical insight. Few human diseases are pathogenic exclusively at the molecular or cellular level; instead they cross biological scales to act at a 'systems' level that impacts the organism as a whole. Even cancer, a classic case of altered genotype driving altered cellular phenotype, has its most grave manifestations not in the cell-autonomous increased growth but in its communications and interactions with neighboring and distant cells.

The point is that the approaches that made examining embryos so appealing in the past also make the study of mature tissues attractive today. Importantly, tackling these questions requires not only the same technical but also the same intellectual tools –especially free-ranging curiosity and a flexible mindset—that have always characterized the best developmental biologists. Rafi Kopan nicely expresses this sentiment, which I have been trying to articulate to my trainees for over a decade:

I see developmental biologists as retaining a working multidimensional zoom, allowing them to travel in scale and in time and through any appropriate model organism, to continually convert original observations into discoveries of unexpected new mechanisms with relevance ranging from basic biological mechanisms to human disease. In this analogy, cell biologists rarely zoom up to the organ and the organism levels, while the stem-cell biologist are not always interested to zoom forward in time to look at the differentiated cells or organ. A stem cell biologist may look at stem cell aging only as an obstacle limiting the function of a perfect regenerative engine. In contrast, a developmental biologist would consider stem cell aging as a component in a complex developmental

program that matches lifespan with the mode of reproduction (sexual vs. asexual), reproductive strategy (K vs. R), and niche availability. Only developmental biologists with a working zoom lens and a self-issued license to ponder any and all of these subjects, would consider all of them fair game.

So what does development mean today? I favor a definition more comprehensive than the ‘egg to organism’ constraints that have often been placed on it, expanded to encompass the entire lifespan of the organism until its demise. With the freedom provided by technical advances, we can now see development for what it really is—the general study of how cells behave in response to both intrinsic gene expression and extrinsic signals from neighbors and the broader environment. The essence of the discipline that I love is thus not the stage of animal life history that is being investigated. Rather, it is the permission to not stop at boundaries (the molecular complex, the cell, the tissue) but to smoothly transition between them, returning to integrate all levels of analysis into a working model of how animals function.

Acknowledgments

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