What Is the Future of Developmental Biology?

It's Evolving!

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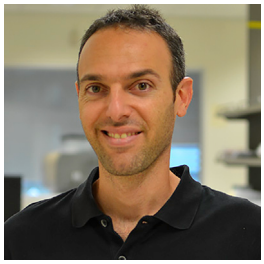
In the pre-molecular era, experimental embryology defined the concepts of induction, morphogen gradients, and signaling centers. In the 1980s, developmental genetics identified the genes and signaling cascades that underlie these concepts. A multitude of papers described how a handful of signaling pathways shape every organ. The joke was that there are two types of developmental biologists: those who know they work on Notch (or Hedgehog, BMP, or Wnt) and those who don't. This became repetitive, which seriously hurt the field. However, quantitative cell biology is now providing a real mechanistic understanding of morphogenesis orchestrated by signaling pathways. In parallel, evo-devo has explored how species tweak developmental pathways to produce adapted body plans, but until recently, it has been largely descriptive. Today, genomics and CRISPR have dramatically expanded the notion of what a model system is, such that we can now use organisms best suited for asking particular questions. Classical model organisms have their strong and weak points: *C. elegans* is amazing for studying cell fate decisions, but not for limb development! Flies or mice are great for neural development, but not for understanding color vision or vocalization center development. Limited almost only by the ability to rear animals in the lab, one can now use butterflies or Egyptian bats to answer these previously inaccessible questions.

New Embryo Users



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The embryo is a phenomenal system for studying how genes, molecules, and cells function in vivo. Yet, their utility as experimental systems is undervalued in the biological sciences. This trend is about to change.

Over the past decade, the gap between the technical difficulties in manipulating cultured cells versus embryos has narrowed significantly. This has enabled developmental biologists to learn new insights about the embryo at a more quantitative and single-cell level. But beyond these advances in the field, many laboratories that do not focus their research in developmental biology will start to include embryos in their arsenal of experimental systems. Geneticists, biochemists, and system biologists, just to name a few, will become more eager to test their ideas in worm, fish, or mice embryos, as they routinely do in cell cultures. Therefore, having an embryo model system in these labs may soon be as common as having a variety of immortalized cell lines or a machine for gene sequencing.

These scientists may never convert into developmental biologists. But the fact that so many become new embryo users will trigger an exponential growth in embryo data. Combined with the work of developmental biologists, these new embryo users will help us to better understand how embryos form and grow.

A Genotype to Phenotype Map

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Some of the most fascinating and still poorly understood aspects of biology concern the translation of linear information in genomes (A's, C's, G's, and T's) to the formation of 3D bodies with different cell types, complex shapes, and color patterns. In other words, unraveling the genotype-phenotype map, which is the focus of developmental biology. I believe that much phenotypic complexity is derived from the reuse of modules from pre-existing gene regulatory networks, deployed in novel combinations and at different places in the body, over the course of development. If the same module of interacting genes is redeployed during development, the *cis*-regulatory regions of the internal genes in the module are also reused to drive gene expression in the different contexts. This may explain why a gene expressed in different regions of a body is often driven by the same *cis*-regulatory element. Furthermore, duplication and sub-functionalization of the original pleiotropic *cis*-regulatory element could lead to increased diversification of networks that may in part explain the large number of regulatory elements currently surrounding a typical developmental gene. Evidence for the presence of such modules and for their repeated deployment during development should leave particular signatures in genomes that need to be more formally addressed in a theory of development in the future.

Teaming with Microbes

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In the laboratory, progeny are perfect in their uniformity, developing with stereotyped precision like cars rolling off an assembly line. But conveyor belt conformity is not the norm in nature. The future of developmental biology will embrace individual variation and delve into its origins at the interface between genomes and the environment. Development builds bodies for the real world. Plasticity in developmental programs is a design feature for adapting to fluctuating environments. The density of an animal's capillaries tell its history of oxygen exposure, the connectivity of its visual cortex reflects its perceptual experiences, and its genome is gnarled with epigenetic marks of its forbearers' sagas of stress and deprivation.

Microbes are ubiquitous and intimate associates of all multicellular organisms that serve as exquisitely perceptive informants on a host's current environment and oracles of times ahead. Microbial metabolic byproducts reflect nutritional resources, and palettes of microbial molecules depict possible future infections. Microbes are not just passive inhabitants but active architects of their host environments, using sophisticated tools like bacterial toxins and mutualism factors to shape their homes. Perturbed microbiomes are a feature of the baffling surge in human diseases of maladaptation: excessive energy hoarding, over-reaction to allergens, and altered sensitivity to sensory stimuli. Understanding developmental programs in the context of confusing microbial cues is likely to hold the key to this mystery.

Toward Precision Engineering

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Embryonic development is extraordinary. Understanding the transformation of a fertilized egg promises to explain how tissues are fashioned and maintained; what goes wrong in conditions ranging from congenital disorders to cancer; and how damaged and dysfunctional organs might be repaired. From its roots in nineteenth century experimental embryology to the successes of developmental genetics, new techniques and technologies have propelled the field. The questions are clear: how are signaling and gene activity controlled, how does this determine cell function, how are tissues shaped and organized from these cells. Today, the answers are beginning to take us beyond static and qualitative explanations towards a dynamic and quantitative understanding. New imaging technology, systems level 'omics analyses, and precision genetic engineering are being coupled with novel in vitro models of development based on differentiating stem cells—including human stem cells. These are providing unprecedented insight and stimulating collaborations with physicists, computer scientists, and engineers. We can look forward to bridging scales from molecules to cells to tissues and understanding the principles behind cellular decisions and tissue assembly, as well as the accuracy and reproducibility of these processes. This knowledge will lay the foundations for regenerative medicine and precision tissue engineering.