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The Importance of Being Specified: Cell Fate Decisions and Their Role in Cell Biology

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Here is a modification of Lewis Wolpert’s famous “gastrulation” quote: “It is not birth, movement, or death, but specification, which is truly the most important decision in a cell’s life.”

There is no other decision that will define the biology of a cell to the extent of its identity. The choice of a cell’s fate affects all aspects of its behavior, defining a cell’s morphology, migratory status, and proliferation and the competence to do a range of specific functions associated with its differentiated state. Liver cells are specialized for detoxification, muscle cells for contraction, neurons for electrical activity, and white blood cells for immunity—each function requiring specific cellular properties, including a cell’s shape, size, and choice of neighbors. Because most cell types gain their identity during development, cell fate specification has mainly been addressed as a developmental biology problem; however, it’s also an integral part of cell biology.

Cell fate decisions are generated through asymmetric cell divisions in cases where there is a fixed cell lineage (Bertrand and Hobert, 2010) or through the action of inductive cues from surrounding tissues, which signal to a field of pluripotent cells (Frasch, 1999; Furlong, 2004). The acquisition of a specific cell identity in both cases requires the progressive restriction of cell fates, where a cell transitions from one regulatory state to another, often more restricted, state. Cell fate specification, and ultimately the characteristics that give a cell its identity, are thereby governed by a regulatory network of specific transcription factors (TFs) that include the effectors of cell signaling cascades and a large number of lineage-inducing TFs. Despite the substantial progress in understanding how cell fate decisions are established, how a cell’s identity imparts the morphological characteristics of a cell remains very poorly understood. This interface is being addressed from two directions; moving from the cell toward its regulatory network by using digital imaging and going from the regulatory network toward the cell’s behavior by using genomics.

Recent advances in high-resolution live imaging have made it feasible to follow single cells during embryonic development, facilitating complete cell lineage fate maps during a tissue’s, or eventually during an entire embryo’s, development (Keller et al., 2008; Olivier et al., 2010). High-resolution microscopy also has enabled the measurement of single cell characteristics, such as cell volume, shape, migration rates, trajectories, extensions, and contacts within the context of a developing embryo (Tassy et al., 2006; Solon et al., 2009). This approach thereby facilitates a quantitative phenotypic readout of a cell’s state. Complementing these digital threedimensional models of cells, tissues, or embryos with a gene expression signature map is one approach to move toward the regulatory network defining a cell’s characteristics. Here, a digital embryo (or tissue) is generated from high-resolution fluorescent in situ hybridization images that are registered and averaged from multiple embryos at the same stage in development (Pereanu and Hartenstein, 2004; Tassy et al., 2010). This virtual embryo is then used as a template for in silico multiplex in situ hybridizations, where the expression patterns of hundreds, and in theory thousands, of genes can be overlaid on top of each other (Fowlkes et al., 2008). Although these efforts are still far from obtaining a complete picture of the transcriptional status of a cell at any given stage of development, they provide information at a single (although averaged) cell resolution in its native in vivo context.

A complementary strategy is to use genomic approaches to construct a regulatory network defining the transition state of a cell and directly measure the downstream transcriptional cascade, or effector molecules that impart a cell with its specific characteristics (Sandmann et al., 2006, 2007; Jakobsen et al., 2007). Integrating information on TF occupancy, chromatin status, gene expression levels, and mutant analysis will not only yield a comprehensive picture of all genes that are expressed within a cell at any given time, but also uncover the regulatory network controlling their expression. To reach this goal, it is essential to obtain cell type–specific information on TF occupancy and gene activity in the context of a multicellular embryo, which is a current...
major challenge that is only beginning to be addressed. The advantage, however, is sensitivity and completeness where information is generated over the entire genome, even if a transcript is not annotated, which is important for modeling network activity. Next generation sequencing (NGS) and its future descendants hold the promise to dramatically advance the field, as they will provide unparalleled sensitivity and importantly quantitative information about transcript levels, which is currently very difficult to achieve by in situ hybridization. Combining approaches that facilitate the isolation of single cells (Kamme et al., 2004; Deal and Henikoff, 2010) with NGS should provide a very powerful genomewide approach that is highly sensitive, quantitative, and at a single-cell resolution (Tang et al., 2010). Similar advances in proteomics complement these efforts, where it is now possible to quantitate the levels of a selected set of proteins at a given cell state (Domon and Aebersold, 2010) or to measure dynamic changes in protein composition as a cell transitions to a differentiated state.

Because there are many cell types and possible states, we are only beginning to measure all their cellular characteristics and to generate cell type–specific regulatory networks. However, as the methods are mainly in place, let’s assume that we will have this level of information for at least the major states of a given cell type during the next decade. The future big challenge then becomes how to bridge these two levels of information. What is the interface between the genetic transcriptional program that gives rise to a differentiated cell and its end state, the cell’s morphological characteristics? Tackling this issue is a formidable challenge, and it is currently not at all clear how to do this. The problem may be made simpler from the network perspective. Gene regulatory networks are structured, where subroutines within the network process certain traits. Genes involved in specific processes tend to be coregulated in batteries; therefore the network can be simplified by looking at the activity of functional modules at a coarse grain level, such as “cell migration” or “cell adhesion.” This approach is akin to what has been applied to cell signaling cascades where the activity of few molecules at critical positions within the pathway are used as a read-out for the flow of information through the system. It remains to be determined whether a similar approach will work in global regulatory networks, given their inherent complexity and scale and the high degree of cross-regulation. What is clear however is that bridging this classic genotype to phenotype gap within the context of a multicellular organism is an enormous problem that must be addressed from multiple disciplines, and here cell biologists will play an essential role.

REFERENCES


