



Stem cells offer biologists the chance to unpick the molecular differences that define cell types.

Beyond HeLa cells

To find out what distinguishes one cell type from another, cell biologists must renounce popular cell lines, argue **Anthony H. Hyman** and **Kai Simons**.

In 1896, E. B. Wilson defined the cell as the basis of the life of all organisms. Subsequent discoveries in enzymology and molecular biology demonstrated the unity of life: the basic machinery is similar in all cells, giving rise to Jacques Monod's famous dictum that what is true for *Escherichia coli* is also true for an elephant.

This understanding would have been impossible without the use of single-celled organisms and animal and human cell lines that will grow indefinitely in culture. The most famous of these is the continuously dividing HeLa line, derived from the cervical cancer cells of a woman named Henrietta Lacks. More than 65,000 scientific studies using HeLa cells have been published since the 1950s, and the cells have been used to study every conceivable aspect of cell physiology as well as the basic machinery common to all cells.

However, cancer cells, such as those from which the HeLa line was derived, have a physiology far removed from that of normal cells in tissue, where cells interact with and receive signals from other cells nearby. Furthermore, HeLa cells cannot tell researchers anything about what distinguishes one cell type from another — a liver cell from a pancreatic cell, for instance. So, although HeLa cells and other immortal cells derived from cancer patients are good

for investigating what cells have in common, they are completely inadequate for addressing the next big topic in cell biology: cellular diversity in normal tissue. In other words, how do cells' DNA, RNA and proteins act together to specify the properties of different cell types? To answer this question, we need to make the difficult transition to a new research tool in cell biology: stem cells.

Cytologists can look at a cell under the microscope and give it a label, but they do so on the grounds of its morphology — its external shape and the appearance of its internal structures, for instance. On this basis, we assign labels such as 'pyramidal cells', 'medium spiny neurons' or 'cuboidal epithelial cells'. But this is a crude approach, akin to how microbial species were defined before the invention of DNA sequencing. What really distinguishes one cell type from another is how the various molecular elements function and interact.

Understanding the molecular basis of cell identity has important medical implications. Pathologists generally define the type of cancer by cell morphology. But cancer genomics projects are showing that each type of cancer is very diverse: patterns of mutation in tumours of the same organ have little in common in different individuals. The literature is full of cases in which, for example, scientists believed they

were studying a breast-cancer cell line that turned out to be derived from melanoma cells instead. Only a molecular understanding of why cells look and behave differently will allow unambiguous definition of both normal and altered cell types.

One way to achieve this is to move away from immortalized tissue-culture cells; the days of HeLa cells are over. Instead, cell biologists should use embryonic stem cells derived from mice or other model organisms, or convert differentiated cells into precursors using a cocktail of transcription factors, and study in detail how these cells become various cell types.

At the moment, stem-cell research is heavily driven by the hope of new therapies that can replace malfunctioning cells in our body. To expand the field, cell and stem-cell biologists need to work together to derive, maintain and differentiate cell lines representing different cell types, and to use modern imaging and other methods in the cell biologist's tool-kit to study these cells. Just as developmental biology was transformed by insights and approaches from cell biology, it will be crucial to introduce those same approaches into stem-cell biology.

The movement of cell biologists into stem-cell biology will also aid attempts to harness the healing potential of stem cells in medicine. Currently, stem-cell research relies heavily on transcription factors to differentiate and to identify cells, because different cell types express different transcription factors. But this characterization is too narrow; cell identity encompasses more than a handful of transcriptional networks. If cell biologists could uncover the molecular machinery that distinguishes different cell types, this would make stem-cell research safer. To avoid the catastrophes of the early days of gene therapy, in which genetic modifications induced cancer, we must understand the cell biology of the cells that will be reintroduced. Do they really function as normal counterparts in our body? Or could they potentially turn into cancer cells in their new environment?

A switch from cell lines such as HeLa, which are simple to grow and maintain, to stem cells, which require more precise conditions, will be difficult. Consequently, funding organizations must develop standardized protocols and other tools that make it easier to produce the plethora of different cells that we need to study. In the 1960s, agencies dedicated funds to establish the first techniques that maintained cells in culture — it is time for a new technological breakthrough. ■

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