Flexible arrangement

Cell plasticity

Elucidation of all of the mechanisms that regulate developmental potential will allow us to discover the true limits of cell differentiation.

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Until recently it was generally thought that cells move forwards along their respective differentiation paths, but never backwards, and certainly do not jump from one path to another. This dogma of unidirectional, hierarchical cell lineages in tissue development, maintenance and repair is explained by the action of irreversible gene restrictions. As cells differentiate in a lineage, genes that might be required for other pathways are irreversibly repressed.

However, exceptions to the loss of plasticity associated with such lineage restrictions have long been recognized in disease and repair. For example, the epithelium that lines the lungs of smokers is often seen to change from simple columnar cells to a stratifed configuration (a process called squamous metaplasia), and bone can be formed in injured skeletal muscle (osseous metaplasia). Experimentally, heterokaryons, which are created by transferring a nucleus from a cell of one type into a cell of a different type, show changes in nuclear gene expression that reflect the character of the host cell, demonstrating that differentiation is an actively maintained, dynamic state rather than a one-way street.

With the blossoming of stem-cell research, demonstrations of heretofore implausible genomic plasticity are now published almost weekly. Many reports describe the derivation of cells of several tissues from a single source population. Although the mechanisms of genomic plasticity remain poorly understood, the presence of plasticity suggests that gene-restriction mechanisms are not irreversible after all.

Four plasticity pathways have been documented *in vivo* and experimentally. These pathways may involve undifferentiated cells, situated within specialized tissues, that can switch developmental programmes in response to injury. In the liver, for example, the tiniest cells lining the bile duct are 'bipotent' — they can regenerate either hepatocytes or other, larger bile-duct-lining cells in the face of injury. If tissues contain truly totipotent cells, these cells might be 'embryonic rests' persisting in adult tissues long after embryonic development is completed. Another possibility is that differentiated cell types may 'de-differentiate' to an earlier, progenitor phenotype. This process is probably more common in neoplasia, particularly malignancy. Alternatively, differentiative leaps can be induced by experimental manipulation or, *in vivo*, in response to injury. Thus, cells of differentiated phenotypes can have wide developmental ranges, and are not confined to the tissues from which they are derived. In such 'transdifferentiation' events, the influence of microenvironment, perhaps through changes in response to injury, would be key. Finally, fusion between cells in some injury models can lead to reprogramming of nuclei, similar to that seen in *in vitro* heterokaryon experiments.

The most dramatic demonstrations of nuclear plasticity have been provided by the birth of offspring after the transfer of nuclei from adult somatic cells — the most famous case being Dolly the sheep. This process depends on the reprogramming of the transplanted nucleus by factors in the egg's cytoplasm. Although offspring have so far been obtained with a variety of donor cells in seven mammalian species, the process is very inefficient: less than 5% of embryos survive to adulthood, signifying a failure to 'reset' most somatic nuclei. Oocytes evolved to bring together nuclei packed in oocyte and sperm proteins, respectively, and to establish appropriate chromatin structure for normal development. It is no surprise, then, that their cytoplasm is unable to remodel efficiently the transferred nuclei that are organized for an alternative pattern of gene expression.

However, it is clear that at least two nuclear transcription factors, called Oct-4 and Nanog, have some ability to restore embryonic-like plasticity to mature adult cells. It is likely that at least some of the cytoplasmic reconditioning of nuclei — as seen in experiments involving cloning, heterokaryon/cell fusion, or reprogramming by administration of cytoplasmic extracts — may work through induction of these nuclear factors.

Molecular mechanisms of gene repression are the barriers over which adult cells must leap to become plastic. Such repression can arise from direct molecular modifications of DNA, such as methylation of cytosine residues in clustered C–G pairs near promoter sites, which usually suppresses the associated gene. It can also result from methylation and/or deacetylation of histone proteins, around which the DNA is coiled, forming 'heterochromatin' regions that are unavailable for transcription. Furthermore, such regions are often topographically located at points of attachment to other structures within the nucleus, providing exceptionally stable, if not actually rigid, three-dimensional structures. This conformation then leaves other regions (euchromatin) flexible and exposed to factors that can initiate transcription.

While these mechanisms of gene restriction serve to explain cell lineages that appear, at the grossest level of examination, to be unidirectional and hierarchical, several researchers are now demonstrating physiological mechanisms for their reversal. For example, passive reversal of DNA methylation can occur during gene replication when cytosine residues of the newly formed DNA strand are left unmethylated. Methylation must also therefore be actively maintained; if it is not, de-repression will occur. Demethylases are also responsible for the active demethylation of both methylated cytosines and some methylated histones. Tissue- and cell-specific histone acetyltransferases have been identified — these molecules allow heterochromatin and euchromatin domains to shift, resulting in de-repression of tissue-specific genes.

Elucidation of all of the mechanisms that regulate developmental potential will allow us to discover the true limits of cell plasticity. Progress will depend upon studies and manipulation of both the extra- and intracellular factors that influence the fate of cells. Furthermore, exploration of likely overlapping mechanisms between genetic de-repression in cloning and adult-plasticity experiments, as well as the mechanisms that maintain unrepressed gene states in embryonic stem cells, may be particularly fruitful. The rewards for this research will be a far better understanding of developmental mechanisms, and important new opportunities to derive cells of specific phenotypes for research and medicine. ■

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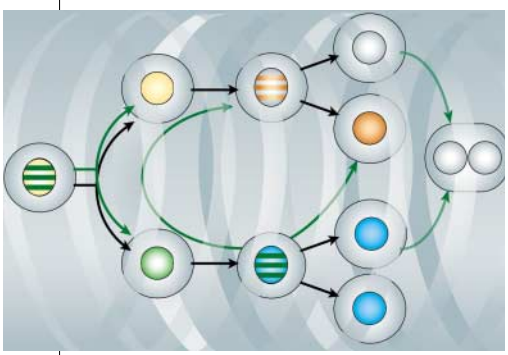

The winding road: cell differentiation involves more than a simple one-way progression.

FURTHER READING

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