A twist of fate

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It has long been known that sperm and eggs fuse together selectively, and not randomly with any other cell type. Some viruses, which are among the most primitive of organisms, express fusion proteins that allow them to penetrate mammalian cells. Furthermore, cells transformed by polyoma virus have been found to fuse spontaneously with other cells *in vivo*. Damaged muscle fibres — cells that each contain hundreds of nuclei — are repaired by the fusion into each cell of single-nucleus, undifferentiated cells (myoblasts). Thus, fusion has long been known to hold advantages for specialized cell types and primitive organisms. But it was a great surprise to learn that 'stem cells' derived from adults, rather than from developing tissue, might use fusion as a mechanism to change their fate.

Recent findings in tissue culture, showing that embryonic stem cells can fuse either with the precursors of neuronal cells or with adult bone-marrow cells, have initiated a new and important debate. As these experiments were carried out in culture with strong selective pressure, rather than under more natural *in vivo* conditions, some technical objections remain to be addressed. Nonetheless, these studies have spawned the new and important idea that fusion could be a significant means by which some cells might be 'reprogrammed' for a different function in adulthood.

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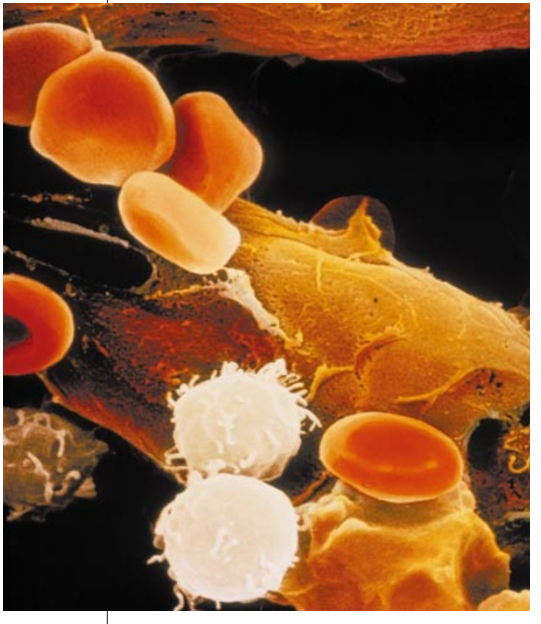

Could cells from bone marrow (brown), such as blood cells, be engineered for use in gene therapy?

One can envision several mechanisms that might cause adult bone-marrow-derived cells (stem cells) to change their morphology and activate new genes. The new work suggests that cell fusion could constitute one such mechanism. As a result, numerous earlier reports claiming that stem cells can activate previously silent genes, characteristic of a different cell type within diverse tissues, are now being questioned. Although it seems likely that some of the recently observed results reflect completely new changes in the fate of cells originally destined for some other function, others may merely be due to cell fusion.

But is there also something profound and exciting about the idea of 'mere' fusion? It seems quite possible that fusion of adult bone-marrow-derived cells may have an unexpected function, such as preventing cells from dying by providing a healthy and entire genetic complement. For instance, one might imagine that the highly specialized cells of tissues such as liver, brain and muscle would be difficult to form *de novo* in an adult, and might therefore be more amenable to 'rescue' through fusion.

Fusion of bone-marrow-derived cells might also serve as a means of supplying cells with new genes, such as tumour-suppressor genes, or of correcting genetically defective cells. If this proves to be possible, how exciting it will be to think that this might be a repair mechanism that continues to function throughout our lives and was also active in the lives of our evolutionary predecessors. It is possible that much more damage occurs in differentiated tissues than we imagined, because bone-marrow-derived cells gain access to the injured cells and restore them — at least up to a point. Beyond that point, when the balance between damage and repair shifts and fusion cannot cope with the demand, disease ensues.

Cell fusion has long been known to achieve effective reprogramming of cells. Almost two decades ago, my laboratory produced stable 'heterokaryons' by fusing specialized human cells of all three lineages with mouse skeletal-muscle cells to determine whether differentiation is irreversible. 'Terminal differentiation' implies a finality of fate that was, at that time, generally accepted. However, in the non-dividing multinucleate heterokaryons we produced, muscle genes were activated in primary human diploid keratinocytes, fibroblasts and hepatocytes that had no need of those genes.

Since then, others have replicated these findings in heterokaryons, using similar and different cell types. We went on to show that this reactivation of previously silent genes occurs in the absence of DNA replication. Gene dosage, or the balance of proteins derived from the two cell types, determines which genes are activated. These results overturned the dogma that differentiation is fixed and irreversible, and showed that the phenotype of a differentiated cell is plastic, dynamic and determined by the balance of regulators at any given time.

These discoveries of genetic reprogramming in different cell systems redefined how differentiation was viewed — as an active rather than passive process. The exciting possibility that heterokaryons can exist *in vivo* is an extension of these findings that may soon be demonstrated in reality. Understanding the underlying mechanism of this process would not only be of great fundamental interest, but also should allow increased efficiency of fusion, which could lead, for example, to the rescue of muscle cells in muscular dystrophies, diseases for which there still is no cure, despite the fact that for some types of dystrophy a gene has been cloned.

Once the signals and underlying mechanisms are better understood, adult bone-marrow-derived cells could be genetically engineered to deliver genes to specific targets, giving rise to a new form of gene therapy. The prospect of heterokaryons that occur naturally in humans is therefore a matter of wonder, a feast for the imagination. The fusion that takes place when sperm meets egg, the beginning of organismic life, may also underlie a process of repair in adulthood that helps to maintain life. As the poet Robert Browning wrote: "Come grow old with me! The best is yet to be." ■

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Stem-cell fusion

The possibility has emerged that fusion could be a significant means by which cells might be 'reprogrammed' for a different function in adulthood.

FURTHER READING

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