

the gene, or defects at a different, but related, genetic locus. It is of interest that, for an unknown reason, BMI is increased in those patients with muscular hypertrophy. This finding is in contrast with the frequency of low to low-normal BMI values in children with ISS. A recent report¹ showed that similar stimulation of growth was obtained in ISS with SHOX insufficiency and in a group of girls with Turner syndrome who received growth

hormone treatment of 50 µg/kg/day. This study also showed the importance of carefully analyzed familial histories using clinical scoring and radiographic examination of the forearm and hand.

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Reference

1. Blum WF, Crowe BJ, Quigley CA, et al. J Clin Endocrinol Metab. 2007;92:219-28.

Stem Cells: A New Kind of Breakthrough

Stem cells have received much attention in recent years because of their potential to regenerate damaged and diseased tissues. Two types of stem cells have been distinguished historically—embryonic stem cells (ESC) and adult stem cells. Because of the potential to differentiate into any cell type, pluripotentiality, the former have more potential in regenerative medicine than the latter. In fact, this principle is illustrated well in knock-in and knock-out mice in which new mouse strains are generated from ESC into which mutations have been introduced. However, serious ethical issues are raised in human ESC research since until now, they could only be obtained from human embryos. Moreover, if this technology is to be applied to adult disease, sometimes referred to as custom transplantation therapy, means must be developed to produce cells equivalent to ESC from the patient needing treatment, which has raised controversial issues of human cloning with its own set of ethical concerns. Attempts to convert easily accessible cells such as fibroblasts to ESC-like cells have been unsuccessful until now. But 3 papers have recently been published which signal a major breakthrough in the field.

The recent story starts with the realization that converting somatic cells to ESC-like cells requires nuclear or epigenetic reprogramming of the cells, ie, resetting of DNA methylation, histone modification and chromatin structure, to that of ESC. Last year a Japanese group headed by Yamanaka¹ generated ESC-like cells from mouse embryonic fibroblasts by expressing 4 transcription factors (Oct3/4, Sox2, c-myc and Klf 4) and subsequently selecting cells that expressed another transcription factor, Fbx15. The concept was that the 4 transcription factors would trigger expression of genes highlighted by Fbx15 that induced the pluripotent state, and the cells were termed induced pluripotent stem cells or iPS cells. While these cells exhibited many stem cell properties, they were not fully reprogrammed epigenetically and did not produce chimeras when injected into mouse embryos. Chimeras are mice containing cells from the recipient mouse embryo and cells from a donor source—iPS cells in this case.

Technical modifications have now led to a second generation of mouse iPS cells with properties that more closely approximate those of ESC, including the ability to produce chimeras in the next generation of mice. The work was reported by Okita et al, Wernig et al and

Maherali et al. Although each group differed in certain methodologic details, their common protocol started as before, but utilized different transcription factors—Nanog and Oct4—to identify and isolate iPS cells.

The second generation iPS cells possessed an epigenetic signature remarkably similar to ESC; they differentiated into cells of different lineages and germ layers and all 3 groups were able to establish chimeras and in 2 cases germ-line transmission in the next generation, the most stringent evidence of developmental potency.

Two concerns were raised relative to the potential use of this technology in humans. One is the development of tumors in nearly 15% of mice derived from iPS cells. This risk was attributed to expression of c-myc, which is a known oncogene and possibly reactivation of its expression at a later time. The second and related issue is the use of retroviral vectors to introduce the transcription factors that trigger nuclear reprogramming. They may predispose to oncogenesis through insertional mutagenesis as well. However, one of the conclusions from the studies is that the triggering mechanism may require only transient expression of the transcription factors, ie, once initiated, reprogramming may drive itself. If so, then transient expression, perhaps by using adenoviral vectors with less risk of problems, may suffice. All groups acknowledge that application of this technology to humans is still some time away.

Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. Nature. 2007 [epub ahead of print].

Wernig M, Meissner A, Foreman R, et al. In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state. Nature. 2007 [epub ahead of print].

Maherali N, Sridharan R, Xie W, et al. Directly reprogrammed fibroblasts show global epigenetic remodeling and widespread tissue contribution. Cell Stem Cell. 2007;1:55-70.

Editor's Comment: *These reports are very encouraging and give regenerative medicine a major boost.² But as stated repeatedly, more research will be needed to translate this breakthrough to the clinic. Nevertheless, the findings and especially that the three groups are able to confirm each other's results are very exciting.*

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References

1. Takahashi K, Yamanaka S. Cell. 2006;126:663-76.
2. Cyranoski D. Nature. 2007;447:618-9.