Meeting report

# Stem cells in the genomic age

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A report on the 2006 Joint Spring Meeting of the British Society for Developmental Biology and the British Society for Cell Biology, York, UK, 20-23 March 2006.

Stem cells span the divide between cell biology and developmental biology, and so were an especially appropriate subject for the recent joint meeting of the British Society for Developmental Biology (BSDB) and the British Society for Cell Biology (BSCB) this spring. Speakers from around the world explored this fascinating topic from a wide variety of perspectives and it was particularly interesting to see how new and emerging technologies are being used to uncover some of the mysteries of cell-fate determination.

## A new look at old model systems

Cheryll Tickle (University of Dundee, UK) opened the meeting by telling us that the chick, which has been a model system for embryology since the time of Aristotle, is now entering the genomic age. The chicken genome sequence was published a year ago, and chick DNA microarrays are just now becoming available. Tickle exemplified the power of combining these new genetic tools with the more traditional strengths of the chick embryo in the analysis of the spontaneous mutant *Talpid3*. Talpid3 protein appears to be required specifically at sites of signaling by the Sonic hedgehog (Shh) protein, and experimental manipulation of Shh availability confirms a failure to respond properly to Shh in this mutant. Tickle outlined how Dave Burt and colleagues at the Roslin Institute have isolated the *Talpid3* gene by positional cloning but the sequence gives no real clue as to the gene's function. The mechanism by which Talpid3 interacts with the Shh pathway is thus still under investigation.

The theme of using traditional model systems in novel ways was continued by Ethan Bier (University of California at San Diego, La Jolla, USA). The fruit fly *Drosophila* is a powerful tool for genetic analysis that has revealed many general principles of developmental patterning. Bier convinced us that flies are also surprisingly efficient tools for understanding the genetic basis of human disease. He pointed out that of the 2,500 or so genes that have been linked to human diseases, around three-quarters have counterparts in the fly. He then described a myriad of ways in which flies can be exploited to yield important insights into these diseases. For example, a disease gene of unknown function can readily be placed in a particular signaling pathway, such as those triggered by Notch, Hedgehog, or transforming growth factor-β, thanks to the fact that mutations in the pathways give characteristic phenotypes in the fly's wing. He also explained how standard screens for suppressors or enhancers could identify the *Drosophila* equivalents of 'human modifier loci', loci that give clues as to why particular human populations are especially resistant, or susceptible, to certain diseases.

## Stem-cell lineage commitment

Murine embryonic stem (ES) cells provide a powerful model system. If we are to use these cells to investigate the mechanisms of lineage commitment we need to be able to identify and isolate cells at early commitment stages, and this is often a major factor limiting progress in the field. Both Gordon Keller (Mount Sinai School of Medicine, New York, USA) and Shinichi Nishikawa (Riken Centre for Developmental Biology, Kobe, Japan) are tackling this problem by developing reporter cell lines in which fluorescent proteins or cell-surface tags are expressed under the control of the regulatory elements of genes that mark first stages of early mesoderm and endoderm differentiation. Keller used his genetic reporters to show that the signal proteins activin and Wnt cooperate in a dose-dependent manner to induce populations of mesoderm or mesendoderm cells (mesendoderm can develop into either mesoderm or endoderm). He then used the same genetic markers to isolate these subpopulations and succeeded in guiding their differentiation further using a variety of growth factors to generate particular mesodermal

cell types such as blood, or endodermal cell types such as liver.

Nishikawa also described an activin-based protocol for generating endoderm progenitors from ES cells, this time based on monolayer culture of ES cells, rather than suspension culture (suspension culture leads to the formation of cell aggregrates called embryoid bodies). He reported the transcriptional profiling of early endoderm and mesoderm populations, isolated using the genetic-reporter cell lines and cell-surface markers developed in his group. This, he told us, is just the beginning of an ambitious and far-reaching transcriptional profiling project. As other labs around the world develop reporter lines for their favorite cell types, Nishikawa hopes to incorporate these into his analysis. The result will be a huge database containing transcriptional profiles of many cell types at different stages of differentiation and commitment. Key regulators could then be identified according to their characteristic expression profile. For example, *Arid3b* has already been identified as a gene in mice that becomes expressed as ES cells generate mesenchyme (loosely organized tissue), and this gene also turns out to be required for the generation of mesenchyme by neural crest cells. Nishikawa's group is developing optimized bioinformatic tools for the formidable task of analyzing their ever-expanding dataset, and also tools for relatively high-throughput functional analysis of candidate gene regulators, such as a retrovirus-delivered short hairpin RNA (shRNA) system for RNA interference (RNAi). The power of this approach comes from feeding back information from the microarray and functional analysis to develop improved differentiation protocols and specification markers (Figure 1).

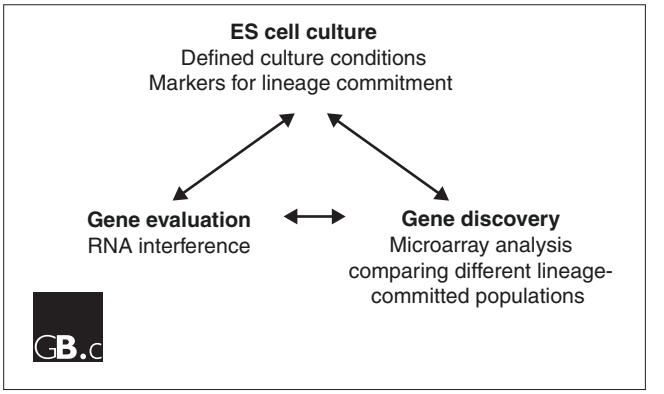


**Figure 1**
An iterative approach to investigating the mechanisms of lineage specification of ES cells. Information obtained from functional studies and microarray analysis can be used to identify specification markers and improve differentiation protocols.

## Reprogramming for pluripotency

Austin Smith (Institute for Stem Cell Research, Edinburgh, UK) has developed similar genetic reporter lines for investigating the question of how ES cells commit to the neural lineage. He turned this question on its head by asking how somatic cells such as neural stem cells can become reprogrammed to a pluripotent ES-cell-like state (that is a state in which they can give rise to all embryonic cell types). Although we know that somatic nuclei can become reprogrammed when transferred into an oocyte or fused with an ES cell, the underlying mechanisms remain obscure. Using the ES fusion system, Smith has found an unexpected role for the homeodomain-containing protein Nanog in this process. By boosting levels of Nanog it is possible to increase the efficiency of nuclear reprogramming up to 100-fold in cell fusions between ES cells and neural stem cells, and further experiments demonstrate that Nanog is in fact a key limiting factor for establishment of pluripotency in cell hybrids.

Takashi Shinohara (University of Kyoto, Japan) continued with the theme of reacquiring pluripotency. Some years ago he developed methods for long-term culture of spermatogonial cells that can generate functional sperm after transplantation into mouse testis. These cells are normally restricted to spermatogenesis but Shinohara observed that occasionally they give rise in culture to a pluripotent cell type that could contribute to germline chimeras after transplantation into a mouse blastocyst, and so can be considered to be equivalent to a blastocyst-derived ES cell. He reported that these pluripotent cells can be derived at low frequency from neonatal spermatogonial cultures of wild-type mice, and that this frequency is significantly increased in a p53-mutant background.

One key difference between germ cells and ES cells is their epigenetic imprint status. Shinohara reported that while the spermatagonial cells retain a stable androgenic imprint over long-term culture, the pluripotent cells derived from them have a somewhat less stable imprint. They do, however, still retain some germline-specific imprinting. So far, this is the only discernable difference between the germline-derived pluripotent cells and blastocyst-derived pluripotent cells and it will be interesting to explore its implications, if any. One of the practical consequences of the culture and clonal selection of spermatogonical cells is that it allows for the generation of gene-targeted offspring without using ES cells. Rats are a much better model system than mice in certain fields, particularly neuroscience, and progress has been greatly hampered by our inability to derive rat ES cells. Shinohara hinted that he was making progress in applying his findings to the rat.

Finally, Tariq Enver (University of Oxford, UK) described a mathematical model, developed in collaboration with Sui Huang (Harvard University, Boston, USA), which explains how cross-repression and autoregulation of key transcription factors could maintain a stable stem-cell-type state. He has also carried out microarray analysis of hematopoietic

stem cells, following the changes in their transcriptional profile as they escape from the stem-cell state and commit to differentiation. When two cells chose different fates they must of course diverge at some point in their transcriptional profile, but, interestingly, Enver found that this does not happen immediately - they initially travel together, undergoing the same transcriptional changes for the first 24 hours. This implies that there is a common transcriptional program for 'loss of potency' that can be uncoupled from lineage-specific differentiation programs. One gene, *Nov*, which is downregulated as cells journey towards commitment, was functionally tested through gain- and loss-of-function, and did indeed fit the criteria of a key regulator of the undifferentiated stem-cell state.

Developmental biology and cell biology have been transformed in recent years, not only by new technologies but also by the creativity with which these powerful tools have been used. As the pace continues to increase, we can look forward to exciting times ahead.

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