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Current Opinion in Genetics & Development

Cell reprogramming

Editorial overview

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Current Opinion in Genetics & Development 2012, **22**:401–402

For a complete overview see the Issue

0959-437X/$ – see front matter,

http://dx.doi.org/10.1016/j.gde.2012.10.001

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Martin Pera is the Program Leader of Stem Cells Australia. He has over 25 years experience in human pluripotent stem cell research and has authored over 100 peer reviewed publications. Pera was among a small number of researchers who pioneered the isolation and characterisation of pluripotent stem cells from human germ cell tumours of the testis, work that provided an important framework for the development of human embryonic stem cells.

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Kathrin Plath earned her doctorate degree in cell biology from Humboldt University and carried out her postdoctoral training at UCSF and the Whitehead Institute. Currently, she is Associate Professor in the Department of Biological Chemistry at UCLA. Her research focuses on mechanisms underlying the establishment and maintenance of pluripotency.

Cellular reprogramming, broadly defined as the re-specification of cell fate through natural or experimental means, has been studied in a number of diverse biological contexts for over half a century. The recent discovery of the induction of pluripotency through reprogramming by defined factors [1] has led to an explosion of interest in the plasticity of the differentiated state, and in the potential for the application of cell reprogramming in research and medicine. This issue examines the current state of knowledge of cellular reprogramming, from basic biological studies in model systems through to its application in the study of human disease. Our contributors cover not only the induction of pluripotency in mammalian cells, but also a fascinating range of examples of cellular reprogramming across animal phyla.

From a mechanistic viewpoint, reprogramming of a terminally differentiated cell to the pluripotent state certainly represents one of the most dramatic experimental examples of redirection of cell fate. And, because pluripotent stem cells provide an indefinitely renewable source of normal human cells for research and medicine, they are also the focus of much applied research. Gokhale and Andrews survey the origins and history of the study of pluripotent stem cells in the mouse and human. They point out the seminal role that experimental studies of teratocarcinoma played in shaping concepts of cancer stem cells, cell differentiation, and pluripotency and illustrate how these concepts relate to current concerns about the safety of pluripotent stem cell based cell therapy. This historical overview is followed by several commentaries on the molecular mechanisms involved in reprogramming to pluripotency. Gifford and Meissner discuss the considerable epigenetic barriers that must be overcome to return a cell to the pluripotent state, with a focus on chromatin remodeling events and consider the possibility that the reprogramming factors act as pioneer transcription factors in reconfiguring chromatin. Adachi and Schöler examine the role of transcription factors in reprogramming, and how regulatory networks are switched on and off in the process. Esteban et al. discuss the cell biology of a mesenchymal to epithelial transition, which is critical to conversion of fibroblast to induced pluripotent stem cell. The authors speculate that the mesenchymal to epithelial transition might play an important role in driving the epigenetic plasticity required for reprogramming.

While it is clear that differentiated cells of diverse phenotype can be converted to pluripotency, there are many practical issues that confront those wishing to apply this technology to disease modeling or to therapy. Since the first report of the induction of pluripotency by defined factors, a key question has been whether induced pluripotent stem cells are indeed biologically equivalent to pluripotent stem cell lines derived from embryos. Addressing this issue, Lowry concludes that while differences between the two cell types have been described, in the not too distant future it will be

possible to create reprogrammed cell lines that are essentially identical to embryonic stem cells. Rapid technical advances in the methodology for reprogramming promise soon to overcome the problems associated with low reprogramming efficiency and the need for genetic modification that initially presented barriers to its widespread application. Hussein and Nagy survey the state of the art of reprogramming technology, and draw attention to the importance of the stoichiometry of reprogramming factors in the cell and manipulation of the global chromatin landscape. For therapeutic applications in particular, it is important that cells and tissues derived from pluripotent stem cells be free of mutations that could cause neoplastic transformation or other unwanted phenotypes. Ronen and Benvenisty examine current knowledge concerning genetic stability and mutations in induced pluripotent stem cells, and, in commenting on a controversial area in the field, they conclude that the reprogramming process itself can indeed induce mutations into induced pluripotent stem cell lines.

Although much recent work focuses on reprogramming to pluripotency by defined factors, there are many examples of cellular reprogramming in various model systems and in pathological states that provide us with important insight into the stability of cell fate specification and differentiation. Narbonne et al. review research on somatic cell nuclear transfer, the gold standard for reprogramming to pluripotency. These authors suggest that interspecies nuclear transfer, though controversial from a bioethics perspective, might represent an invaluable tool to overcome some of the roadblocks facing application of the technique in the human. Historically, studies of cell fusion provided much insight into the regulation of cellular differentiation. Soza-Reid and Fisher focus on advances in the field of cell fusion, and argue that efficient high throughput methodology for cell fusion combined with techniques such as shRNA library screening will provide a powerful platform for mechanistic studies of reprogramming. Magnúsdóttir et al. focus on a special and dramatic example of epigenetic remodeling, the development of the germline, and consider the role of chromatin and transcriptional priming in cell fate decisions. Tursun reflects on some remarkable examples of cellular reprogramming in two powerful animal model systems, *Drosophila* and *C. elegans*, and concludes with a discussion of lineage specific barriers to cell fate transitions in these models and the means by which they may be overcome. Knapp and Tanaka ponder what lessons we can learn from studies of regeneration in lower vertebrates. While it is now clear that regeneration of appendages does not involve fundamental re-specification of cell fate, regeneration of, for example, the newt lens and the zebrafish retina certainly do, and research into these processes in fish might yield clues to means of enabling regeneration in mammals. Burke and Tosh review our understanding of a pathological process that has long been considered a classical example of reprogramming, intestinal metaplasia, the defining feature of Barretts esophagus, a fairly common disorder that can lead to esophageal carcinoma. Recent findings on the cell of origin of Barrett's esophagus cast doubt on canonical interpretation of this disorder as reprogramming of squamous epithelium to intestine.

Finally several authors report on the potential application of reprogramming in research and medicine. Onder and Daley and Trounson et al. discuss the potential uses of patient specific induced pluripotent stem cells in disease modeling, and highlight the challenges that face the field. Daley and colleagues show that disease modeling has been successful in some instances but has failed to reproduce key elements of cellular pathology in others. Trounson and colleagues point out several interesting applications of this technology to cardiac disorders, aneuploidy syndromes, and infectious disease. Finally, Lujan and Wernig highlight a different approach to therapy via cell reprogramming, the conversion of one differentiated cell type into another, in particular fibroblasts to neurons. They point out that transient introduction of pluripotency reprogramming factors into a cell can induce plasticity and yield a partially reprogrammed state that can then be directed towards a desired outcome.

Together these timely overviews of cellular reprogramming illustrate how a number of exciting developments in basic research are already impacting on the application of reprogramming to the study of human biology and to therapeutics. This snapshot of the field in 2012 suggests that we are on the verge of a revolution in our understanding of cell state transitions that will fundamentally change how we understand and treat disease.

References

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