Small steps towards the clinic

Euroepistem 2011, a multidisciplinary conference on stem cell biology and epigenetic regulation, was the second of a planned series of biennial international conferences convened by Krishnarao Appasani (GeneExpressions Inc., USA). The meeting brought together small groups of scientists from academia, the clinic and industry to present new research into the epigenetic mechanisms of stem cell regulation and potential therapeutic applications of this important field. The main themes included epigenetic regulation of gene expression by chromatin remodeling; micro-environmental and genetic factors mediating differentiation versus pluripotency; and the potential therapeutic applications of these research findings to cancer, neurological diseases and hematological disorders.

The research presented in each of these areas represented interesting and sometimes important advances; however, the most important take home message was that much more groundbreaking research is required before any potential clinical benefit of stem cell research can be realized. Of course, a small group gathering for 2 days cannot possibly cover the spectrum of topics relevant to this important field; however, even in this small venue one could not escape the reality that recent research developments in this area are largely incremental and lacking the groundbreaking progress that will be necessary to realize the therapeutic potential of stem cell research. Here, I discuss the major research findings presented and the important roadblocks to therapeutic applications highlighted by these ongoing research efforts in stem cell biology.

Abstract

A report on the Euroepistem 2011 meeting ‘Epigenomic Programming and Stem Cells for Drug Discovery’, Paris, France, 21-22 November 2011.

New insights into epigenomics and transcriptional control

Karl Ekwall (Karolinska Institute, Sweden) delivered the keynote address focusing on inherited epigenomic modifications of chromatin structure. He discussed recent findings on the role of a complex group comprising over 50 remodeling factors, called SNF2 factors, in chromatin structure. Ekwall’s laboratory has developed a genome-wide methodology for mapping nucleosome positions in *Schizosaccharomyces pombe*. These chromatin mapping studies have revealed a uniform pattern of nucleosome positioning in gene coding regions characterized by nucleosome-free regions at transcriptionally active promoters. Topoisomerase 1 activity required for nucleosome disassembly at these sites seems to be associated with chromodomain helicase DNA binding protein 1 (Chd1) and may represent an important mechanism in the epigenetic reprogramming of stem cells.

Faycal Boussouar (Institut Albert Bonniot, France) presented research on the ATPase family, AAA domain containing 2 (*ATAD2*), which is activated in many types of cancer in association with the proto-oncogene *Myc*. In embryonic stem cells (ESCs), *ATAD2* is a positively regulated target of the master pluripotency genes *Oct4* and *Nanog*. Elevated levels of *ATAD2* are observed in induced pluripotent stem cells (iPSCs) in humans and mice. Recent research has identified an *ATAD2*-dependent transcriptome in ESCs with links to *Oct4/Nanog* activity and transforming growth factor β. This research also showed that knockdown of *ATAD2* severely affected ESC growth in teratomas without affecting their capacity to differentiate, suggesting an important role in sustaining proliferation in undifferentiated cells.

New studies on the role of Repressor element-1 silencing transcription factor (REST) were presented by Angela Bithell (MRC Centre for Neurodegenerative Research, UK). Chromatin immunoprecipitation showed that REST binds to several thousand loci in epithelial stem cells and neural stem cells. In epithelial stem cells, REST binds to the promoter of several pluripotency genes, including *Nanog, Sox-2* and *Oct4*, but is not required to maintain epithelial stem cell pluripotency. However, REST knockout delays the repression of pluripotency genes in differentiated cells.

Ernst Wolvertang (Australian Institute for Bioengineering and Nanotechnology, Australia) presented research
on the effects of vitamin C (ascorbate) in culture media on chromatin remodeling, associated with a genomewide site-specific DNA methylation in human pluripotent stem cells. Ascorbate-induced transcriptome modifications were associated with the upregulation of CD30 expression, a biomarker for abnormal human ESCs. This research highlights the potential of culture media components to generate epigenetic changes in gene expression patterns in vitro, an area that needs much more attention than it currently receives.

Yuhong Fan (Georgia Institute of Technology, USA) presented research on the H1 cell line of ESCs showing extensive chromatin decondensation that correlates with decreased differentiation. She proposed a model that H1 may function to silence pluripotency genes during ESC differentiation. Christian Muchardt (Institut Pasteur, France) discussed the role of the chromatin proteins HP1 and Polycomb in the silencing of repeated DNA sequences and the induced expression of morphogenetic genes. A novel mechanism involving the citrullination of histone H3 Arg8 by peptidyl arginine deaminase 4 (PADH4) weakens the binding of HP1α, resulting in the derepression of several cytokine genes and several human endogenous retroviruses that are normally repressed by HP1 proteins. This pattern of derepression is observed in some human autoimmune diseases, including multiple sclerosis, suggesting a possible disease association.

Insights into therapeutic applications

Eric Bouhassira (Albert Einstein College of Medicine, USA) discussed potential applications of iPSCs in the treatment of hemoglobin disorders. Problems impeding their therapeutic application involve a need to develop consistent and standardized protocols for producing iPSCs without genotoxic or epigenetic changes. Better methods for therapeutic gene correction and to promote iPSC differentiation into transplantable hematopoietic cells are also needed. Significant progress has been made to produce transgene-free iPSCs using a zinc-finger strategy to correct a mutation that causes α-thalassemia (hydrops fetalis) in iPSCs. This approach restores the function of α-globin genes by inserting locus-control-region-driven globin transgenes at a specific ‘landing pad.’ The current bottleneck in this ongoing research is to produce erythroid cells with an adult phenotype for therapeutic application.

Luc Douay (Université Pierre et Marie Curie-Saint Antoine Hospital, France) presented research on progress to generate red blood cells from stem cells in vitro and to track their in vivo fate. This research has shown that cultured red blood cells can be generated in vitro from human hematopoietic stem cells, ESCs or iPSCs. The goal is to use iPSCs to generate red blood cells, as a source of a new generation of allogeneic transfusion products. Research data so far suggest that using only three human iPSC clones would be sufficient to meet the requirements of over 99% of all red blood cell transfusion patients. Areas requiring further research include choice of initial cell type, method of genetic reprogramming, clinical grade safety issues and optimization of red blood cell differentiation.

Alexandrina Burlaca (Institute of Cellular Biology and Pathology, Romania) presented another potential therapeutic application and discussed some of the problems in implementing stem cell therapy to promote myocardial regeneration. The low survival rate of transplanted cells in damaged myocardial tissue is attributed to the inflammatory conditions in the infarcted myocardium. Burlaca’s research showed that conditioned medium from endothelial progenitor cells promotes endothelial cell proliferation only after cell adhesion is induced by conditioned medium from mesenchymal stem cells. These results suggest that combining different populations of mesenchymal and endothelial stem cells, particularly in hypoxic conditions, could be used to promote angiogenesis and myocardial regeneration.

I presented an assessment of physiological components that drive morphological transformation and solid tumor progression arising from the self-propagating tumor microenvironment. These essential components are hypoxia, inflammation and altered cell redox potential. Each of them could serve as a biomarker for disease progression and each represents a preventive or therapeutic target to delay or prevent tumorigenesis.

Future perspectives

The research presented at this conference revealed some of the important bottlenecks to therapeutic application of stem cell research, which are fundamentally related to gaps in our understanding of basic stem cell biology and tissue differentiation. Among the core issues that figured most prominently were: (i) the need for a better understanding of the interplay between biomechanical and biochemical signals as global regulators of gene expression pathways; (ii) the design of new ex vivo systems to facilitate microdissection of the role of epigenetic mechanisms that recapitulate or at least approximate tissue-specific differentiation pathways in vivo; and (iii) the design of new methods for site-directed recombination to facilitate correctional gene therapy.

These are lofty goals, and the stem cell journey from bench to bedside has many miles to go, but as this conference demonstrated, each individual step moves us closer to this important destination, one that will some day transform clinical medicine.

Abbreviations

ATAD2, ATPase family, AAA domain containing 2; ESC, embryonic stem cell; HP1, heterochromatin protein 1; iPSC, induced pluripotent stem cell; REST, repressor element silencing transcription factor.
Competing interests
The author declares that they have no competing interests.

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