Journals in Science

BioScience

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Phytosequestration: Carbon Biosequestration by Plants and the Prospects of Genetic Engineering

C. Jansson et al.

Photosynthetic assimilation of atmospheric carbon dioxide by land plants offers the underpinnings for terrestrial carbon sequestration. A proportion of the carbon captured in plant biomass is partitioned to roots, where it enters the pools of soil organic carbon and soil inorganic carbon and can be sequestered for millennia. Bioenergy crops serve the dual role of providing biofuel that offsets fossil-fuel greenhouse gas emissions and sequestering carbon in the soil through extensive root systems. Carbon captured in plant biomass can also contribute to carbon sequestration through the deliberate addition of biochar to soil, wood burial, or the use of durable plant products. Increasing our understanding of plant, microbial, and soil biology, and harnessing the benefits of traditional genetics and genetic engineering will help us fully realize the greenhouse gas mitigation potential of phytosequestration.

Cell

Volume 142, Number 3
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Direct Reprogramming of Fibroblasts into Functional Cardiomyocytes by Defined Factors

M. Ieda et al.

The reprogramming of fibroblasts to induced pluripotent stem cells raises the possibility that a somatic cell could be reprogrammed to an alternative differentiated fate without first becoming a stem/progenitor cell. A large pool of fibroblasts exists in the postnatal heart, yet no single "master regulator" of direct cardiac reprogramming has been identified. Here, the authors report that a combination of three developmental transcription factors (i.e., Gata4, Mef2c, and Tbx5) rapidly and efficiently reprogrammed postnatal cardiac or dermal fibroblasts directly into differentiated cardiomyocyte-like cells. Induced cardiomyocytes expressed cardiac-specific markers, had a global gene expression profile similar to cardiomyocytes, and contracted spontaneously. Fibroblasts transplanted into mouse hearts one day after transduction of the three factors also differentiated into cardiomyocyte-like cells. The authors believe these findings demonstrate that functional cardiomyocytes can be directly reprogrammed from differentiated somatic cells by defined factors. Reprogramming of endogenous or explanted fibroblasts might provide a source of cardiomyocytes for regenerative approaches.

Cell Stem Cell

Volume 6, Number 4
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An Expanded Oct4 Interaction Network: Implications for Stem Cell Biology, Development, and Disease

M. Pardo et al.

The transcription factor Oct4 is key in embryonic stem cell identity and reprogramming.

Insight into its partners should illuminate how the pluripotent state is established and regulated. Here, the authors identify a considerably expanded set of Oct4-binding proteins in mouse embryonic stem cells. The authors find that Oct4 associates with a varied set of proteins including regulators of gene expression and modulators of Oct4 function. Half of its partners are transcriptionally regulated by Oct4 itself or other stem cell transcription factors, whereas one-third display a significant change in expression upon cell differentiation. The majority of Oct4-associated proteins studied to date show an early lethal phenotype when mutated. A fraction of the human orthologs is associated with inherited developmental disorders or causative of cancer. The Oct4 interactome provides a resource for dissecting mechanisms of Oct4 function, enlightening the basis of pluripotency and development, and identifying potential additional reprogramming factors.

An Oct4-Centered Protein Interaction Network In Embryonic Stem Cells

D. L. C. van den Berg et al.

Transcription factors, such as Oct4, are critical for establishing and maintaining pluripotent cell identity. Whereas the genomic locations of several pluripotency transcription factors have been reported, the spectrum of their interaction partners is underexplored. Here, the authors use an improved affinity protocol to purify Oct4-interacting proteins from mouse embryonic stem cells. Subsequent purification of Oct4 partners Sall4, Tcfcp2l1, Dax1, and Esrrb resulted in an Oct4 interactome of 166 proteins, including transcription factors and chromatin-modifying complexes with documented roles in self-renewal, but also many factors not previously associated with the embryonic stem cell network. The authors find that Esrrb associated with the basal transcription machinery and they also detect interactions between transcription factors and components of the TGF-β, Notch, and Wnt signaling pathways. Acute depletion of Oct4 reduced binding of Tcfcp2l1, Dax1, and Esrrb to several target genes. In conclusion, the authors' purification protocol allowed them to bring greater definition to the circuitry controlling pluripotent cell identity.

Volume 6, Number 5
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Tracing the Derivation of Embryonic Stem Cells from the Inner Cell Mass by Single-Cell RNA-Seq Analysis

F. Tang et al.

During the transition from the inner cell mass cells of blastocysts to pluripotent embryonic stem cells in vitro, a normal developmental program is replaced in cells that acquire a capacity for infinite self-renewal and pluripotency. The authors explored the underlying mechanism of this switch by using RNA-Seq transcriptome analysis at the resolution of single cells. They detected significant molecular transitions and major changes in transcript variants, which include genes for general metabolism. Furthermore, the expression of repressive epigenetic regulators increased with a concomitant decrease in gene activators that might be necessary to sustain the inherent plasticity of embryonic stem cells. Furthermore, the authors detected changes in microRNAs, with one set that targets early differentiation genes while another set targets pluripotency genes to maintain the unique embryonic stem cell epigenotype. Such genetic and epigenetic events may contribute to a switch from a normal developmental program in adult cells during the formation of diseased tissues, including cancers.

Volume 7, Number 1
July 2, 2010

Reprogramming of T Cells from Human Peripheral Blood

Y. H. Loh et al.

The authors of this paper have successfully reprogrammed cells from peripheral blood sources including samples obtained through routine venipuncture. Their study provides a strategy for the reliable generation of induced pluripotent stem cells from peripheral blood mononuclear cells.

Generation of Induced Pluripotent Stem Cells from Human Terminally Differentiated Circulating T Cells

T. Seki et al.

The authors of this paper have developed a minimally invasive method for human induced pluripotent stem cell generation without genomic integration that uses low numbers of human terminally differentiated circulating T (hTDCT) cells from peripheral blood. This method has advantages for research into stem cell reprogramming, T cell receptor rearrangement, immunologic disorders, and the development of genetic markers for future applications of regenerative medicine. T cell-derived induced pluripotent stem (TiPS) cells may well be relatively easy to use in a clinical setting.

Reprogramming of Human Peripheral Blood Cells to Induced Pluripotent Stem Cells

J. Staerk et al.

The authors' study demonstrates that peripheral blood can be utilized as an easily accessible source of patient tissue for reprogramming without the need to extensively maintain cell cultures prior to reprogramming experiments. This is an important step to make the induced pluripotent stem cell technology more broadly applicable.

Volume 7, Number 2
August 6, 2010

Chromatin Structure and Gene Expression Programs of Human Embryonic and Induced Pluripotent Stem Cells

M. G. Guenther et al.

Knowledge of both the global chromatin structure and the gene expression programs of human embryonic stem cells and induced pluripotent stem (iPS) cells should provide a robust means to assess whether the genomes of these cells have similar pluripotent states. Recent studies have suggested that human embryonic stem cells and iPS cells represent different pluripotent states with substantially different gene expression profiles. The authors describe here a comparison of global chromatin structure and gene expression data for a panel of human embryonic stem cells and iPS cells. Genome-wide maps of nucleosomes with histone H3K4me3 and H3K27me3 modifications indicate that there is little difference between embryonic stem cells and iPS cells with respect to these marks. Gene expression profiles confirm that the transcriptional programs of embryonic stem cells and iPS cells show very few consistent differences. Although some variation in chromatin structure and gene expression was observed in these cell lines, these variations did not serve to distinguish embryonic stem cells from iPS cells.

Lab-Specific Gene Expression Signatures in Pluripotent Stem Cells

A. M. Newman and J. B. Cooper

Pluripotent stem cells derived from both embryonic and reprogrammed somatic cells have significant potential for human regenerative medicine. Despite similarities in developmental potential, however, several groups have found fundamental differences between embryonic stem cell and induced pluripotent stem (iPS) cell lines that may have important implications for iPS cell-based medical therapies. Using an unsupervised clustering algorithm, the authors further studied the genetic homogeneity of iPSC and embryonic stem cells lines by reanalyzing microarray gene expression data from seven different laboratories. Unexpectedly, this analysis revealed a strong correlation between gene expression signatures and specific laboratories in both embryonic stem cell and iPS cell lines. Nearly one-third of the genes with lab-specific expression signatures are also differentially expressed between embryonic stem cells and iPS cells. These data are consistent with the hypothesis that in vitro microenvironmental context differentially impacts the gene expression signatures of both iPS cells and embryonic stem cells.

Volume 7, Number 5
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Highly Efficient Reprogramming to Pluripotency and Directed Differentiation of Human Cells with Synthetic Modified mRNA

L. Warren et al.

Clinical application of induced pluripotent stem (iPS) cells is limited by the low efficiency of iPS cell derivation and the fact that most protocols modify the genome to effect cellular reprogramming. Moreover, safe and effective means of directing the fate of patient-specific iPS cells toward clinically useful cell types are lacking. Here the authors describe a simple, nonintegrating strategy for reprogramming cell fate based on administration of synthetic mRNA modified to overcome innate antiviral responses. They show that this approach can reprogram multiple human cell types to pluripotency with efficiencies that greatly surpass established protocols. The authors further show that the same technology can be used to efficiently direct the differentiation of RNA-induced pluripotent stem (RiPS) into terminally differentiated myogenic cells. This technology represents a safe, efficient strategy for somatic cell reprogramming and directing cell fate that has broad applicability for basic research, disease modeling, and regenerative medicine.

Nature

Volume 467, Number 7313
September 16, 2010

Transfusion Independence and HMGA2 Activation after Gene Therapy of Human β-thalassemia

M. Cavazzana-Calvo et al.

The β-hemoglobinopathies are the most prevalent inherited disorders worldwide. Gene therapy of β-thalassemia is particularly challenging given the requirement for massive hemoglobin production in a lineage-specific manner and the lack of selective advantage for corrected hematopoietic stem cells. Compound β^E/β^0-thalassemia is the most common form of severe thalassemia in Southeast Asian countries and their diasporas. The β^E-globin allele bears a point mutation that causes alternative splicing. The abnormally spliced form is non-coding, whereas the correctly spliced messenger RNA expresses a mutated β^E-globin with partial instability. When this is compounded with a non-functional β^0-allele, a profound decrease in β-globin synthesis results, and approximately half of β^E/β^0-thalassemia patients are transfusion-dependent. The only available curative therapy is allogeneic hematopoietic stem cell transplantation, although most patients do not have a human-leukocyte-antigen-matched, geno-identical donor, and those who do still risk rejection or graft-versus-host disease. Here the authors show that, thirty-three months after lentiviral β-globin gene transfer, an adult patient with severe β^E/β^0-thalassaemia dependent on monthly transfusions since early childhood has become transfusion independent for the past twenty-one months. Blood hemoglobin is maintained between 9 and 10 g dl^{-1}, of which one-third contains vector-encoded β-globin. Most of the therapeutic benefit results from a dominant, myeloid-biased cell clone, in which the integrated vector causes transcriptional activation of HMGA2 in erythroid cells with further increased expression of a truncated HMGA2 mRNA insensitive to degradation by let-7 microRNAs. The clonal dominance that accompanies therapeutic efficacy may be coincidental and stochastic or result from a hitherto benign cell expansion caused by dysregulation of the HMGA2 gene in stem/progenitor cells.

Epigenetic Memory in Induced Pluripotent Stem Cells

K. Kim et al.

Somatic cell nuclear transfer and transcription-factor-based reprogramming revert adult cells to an embryonic state, and yield pluripotent stem cells that can generate all tissues. Through different mechanisms and kinetics, these two reprogramming methods reset genomic methylation, an epigenetic

modification of DNA that influences gene expression, leading us to hypothesize that the resulting pluripotent stem cells might have different properties. Here the authors observe that low-passage induced pluripotent stem (iPS) cells derived by factor-based reprogramming of adult murine tissues harbor residual DNA methylation signatures characteristic of their somatic tissue of origin, which favors their differentiation along lineages related to the donor cell, while restricting alternative cell fates. Such an "epigenetic memory" of the donor tissue could be reset by differentiation and serial reprogramming, or by treatment of iPS cells with chromatin-modifying drugs. In contrast, the differentiation and methylation of nuclear-transfer-derived pluripotent stem cells were more similar to classical embryonic stem cells than were iPS cells. The authors data indicate that nuclear transfer is more effective at establishing the ground state of pluripotency than factor-based reprogramming, which can leave an epigenetic memory of the tissue of origin that may influence efforts at directed differentiation for applications in disease modelling or treatment.

Nature Biotechnology

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Cell Type of Origin Influences the Molecular and Functional Properties of Mouse Induced Pluripotent Stem Cells

J. M. Polo et al.

Induced pluripotent stem (iPS) cells have been derived from various somatic cell populations through ectopic expression of defined factors. It remains unclear whether iPS cells generated from different cell types are molecularly and functionally similar. Here the authors show that iPS cells obtained from mouse fibroblasts, hematopoietic and myogenic cells exhibit distinct transcriptional and epigenetic patterns. Moreover, the authors demonstrate that cellular origin influences the in vitro differentiation potentials of iPS cells into embryoid bodies and different hematopoietic cell types. Notably, continuous passaging of iPS cells largely attenuates these differences. The authors results suggest that early-passage iPS cells retain a transient epigenetic memory of their somatic cells of origin, which manifests as differential gene expression and altered differentiation capacity. These observations may influence ongoing attempts to use iPS cells for disease modeling and could also be exploited in potential therapeutic applications to enhance differentiation into desired cell lineages.

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Non-invasive Imaging of Human Embryos before Embryonic Genome Activation Predicts Development to the Blastocyst Stage

C. C. Wong et al.

The authors report studies of preimplantation human embryo development that correlate time-lapse image analysis and gene expression profiling. By examining a large set of zygotes from in vitro fertilization, the authors find that success in progression to the blastocyst stage can be predicted with greater than 93 percent sensitivity and specificity by measuring three dynamic, noninvasive imaging parameters by day two after fertilization, before embryonic genome activation. These parameters can be reliably monitored by automated image analysis, confirming that successful development follows a set of carefully orchestrated and predictable events. Moreover, the authors show that imaging phenotypes reflect molecular programs of the embryo and of individual blastomeres. Single-cell gene expression analysis reveals that blastomeres develop cell autonomously, with some cells advancing to embryonic genome activation and others arresting. These studies indicate that success and failure in human embryo development is largely determined before embryonic genome activation. The authors methods and algorithms may provide an approach for early diagnosis of embryo potential in assisted reproduction.

PLoS One

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Risky Decisions and Their Consequences: Neural Processing by Boys with Antisocial Substance Disorder

T.J. Crowley et al.

Background: Adolescents with conduct and substance problems ("Antisocial Substance Disorder" (ASD)) repeatedly engage in risky antisocial and drug-using behaviors. The authors hypothesized that, during processing of risky decisions and resulting rewards and punishments, brain activation would differ between abstinent ASD boys and comparison boys. *Methodology/Principal Findings*: The authors compared twenty abstinent adolescent male patients in treatment for ASD with twenty community controls, examining rapid event-related blood-oxygen-level-dependent (BOLD) responses during functional magnetic resonance imaging. In ninety decision trials participants chose to make either a cautious response that earned one cent, or a risky response that would either gain five cents or lose ten cents; odds of losing increased as the game progressed. The authors also examined those times when subjects experienced wins, or separately losses, from their risky choices. The authors contrasted decision trials against very similar comparison trials requiring no decisions, using whole-brain BOLD-response analyses of group differences, corrected for multiple comparisons. During decision-making, ASD boys showed hypoactivation in numerous brain regions robustly activated by controls, including orbitofrontal and dorsolateral prefrontal cortices, anterior cingulate, basal ganglia, insula, amygdala, hippocampus, and cerebellum. While experiencing wins, ASD boys had significantly less activity than controls in anterior cingulate, temporal regions, and cerebellum, with more activity nowhere. During losses ASD boys had significantly more activity than controls in orbitofrontal cortex, dorsolateral prefrontal cortex, brain stem, and cerebellum, with less activity nowhere. *Conclusions/Significance*: Adolescent boys with ASD had extensive neural hypoactivity during risky decision-making, coupled with decreased activity during reward and increased activity during loss. These neural patterns may underlie the dangerous, excessive, sustained risk-taking of such boys. The findings suggest that the dysphoria, reward insensitivity, and suppressed neural activity observed among older addicted persons also characterize youths early in the development of substance use disorders.

From Preferred to Actual Mate Characteristics: The Case of Human Body Shape

A. Courtiol et al.

The way individuals pair to produce reproductive units is a major factor determining evolution. This process is complex because it is determined not only by individual mating preferences, but also by numerous other factors such as competition between mates. Consequently, preferred and actual characteristics of mates obtained should differ, but this has rarely been addressed. The authors simultaneously measured mating preferences for stature, body mass, and body mass index, and recorded corresponding actual partner's characteristics for 116 human couples from France. Results show that preferred and actual partner's characteristics differ for male judges, but not for females. In addition, while the correlation between all preferred and actual partner's characteristics appeared to be weak for female judges, it was strong for males: while men prefer women slimmer than their actual partner, those who prefer the slimmest women also have partners who are slimmer than average. This study therefore suggests that the influences of preferences on pair formation can be sex-specific. It also illustrates that this process can lead to unexpected results on the real influences of mating preferences: traits considered as highly influencing attractiveness do not necessarily have a strong influence on the actual pairing, the reverse being also possible.