

FEATURES

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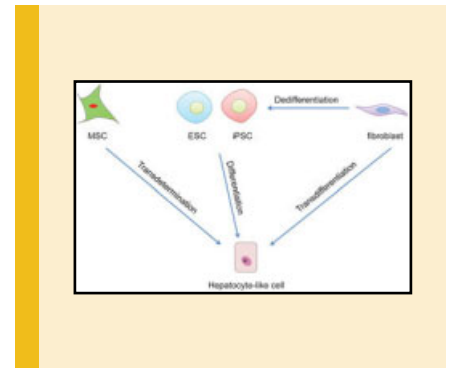
Cell Fate Conversion: Direct Induction of Hepatocyte-Like Cells From Fibroblasts

Shuyi Ji, Ludi Zhang, and Lijian Hui

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One of the essential features of stem cells is their cellular plasticity to differentiate into daughter cells with defined functions. Recently, induction of pluripotent stem cells from somatic cells by defined transcription factors led to the focus on cellular plasticity of terminally differentiated cells. This approach is adopted by other studies to demonstrate the cell fate conversion between different lineages of terminally differentiated cells. We and others showed that induced hepatocyte-like (iHep) cells are directly converted from mouse fibroblasts by overexpression of liver-enriched transcription factors. iHep cells as well as pluripotent stem cell- or mesenchymal stem cell-derived hepatocyte-like cells provide potential cell sources for disease modeling, transplantation, and tissue engineering independent of donor organs. Here, the latest advances in generating hepatocyte-like cells and summarize general criteria for evaluating these cells are reviewed. In addition, a possible role of the p19Arf/p53 pathway in cell fate maintenance is proposed, which apparently limits the formation of induced pluripotent stem (iPS) cells and iHep cells.



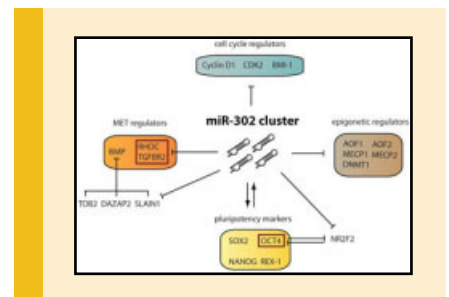
MicroRNA-Mediated Somatic Cell Reprogramming

Chih-Hao Kuo and Shao-Yao Ying

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Since the first report of induced pluripotent stem cells (iPSCs) using somatic cell nuclear transfer (SCNT), much focus has been placed on iPSCs due to their great therapeutic potential for diseases such as abnormal development, degenerative disorders, and even cancers. Subsequently, Takahashi and Yamanaka took a novel approach by using four defined transcription factors to generate iPSCs in mice and human fibroblast cells. Scientists have since been trying to refine or develop better approaches to reprogramming, either by using different combinations of transcription factors or delivery methods. However, recent reports showed that the microRNA expression pattern plays a crucial role in somatic cell reprogramming and ectopic introduction of embryonic stem cell-specific microRNAs revert cells back to an ESC-like state, although, the exact mechanism underlying this effect remains unclear. This review describes recent work that has focused on microRNA-mediated approaches to somatic cell reprogramming as well as some of the pros and cons to these approaches and a possible mechanism of action. Based on the pivotal role of microRNAs in embryogenesis and somatic cell reprogramming, studies in this area must continue in order to gain a better understanding of the role of microRNAs in stem cells regulation and activity.

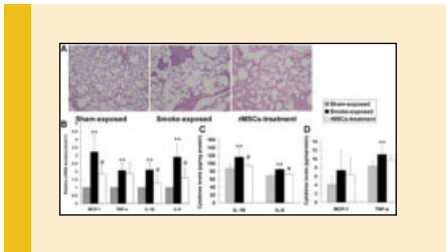


Mesenchymal Stem Cells Protect Cigarette Smoke-Damaged Lung and Pulmonary Function Partly via VEGF-VEGF Receptors

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Xiao-Jun Guan, Lin Song, Feng-Feng Han, Zhi-Lei Cui, Xi Chen, Xue-Jun Guo, and Wei-Guo Xu

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Progressive pulmonary inflammation and emphysema have been implicated in the progression of chronic obstructive pulmonary disease (COPD), while current pharmacological treatments are not effective. Transplantation of bone marrow mesenchymal stem cells (MSCs) has been identified as one such possible strategy for treatment of lung diseases including acute lung injury (ALI) and pulmonary fibrosis. However, their role in COPD still requires further investigation. The aim of this study is to test the effect of administration of rat MSCs (rMSCs) on emphysema and pulmonary function. To accomplish this study, the rats were exposed to cigarette smoke (CS) for 11 weeks, followed by administration of rMSCs into the lungs. Here it is shown that rMSCs infusion mediates a down-regulation of pro-inflammatory mediators (TNF- α , IL-1 β , MCP-1, and IL-6) and

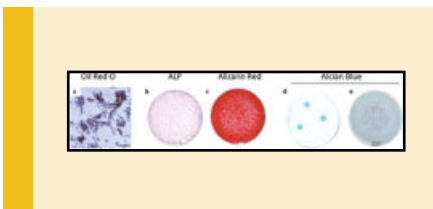
proteases (MMP9 and MMP12) in lung, an up-regulation of vascular endothelial growth factor (VEGF), VEGF receptor 2, and transforming growth factor (TGF β -1), while reducing pulmonary cell apoptosis. More importantly, rMSCs administration improves emphysema and destructive pulmonary function induced by CS exposure. In vitro co-culture system study of human umbilical endothelial vein cells (EA.hy926) and human MSCs (hMSCs) provides the evidence that hMSCs mediates an anti-apoptosis effect, which partly depends on an up-regulation of VEGF. These findings suggest that MSCs have a therapeutic potential in emphysematous rats by suppressing the inflammatory response, excessive protease expression, and cell apoptosis, as well as up-regulating VEGF, VEGF receptor 2, and TGF β -1.

Efficient Differentiation of Human iPSC-Derived Mesenchymal Stem Cells to Chondroprogenitor Cells

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Rosa M. Guzzo, Jason Gibson, Ren-He Xu, Francis Y. Lee, and Hicham Drissi

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Induced pluripotent stem cells (iPSC) hold tremendous potential for personalized cell-based repair strategies to treat musculoskeletal disorders. To establish human iPSCs as a potential source of viable chondroprogenitors for articular cartilage repair, the in vitro chondrogenic potential of the pluripotent population versus an iPSC-derived mesenchymal-like progenitor population is assessed. It was found that the direct plating of undifferentiated iPSCs into high-density micromass cultures in the presence of BMP-2 promoted chondrogenic differentiation, however these conditions resulted in a mixed population of cells resembling the phenotype of articular cartilage, transient cartilage, and fibrocartilage. The progenitor cells

derived from human iPSCs exhibited immunophenotypic features of mesenchymal stem cells (MSCs) and developed along multiple mesenchymal lineages, including osteoblasts, adipocytes, and chondrocytes in vitro. The data indicate the derivation of a mesenchymal stem cell population from human iPSCs is necessary to limit culture heterogeneity as well as chondrocyte maturation in the differentiated progeny. Moreover, as compared to pellet culture differentiation, BMP-2 treatment of iPSC-derived MSC-like (iPSC \dot{c} MSC) micromass cultures resulted in a phenotype more typical of articular chondrocytes, characterized by the enrichment of cartilage specific type II collagen (*Col2a1*), decreased expression of type I collagen (*Col1a1*) as well as lack of chondrocyte hypertrophy. These studies represent a first step toward identifying the most suitable iPSC progeny for developing cell-based approaches to repair joint cartilage damage.