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Identification of Genes Regulating Differentiation and Stemness of Human Mesenchymal Stem Cells for Gene Therapy in Regenerative Medicine

Authors : Tong Ming Liu

Abstract : Human mesenchymal stem cells (MSCs) represent the most used stem cells for clinical application, which have been used in over 1000 clinical trials to treat over 30 diseases due to multilineage differentiation potential, secretome and immunosuppression. Gene therapies of MSCs hold great promise in the treatment of many diseases due to enhanced MSC-based clinical outcomes. To identify genes for gene therapy of MSCs, by comparing gene expression profile before and after MSC differentiation following by functional screening, we have identified ZNF145 that regulated MSC differentiation. Forced expression of ZNF145 resulted in enhanced in vitro chondrogenesis of MSCs as an upstream factor of SOX9 and improved osteochondral repair upon implant into osteochondral defects in rodents. By comparing gene expression profile during differentiation of iPSCs toward MSCs, we also identified gene HOX regulating MSC stemness, which was much downregulated in late-passaged MSCs. Knockdown of this gene greatly compromised MSC stemness including abolished proliferation, decreased CFU-F, promoted senescence and reduced expression of cell surface antigens linked to the MSC phenotype. In addition, multi-linage differentiation was also greatly impaired. Notably, HOX overexpression resulted in improved multi-lineage differentiation. In the mechanism, HOX expression significantly deceased in late passage of MSCs compared with early passage of MSCs, correlating with MSC important genes. ChIP-seq data shown that HOX binds to genes related to MSC self-renewal and differentiation. Most importantly, most HOX binding sites are lost in late passage of MSCs. HOX exerts its effects by directing binding Twist1, one important gene of MSCs. The identification of the genes regulating MSC differentiation and stemness will provide and promising strategies for gene therapy of MSCs in regenerative medicine.

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