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Osteogenic differentiation of highly mineralizing human bone marrow-derived MSC is modulated by ALP, IGFBP5, and LRP3 through TGFB signaling pathway

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Understanding regulatory networks underlying human bone marrow stromal cells (hBMSCs)-lineage differentiation and fate determination is a pre-requisite for their use in therapy. The goal of current study was to unravel the novel role for low-density lipoprotein receptor-related protein 3 (LRP3) in regulating osteogenic and adipogenic differentiation of hBMSCs. Using global gene expression profiling, LRP3 exhibited significant up regulation in the highly osteogenic hBMSC clone (CL1) compared to the less osteogenic clone (CL2) and during osteogenic induction of the CL1 clone. Functional and gene expression data demonstrated LRP3 as a molecular switch promoting hBMSC lineage differentiation into osteoblast and inhibiting adipocytic differentiation. Interestingly, microRNA (miRNA) expression profiling identified miR-4739 as the most down regulated miRNA (-36.11 fold) in the CL1 vs CL2 clone. Using TargetScan prediction algorithm, combined with functional and biochemical assays, LRP3 was identified as a novel gene target for miR-4739, with a single potential binding site for miR-4739 in LRP3 3' UTR. Regulation of LRP3 expression by miR-4739 was subsequently confirmed by qRT-PCR, western blotting and luciferase assay. Forced expression of miR-4739 mimicked the effects of LRP3 knockdown on promoting adipogenic and suppressing osteogenic differentiation of hBMSCs. Hence, we report for the first time a novel biological role for the LRP3/hsa-miR-4739 axis in balancing osteogenic and adipocytic differentiation of hBMSCs. Our data support potential utilization of miRNA-based therapies in regenerative medicine.

Biography

Amer Mahmood received his MSc from Copenhagen University in the field of autoimmune destruction of beta cells in Type 1 diabetic patients. He obtained his Ph.D. in Medical Sciences in the field of human Embryonic Pluripotent Stem Cell research and bone biology from the University of Southern Denmark. He is currently working as Associate Professor of Stem cell and regenerative medicine, his recent research focus on the field of Mesenchymal Stem Cells and Regenerative Medicine particular in skeletal-bone disorders. He has published his work in peer reviewed international journals with high impact factor. He recently established a consulting and training company Aracure LLC in partnership with other highly qualified scientists, whereby he gives professional consultation in stem cell and molecular biology including stem cell therapy.