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Baculovirus-mediated MIR-214 suppression shifts osteoporotic ASCS differentiation towards osteogenesis and improves osteoporotic bone defects repair

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Osteoporotic patients often suffer from bone fracture but its healing is compromised due to impaired osteogenesis potential of bone marrow-derived mesenchymal stem cells (BMSCs). Here we aimed to exploit adipose-derived stem cells from ovariectomized (OVX) rats (OVX-ASCs) for bone healing. We unraveled that OVX-ASCs highly expressed miR-214 and identified 2 miR-214 targets: CTNNB1 (β-catenin) and TAB2. We demonstrated that miR-214 targeting of these two genes blocked the Wnt pathway, led to preferable adipogenesis and attenuated osteogenesis, undermined the osteogenesis of co-cultured OVX-BMSCs, enhanced exosomal miR-214 release and altered cytokine secretion. As a result, OVX-ASCs implantation into OVX rats failed to heal critical-size metaphyseal bone defects. However, using hybrid baculoviruses expressing miR-214 sponges to transduce OVX-ASCs, we successfully suppressed miR-214 levels, activated the Wnt pathway, upregulated osteogenic factors -catenin/Runx2, downregulated adipogenic factors PPAR-γ and C/EBP-α, shifted the differentiation propensity towards osteogenic lineage, enhanced the osteogenesis of co-cultured OVX-BMSCs, elevated BMP7/osteoprotegerin secretion and hindered exosomal miR-214/osteopontin release. Consequently, implanting the miR-214 sponge-expressing OVX-ASCs tremendously improved bone healing in OVX rats. Co-expression of miR-214 sponge and BMP2 further synergized the OVX-ASCs-mediated bone regeneration in OVX rats. This study implicates the potential of suppressing miR-214 in osteoporotic ASCs for regenerative medicine.

Biography

Yu-Chen Hu received his BS degree in Chemical Engineering from National Taiwan University (1992) and earned his PhD degree in Chemical Engineering from University of Maryland (USA) in 1999. He worked as a post-doc at the National Institutes of Health from 1999 to 2000 and returned to the Department of Chemical Engineering, National Tsing Hua University, Taiwan, in 2000. Dr. Hu's main research interests include vaccine development, gene therapy, tissue engineering, cancer therapy and synthetic biology. Dr. Hu's lab has developed the enterovirus 71 (EV71) vaccine based on virus-like particle technology and avian influenza vaccine based on baculovirus vector. Dr. Hu also utilizes baculovirus as a gene vector to deliver various genes encoding growth factor or microRNA into adult stem cells/cell sheet for the modulation of cellular differentiation states and tissue regeneration. His recent animal studies have demonstrated that the baculovirus-engineered cells, after implantation into animals, repair massive defects in cartilage and bone. Dr. Hu's lab also exploits baculovirus-engineered stem cell sheet for the management of myocardial infarction and bone infection. Dr. Hu's works have paved a new avenue to the use of baculovirus as a novel vector for regenerative medicine. Dr. Hu has won the Asia Research Award (Society of Chemical Engineers, Japan), Outstanding Research Award (Ministry of Science and Technology, 2006, 2014), BEST Biochemical Engineering Achievement Award, Wu Ta-You Memorial Award (NSC), Outstanding Academia-Industry Research Award and Outstanding Young Investigator Award in Taiwan. He is inducted as a fellow of American Institute for Medical and Biological Engineering (AIMBE), and is elected the Member of the Tissue Engineering International & Regenerative Medicine Society-Asia Pacific (TERMIS-AP) Council and the Vice President of Biotechnology and Biochemical Engineering Society of Taiwan. He is the Program Chair of the TERMIS-AP meeting, 2016. He also sits on the editorial board of 10 international journals and currently serves as the associated editor of Current Gene Therapy and deputy editor of Journal of Taiwan Institute of Chemical Engineers.

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