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MCT4 enables MSCs to improve engraftment in the ischemic wound environment and enhances MSC-based cell therapy

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Mesenchymal stem cell (MSC) transplantation after myocardial infarction holds much promise as a means to regenerate lost cardiac tissue and preserve cardiac function. However, a significantly large portion of cells transplanted into the injured heart die shortly after delivery due to hypoxic wound microenvironment. Poor stem cell survival and engraftment in the host tissue is a major impediment in the progress of stem cell therapy. Although, MSCs have been shown to perform better in hypoxia there are huge gaps in our understanding of the metabolic responses of MSCs to hypoxia. To address this issue, gene expression analysis was performed which showed an upregulation of key glycolytic enzymes (hexokinase and enolase) and the enzymes regulating the switch from aerobic to anaerobic respiration (aldolase, LDHA, PDK1, and PDK3) in MSCs subjected to hypoxia. Interestingly, considerable upregulation of transcript and protein levels of monocarboxylate transporter 4 (MCT4) were identified in hypoxic compared to normoxic MSCs. MCT4 belongs to a family of proton-linked monocarboxylate transporters and facilitates the efflux of lactate across the plasma membrane. Since accumulation of lactate in the cells will cause acidosis and ultimately cell death, upregulation of MCT4 suggests that it helps in MSC homeostasis maintenance and survival by extruding out lactate. MSCs overexpressing MCT4 were able to maintain low levels of lactate in hypoxia and MCT4-knockdown MSCs showed accumulation of lactate in hypoxic microenvironment. Knocking down MCT4 abrogated MSC engraftment while MSCs overexpressing MCT4 engrafted better in our sponge model of tissue repair. These results indicate the exclusive role of MCT4 in lactate efflux and to preserve the integrity of MSCs in hypoxia and can be exploited in order to enhance the therapeutic potential of MSCs.

Biography

Pampee Young is an Associate Professor of Pathology at Vanderbilt University Medical Center and Director of the Transfusion Service at Vanderbilt Medical Center and the adjoining Department of Veterans Affairs. She completed her MD and PhD from UT Southwestern Medical School in Dallas, TX. Her laboratory's research is focused on the study of stem cells in wound and cardiac repair and regeneration. Her current work has highlighted the Wnt pathway as critical in progenitor cell regulation at the wound site. Her group is actively working to develop therapeutic Wnt inhibitors for tissue regeneration. Dr. Young has an active collaboration with stem cell and cardiovascular scientists at Vanderbilt to perform clinical cell therapy trials using bone marrow stem cells. Vanderbilt is one of the five founding institutions in the NIH funded cardiac cell therapy network.

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