METABOLISM REGULATION OF PHENOTYPIC AND THERAPEUTIC PROPERTIES OF HUMAN MESENCHYMAL STEM CELLS

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Introduction

Human mesenchymal stem cells (hMSCs) isolated from various adult tissues are primary candidates in cell therapy and tissue regeneration. The pro-regenerative properties of hMSCs are largely attributed to their trophic effects by the release of factors that coordinately modulate the progression of inflammation and enhance the endogenous tissue repair by host progenitor cells. However, immediately after isolation and upon culture expansion, hMSCs acquire and accumulate genetic and phenotypic changes that significantly alter their phenotypic properties with reduced clonogenic and therapeutic potential. The culture-induced changes are not only correlated with reduced clonogenicity and proliferation but also with reduced therapeutic outcome in various disease models. Thus, preserving hMSC therapeutic potency following in vitro expansion is an important goal in hMSC application. Once viewed as a mere consequence of the state of a cell, metabolism is now known to play active roles in regulating cellular events that govern stem cell phenotype and functional properties. Our long term objective is to understand the role of energy metabolism in regulating hMSC cell fate with ultimate goals of developing metabolic strategies to augment hMSCs therapeutic properties.

Results

Our recent studies show that hMSCs have heterogeneity at the level of primary energy metabolism [1] and possess metabolic plasticity to reconfigure their metabolic network in their reacquisition of stem cell primitive properties and immune-modulatory property [2]. First, ^{13}C-glucose-based metabolomics analysis suggested that hMSC are metabolically heterogeneous and that clonogenic subpopulation of hMSCs enriched in low density culture (100 cells/cm^2) possesses a metabolic phenotype that differs from that of hMSCs in high-density (3,000 cells/cm^2) in their levels of glycolysis metabolism and pentose phosphate pathway (PPP). Metabolic inhibition studies revealed that glycolysis and PPP play active roles in maintaining hMSCs clonogenicity by regulating ATP generation, maintaining cellular redox state, and scavenging exogenous reactive oxygen species [1]. Second, we showed that hMSCs possess metabolic plasticity and effectively reconfigure their metabolism during 3D aggregation culture, and that this metabolic reconfiguration plays a central role in their reacquisition of primitive phenotypic properties [2]. Specifically, aggregate formation of hMSCs remodeled their mitochondrial network with reduced mitochondrial membrane potential, resulting in metabolic reconfiguration with reduced mitochondrial citric acid cycle (TCA cycle) activity, increased aerobic glycolysis, and anaplerotic flux. The effects of metabolic reconfiguration on stem cell gene expression and secretory function was recapitulated in the gain- and loss-of-function experiments using small molecule metabolic modulators, confirming its functional role in regulating hMSC properties. Finally, we showed that hMSC immuno-activation in response to interferon-γ (IFN-γ) treatment is associated with metabolic reconfiguration towards increased aerobic glycolysis, characterized by increased glucose consumption and upregulation of glycolysis-related genes and enzymes. We further demonstrated that both glucose deprivation and glycolysis inhibition were sufficient to abolish the secretion of indoleamine 2,3-dioxygenase (IDO) a critical anti-inflammatory cytokine secreted by hMSCs, suggesting the central role of aerobic glycolysis in regulating hMSC immunomodulatory properties.

Conclusions

Together, the results revealed the mechanistic connection between metabolic regulation and hMSC therapeutic phenotype, and demonstrated the regulation of metabolism as a strategy in potentiating hMSCs properties for cell therapy. In the presentation, the implication of these findings in hMSC bioprocessing and therapeutic application will be discussed.

References

[1]. Liu, Y., N. Munoz, B.A. Bunnell, T.M. Logan, and T. Ma, Density-Dependent Metabolic Heterogeneity in Human Mesenchymal Stem Cells. Stem Cells, 2015. 33(11): p. 3368-81.
[2]. Liu, Y., N. Munoz, A.C. Tsai, B.A. Bunnell, T.M. Logan, and T. Ma, Metabolic Reconfiguration Supports Reacquisition of Primitive Phenotype in Human Mesenchymal Stem Cell Aggregates. Stem Cells, 2016. August 2016, (Accepted)