DETERMINING THE ROLE OF LACTATE IN INDUCED PLURIPOTENT STEM CELL METABOLISM

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Induced pluripotent stem (iPS) cells hold the potential to dramatically improve cell-based therapies and *in vitro* drug screening applications in the near future. Yet, for iPS cells to have a clinical impact, these cells must be generated in sufficient quantity and quality that currently exceeds today's capabilities. To meet these cell needs, a comprehensive understanding of how environmental conditions affect iPS cell metabolism and pluripotency is essential. Rapidly proliferating cells, including cancer and iPS cells, catabolize glucose and secrete lactate at elevated rates, even in the presence of sufficient oxygen, a process referred to as the Warburg effect (Vander Heiden, Cantley, Thompson 2009; Varum et al. 2011; WARBURG 1956). In cancer cell metabolism, lactate accumulation is associated with cancer stem cell-like gene expression, drug-resistance, metastasis, and poor prognosis in breast cancer patients (Martinez-Outschoorn et al. 2011). In addition, lactate has previously been shown to stabilize hypoxia inducible factors and induce a hypoxic response for cells cultured in normoxic environments (Pérez-Escuredo et al. 2016). However, there remains an incomplete understanding of the metabolic role of lactate for iPS cells and its effects on pluripotency. This study examined the impact of extracellular lactate on cellular metabolism and pluripotency of iPS K3 cells grown with sufficient glucose. Extracellular glucose, lactate, and amino acid concentrations were monitored throughout the experiment to determine the extracellular consumption or production fluxes. In addition, [1,2-^{13}C] glucose, [U-^{13}C] glutamine, and [U-^{13}C] lactate isotope tracers were used in parallel labeling experiments to determine the intracellular metabolic contribution of each carbon source to iPS cell metabolism. High extracellular lactate resulted in altered cell metabolism, including a decrease in lactate production and glucose consumption. This was coupled with a decrease in glucose contribution to the TCA cycle. Also, lactate was catabolized to pyruvate, alanine, and TCA intermediate metabolites in the high-lactate condition. Furthermore, high extracellular lactate did not affect iPS cell pluripotency. These results suggest that lactate partially serves as a metabolic substrate for iPS even as it continues to accumulate in the extracellular media. The implications of these findings towards understanding iPS cell metabolism and improving future cell culture conditions will be discussed.

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