EFFECT OF LACTATE MEDIA CONCENTRATION ON INDUCED PLURIPOTENT STEM CELL PROLIFERATION AND METABOLISM

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Induced pluripotent stem (iPS) cells hold the potential to drastically improve cell-based therapies in the near future. Yet, in order for stem cell therapies to become clinically feasible, these cells must be generated in sufficient quantity and quality. Rapidly proliferating cells, including cancer and iPS cells, consume glucose and secrete lactate at high rates, even in the presence of sufficient oxygen; this process is called 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 (Martinez-Outschoorn et al. 2011) . Yet, there remains an incomplete understanding of the role of lactate in stem cell metabolism and pluripotency. The objective of this study was to determine the impact of lactate on stem cell metabolism and pluripotency. Metabolic responses to high and low extracellular lactate concentrations were examined in iPS K3 cells, where these responses included metabolic activity and pluripotency. Specifically, the respective extracellular consumption and production fluxes for glucose, lactate, and amino acids were determined. Growth rates were controlled to not be different between the high and low lactate cultures, which facilitated normalization of the extracellular fluxes. The high extracellular lactate concentrations resulted in a shift in cell metabolism, including a slight decrease in lactate production and glucose consumption fluxes. The high extracellular lactate concentrations also caused significant decreases in pyruvate and glutamine consumption fluxes. These altered fluxes due to the high extracellular lactate concentrations suggest decreased metabolic activity through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. Consequently, it is likely that under high extracellular lactate the mitochondrial activity is also lower, a metabolic characteristic of pluripotent stem cells (Folmes et al. 2011) . The impact of high extracellular lactate on iPS cell metabolism and pluripotency will be discussed. The implications of these findings towards understanding iPS cell metabolism and designing large-scale cell culture conditions to limit lactate accumulation will be discussed.

Folmes CD, Nelson TJ, Martinez-Fernandez A, Arrell DK, Lindor JZ, Dzeja PP, Ikeda Y, Perez-Terzic C, Terzic A. 2011. Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. Cell Metabolism 14(2):264-71.
Martinez-Outschoorn UE, Prisco M, Ertel A, Tsirigos A, Lin Z, Pavlides S, Wang C, Flomenberg N, Knudsen ES, Howell A. 2011. Ketones and lactate increase cancer cell “stemness,” driving recurrence, metastasis and poor clinical outcome in breast cancer: Achieving personalized medicine via metabolo-genomics. Cell Cycle 10(8):1271-86.
Vander Heiden MG, Cantley LC, Thompson CB. 2009. Understanding the warburg effect: The metabolic requirements of cell proliferation. Science 324(5930):1029-33.
Varum S, Rodrigues AS, Moura MB, Momcilovic O, Easley IV CA, Ramalho-Santos J, Van Houten B, Schatten G. 2011. Energy metabolism in human pluripotent stem cells and their differentiated counterparts. PloS One 6(6):e20914.
Warburg O. 1956. On the origin of cancer cells. Science 123(3191):309-14.