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Linking Metabolism, Pluripotency and Epigenetic Changes during Early Differentiation of Embryonic Stem Cells

Authors : Arieh Moussaieff, Bénédicte Elena-Herrmann, Yaakov Nahmias, Daniel Aberdam

Abstract : Differentiation of pluripotent stem cells is a slow process, marked by the gradual loss of pluripotency factors over days in culture. While the first few days of differentiation show minor changes in the cellular transcriptome, intracellular signaling pathways remain largely unknown. Recently, several groups demonstrated that the metabolism of pluripotent mouse and human cells is different from that of somatic cells, showing a marked increase in glycolysis previously identified in cancer as the Warburg effect. Here, we sought to identify the earliest metabolic changes induced at the first hours of differentiation. High-resolution NMR analysis identified 35 metabolites and a distinct, gradual transition in metabolism during early differentiation. Metabolic and transcriptional analyses showed the induction of glycolysis toward acetate and acetyl-coA in pluripotent cells, and an increase in cholesterol biosynthesis during early differentiation. Importantly, this metabolic pathway regulated differentiation of human and mouse embryonic stem cells. Acetate delayed differentiation preventing differentiation-induced histone de-acetylation in a dose-dependent manner. Glycolytic inhibitors upstream of acetate caused differentiation of pluripotent cells, while those downstream delayed differentiation. Our data suggests that a rapid loss of glycolysis in early differentiation down-regulates acetate and acetyl-coA production, causing a loss of histone acetylation and concomitant loss of pluripotency. It demonstrate that pluripotent stem cells utilize a novel metabolism pathway to maintain pluripotency through acetate/acetyl-coA and highlights the important role metabolism plays in pluripotency and early differentiation of stem cells.

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