INVESTIGATION THE ROLE ORPHAN NUCLEAR RECEPTOR NR4A1 IN GLUCOSE METABOLIC PATHWAY OF ACUTE MYELOID LEUKEMIA

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Acute myeloid leukemia (AML) is a group of severe hematological malignancies with poor prognosis. Although many studies have sought to elucidate the biological and molecular basis of AML, the mechanism of pathogenesis remains undefined in the majority of the cases. The glucose metabolism, including glycolysis and tricarboxylic acid (TCA) cycle, is reprogrammed in many malignancies in order to increase the production of energy/biosynthetic precursors for tumor cells. Recently, a panel of metabolite biomarkers related to glucose metabolism including lactate cell production were identified with prognostic value for cytogenetically normal AML. The orphan nuclear receptor NR4A1 is a potent tumor suppressor of acute leukemia that has been associated with the regulation of energy metabolism pathways in specific tissues such as muscle and adipocytes cells. In this study, we hypothesized that NR4A1 expression could exert an essential role in glucose metabolism in leukemia cells. The NR4A1 protein expression was evaluated by Western Blot in acute leukemia cell line (NB4) cultured under progressive absence of normal glucose. NB4 cells were silenced for NR4A1 using lentiviral transfection (short hairpin RNA). The glucose uptake assay was determined using an enzymatic colorimetric method and mitochondrial activity was evaluated with MTT assays. The lactate was measured for a reaction catalysed by lactate dehydrogenase. Glucose deprivation induced a pronounced reduction of NR4A1 protein expression in leukemia cell line. Importantly, the NR4A1 knockdown caused an increase of glucose uptake (p=0.0122 pared t-test) concomitant to the increased of mitochondrial activity. Adding to that, It was observed an increase in cell lactate generation in the NR4A1 Knockdown cells whenever comparing to the control. These results suggest a regulatory role of NR4A1 in glucose metabolism pathway and could contribute to the understanding of lactate generation mechanism due to the energetic demands that are required for the unregulated proliferation and survival of leukemic cells.

Key words: Acute Myeloid Leukemia, Glucose Metabolism, Orphan Nuclear Receptors.