Andrographolide is a novel inhibitor of pyruvate dehydrogenase kinase 1 and induces apoptotic cell death in non-small cell lung carcinoma cells

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Y. Do¹, K. Kim¹, K. Ha²

¹Pusan National University, Yangsan, South Korea, ²Pusan National University, Busan, South Korea

Dysregulated cellular metabolism is regarded as an emerging hallmark of cancer cells via biomass production supporting cell growth and division. Pyruvate dehydrogenase kinases (PDKs) inactivate the PDH activity via phosphorylating the serine residues on its E1α subunit (PDHA1). PDK1 was found to be the most critical enzyme for the development and metastasis of various types of malignant cancer, several PDK1 inhibitors have been investigated for developing novel cancer therapy. In this study, we found that andrographolide, a diterpenoid lactone isolated from Andrographis paniculata (Burm.f.) Nees, reduced the activity of PDK1 according to screening for a natural product library of 630 compounds. Previously, andrographolide has been reported that reduced the glycolytic metabolic phenotype of cancer cells by regulating the expression of enzymes related to glycolysis. However, it was not fully elucidated on the precise molecular target of andrographolide for downregulating aerobic glycolysis. We confirmed the cytotoxic effect of andrographolide in several cancer cells including human non-small cell carcinoma A549, H292, and H522 cells, and human colorectal cancer HCT116 and DLD-1 cells. In addition, andrographolide reduced the activity of PDK1 in both in vitro enzymatic assay and intracellular phosphorylation of PDHA1 in non-small cell lung carcinoma H292 cells. As a result of PDK1 inhibition, andrographolide reduced lactate production and mitochondrial membrane potential, and increased mitochondrial reactive oxygen species and subsequent apoptotic cell death in H292 cells. Exogenous overexpression of PDK1 restored the apoptotic cell death induced by andrographolide. From these results, we postulated that PDK1 is a major molecular target of andrographolide to suppress aerobic glycolysis in non-small cell lung carcinoma.