Abstract

Hippo signaling pathway represents organ size control mechanism constrained between all metazoans. Individual components of the Hippo signaling pathway were identified as key tumor-suppressors which phosphorylate and inhibit activity of several oncogenic factors and signaling pathways (such as YAP/TAZ, PI3K and mTOR). MST1 kinase is a part of central protein complex of the Hippo signaling pathway and its activation is involved in anti-cancer activity of several drugs. We have demonstrated activation of the MST1 kinase by natural compounds in leukemic cells followed by inhibition of proliferation and induction of apoptosis. Shikonin represents natural naphthoquinonic compound isolated from *Lithospermum erythrorhizon* which acts as inhibitor of glycolysis and mitochondrial respiratory chain in human cells. Shikonin induces fast activation of the MST1 protein in leukemic cells however mechanism of this activation remains unknown. Therefore, we tried to characterize posttranslational modifications of the MST1 kinase during shikonin treatment of leukemic cells. Firstly, we isolated MST1 kinase from control and shikonin-treated cells using immunoprecipitation. Then we characterized posttranslational modifications of the MST1 protein employing mass spectrometry. Using this approach we found out phosphorylation of S43, S414 and dephosphorylation of S438 induced by shikonin in leukemic cells. These shikonin-induced changes in phosphorylation of the MST1 may represent inhibition of mTORC2 signaling pathway and activation of ERK signaling pathway. Inhibition/activation of these pathway was confirmed also using immunoblot technique.

(In Czech)

Keywords: MST1 kinase, Shikonin, Hippo signaling pathway, metabolism, leukemia