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Activation of Raf1 and the ERK pathway in response to L-ascorbic acid in acute myeloid leukemia cells

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Abstract

L-ascorbic acid (LAA) shows cytotoxicity and induces apoptosis of malignant cells in vitro, but the mechanisms by which such effects occur have not been elucidated. In the present study, we provide evidence that the ERK MAP kinase pathway is activated in response to LAA (< 1 mM) in acute myeloid leukemia cell lines. LAA treatment of cells induces a dose-dependent phosphorylation of extracellular signal-regulated kinases (ERK) and results in activation of its catalytic domain. Our data also demonstrate that the small G protein Raf1 and MAPK-activated protein kinase 2 are activated by LAA as an upstream and a downstream regulator of ERK, respectively. Although the ERK pathway has been known to activate cell proliferation, pharmacologic inhibition of ERK reduces LAA-dependent apoptosis and growth inhibitory response of acute myeloid leukemia cell lines, suggesting that this signaling cascade positively regulates induction of apoptotic response by LAA.

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Keywords: L-ascorbic acid; Raf1; ERK; MAPKAP kinase 2; Acute myeloid leukemia; Dominant negative ERK1

1. Introduction

LAA was shown to be an important modulator for the growth of a mouse tumor system in an in vitro colony assay

system [1]. It has long been known that L-ascorbic acid (LAA) is one of the major water-soluble anti-oxidants present in cells and plasma [2,3], but there are a number of other studies demonstrating that, under certain conditions, LAA functions as a pro-oxidant and increases DNA damage [4–6]. In line with this, there is evidence that LAA is selectively toxic to some types of tumor as a pro-oxidant, rather than antioxidant [7,8]. LAA at 10 nM–1 mM induces apoptosis in neuroblastoma, melanoma and human myelogenous leukemic cell lines within 24 h by oxidative stress [9,10]. A long series of our studies also have solidly demonstrated that the growth of leukemic progenitor cells from patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) can be profoundly modulated by LAA [11,12]. Further, our recent clinical studies indicate that manipulation of LAA levels in vivo can

Abbreviations: LAA, L-ascorbic acid; MAPKAP kinase 2, MAPK-activated protein kinase 2; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; MAPK, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinases; JNK/SAPK, c-Jun N-terminal kinases/stress-activated protein kinases; RA, all-trans-retinoic acid; MBP, myelin basic protein; FITC, fluorescein-isothiocyanate; PI, propidium iodide; GM-CSF, granulocyte-macrophage colony-stimulating factor.

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