L-Ascorbic Acid Represses Constitutive Activation of NF-κB and COX-2 Expression in Human Acute Myeloid Leukemia, HL-60


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Abstract

There is increasing evidence that L-ascorbic acid (LAA) is selectively toxic to some types of cancer cells at pharmacological concentrations, functioning as a pro-oxidant rather than as an anti-oxidant. However, the molecular mechanisms by which LAA initiates cellular signaling leading to cell death are still unclear. In an effort to gain insight into these mechanisms, the effects of LAA on eukaryotic transcription nuclear factor NF-κB and cyclooxygenase-2 (COX-2) expression were investigated. In the present study, LAA suppressed DNA binding activity of NF-κB, composed of a p65/p50 heterodimer, through inhibition of degradation of inhibitory κB-α (IKB-α) and prevention of nuclear translocation of p65. The inhibitory effect of LAA on NF-κB activity was dependent upon glutathione levels in HL-60 cells, as well as generation of H$_2$O$_2$ but not superoxide anion. LAA also downregulated the expression of COX-2, which has a NF-κB binding site on its promoter, through repression of NF-κB DNA binding activity. Moreover, cotreatment of 1 μM arsenic trioxide (As$_2$O$_3$) with various concentrations of LAA enhanced an LAA-induced repression of NF-κB activity and COX-2 expression. In conclusion, our data suggest that LAA exerts its anti-tumor activity through downregulation of NF-κB activity and COX-2 expression, and these inhibitory effects can be enhanced by co-treatment with As$_2$O$_3$. J. Cell. Biochem. 93: 257-270, 2004. © 2004 Wiley-Liss, Inc.

Key words: L-ascorbic acid; NF-κB; COX-2; arsenic; acute myeloid leukemia

L-Ascorbic acid (LAA) is one of the major water-soluble anti-oxidants present in cells and plasma. There are other studies demonstrating that under certain conditions LAA acts as a pro-oxidant and increases DNA damage [Stich et al., 1976; Speit et al., 1980]. Also, there is increasing evidence that LAA is selectively toxic to some types of tumor, functioning as a pro-oxidant rather than as an anti-oxidant [Bram et al., 1980; Bruchelt et al., 1993]. LAA at concentra-

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