P-39

L-ASCORBIC ACID AND ARSENIC TRIOXIDE SYNERGISTICALLY REPRESS CONSTITUTIVE ACTIVATION OF NF-κB AND COX-2 EXPRESSION IN HUMAN ACUTE PROMYELOCYTIC LEUKEMIA, HL-60

Seong-Su Han[1], Sook J. Lee[1], Seung-Tae Chung[2], Juno H. Eom[2], Young-Joon Surh[3], Hye K. Park[1], Mary H. Park[1], Won S. Kim[1], Kihyun Kim[1], Chulwon Chung[1], Mark H. Lee[1], Keunchil Park[1], Jhin-Gook Kim[1], Jung-Hyun Yang[1], Sung-S Yoon[1,4], Neil H. Riordan[5], Hugh D. Riordan[6], Bruce F. Kimler[7], and Chan H. Park[1,5,6]

[1]Samsung Medical Center, and Sungkyunkwan University School of Medicine, Seoul 135-710, Korea; [2]Department of Immunotoxicology, Korea Food and Drug Administration, Seoul 122-020, Korea; [3]College of Pharmacy, Seoul National University, Seoul 151-742, Korea; [4]Seoul National University College of Medicine, Seoul 110-799, Korea; [5]Aidan Incorporated, Tempe, AZ 85281, U.S.A.; [6]The Center for Improvement of Human Functioning International, Wichita, KS 67219, USA; 7University of Kansas Medical Center, Kansas City, KS 66160, USA.

Eukaryotic nuclear transcription factor, NF-B and cyclooxygenase-2 (COX-2) has been implicated in pathogenesis of many human diseases including tumor and are known to be activated by various external stimuli. Recently, increasing evidences have supported that L-ascorbic acid (LAA) is selectively toxic to some types of tumors at pharmacological concentrations as a prooxidant, rather than antioxidant. However, the molecular mechanisms by which LAA initiates cellular signaling toward cell death are still unclear. Therefore, the effects of LAA on eukaryotic transcripton factor NF-κB and COX-2 expression were investigated. In the present study, LAA suppressed DNA binding activity of NF-κB composed of p65/p50 heterodimer through inhibition of degradation of IB-α and preventing nuclear translocation of p65 subsequently, but not direct-interruption of DNA binding of NF-κB to their consensus sequences. Inhibitory effect of LAA on NF-κB DNA activity was dependent upon GSH level in HL-60 cells as well as H_2O_2 generation but not superoxide anion. LAA also downregulated the expression of COX-2 which has NF-B binding site on its promoter through

repressing the NF-κB DNA binding activity. Moreover, cotreatment of 1 μM As_2O_3 with various concentrations of LAA enhanced LAA induced-repression of NF-B activity and COX-2 expression. In conclusion, it is likely that LAA exerts its anti-tumor promotional effect through downregulation of NF-κB activity and COX-2 expression. Cotreatment of 1 μM As_2O_3 can synergistically enhance inhibitory effect of LAA supressing NF-κB activity and COX-2 expression