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L-ASCORBIC ACID AND ARSENIC TRIOXIDE EXERT THE SYNERGISTIC EFFECT TO INDUCE THE GROWTH ARREST AND THE APOPTOSIS OF HUMAN ACUTE PROMYELOCYTIC LEUKEMIA, HL-60 VIA MODULATING REDOX STATUS, MAPK PATHWAY AND APOPTOSIS-RELATED FACTORS

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, U.S.A.

There are increasing evidences that L-ascorbic acid (LAA) is selectively toxic to some types of tumors at physiological concentrations as a prooxidant, rather than antioxidant. However, the mechanism by which LAA initiates cellular signaling toward cell death is still unclear. Therefore, to determine whether LAA might be useful for the treatment of human acute promyelocytic leukemia (APL), HL-60 cells, the effects of LAA on proliferation, redox system, MAPK and induction of apoptotic cascades were investigated. LAA induced growth inhibition and apoptosis of HL-60 cells at concentrations of 100-1000 μM dose-dependently. [^{3}H]thymidine incorporation assay showed that generation of H_2O_2, not superoxide anion, through preventing GSH function scavenging H_2O_2 and reducing dehydroascorbic acid (DHA) to LAA might be main causation of inhibitory effect of LAA. Interestingly, constitutive activated ERK was strongly inactivated by LAA via time- and dose-dependent manner but constitutive activated p38 was very slightly. However, LAA induced the

activation of JNK, which was reached maximal activation at 4h and then declined to undetectable basal level. In addition, LAA caused apoptosis through decrease of Bcl-2/Bax ratio, release of cytochrome C from mitochondria to cytosol, activation of caspase-9 and caspase-3, and cleavage of PARP. Cotreatment of 1 μM As_2O_3 with various concentrations of LAA enhanced the inhibitory effect of LAA. Based on these findings, we postulated that LAA might act as a prooxidant because fine balance between the production of reactive oxygen species (ROS) and antioxidant defenses may thus be tilted in favour of oxidants, leading to macromolecular damage, growth inhibition and apoptosis. In conclusion, it is likely that LAA with and without 1 μM As_2O_3 induce the growth arrest and the apoptosis of HL-60 cells through modulating redox status, MAPK, as well as a series of apoptotic cascade.