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MAC induces apoptosis via Inhibition of c-Myc and AMPK/mTOR dependent pathway in leukemia cells

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The expression of c-Myc closely correlated with the tumorogenesis, cell proliferation, differntiation, and cell death. In this study, we provide evidence for the 4-O-methyl-ascochlorin (MAC), which is a methylated derivative of the prenyl-phenol antibiotic ascochlorin, is an anti-cancer agent of leukemia that induces cell death via own regulation of c-Myc protein expression. Although the effects of MAC on apoptosis have been reported, the underlying mechanisms remain unknown. In the present study, we show that MAC promoted apoptotic cell death and downregulated expression of c-Myc in K562 human leukemia cells. The effect of MAC on apoptosis was similar to that of 10058-F4 (a c-Myc inhibitor) or c-Myc siRNA, suggesting that the downregulation of c-Myc expression plays a role in the apoptotic effect of MAC. Further investigation showed that MAC downregulated c-Myc by inhibiting protein synthesis. MAC promoted the phosphorylation of AMP-activated protein kinase (AMPK) and inhibited the phosphorylation of mammalian target of rapamycin (mTOR) and its target proteins, including p70S6K and 4EBP1. Treatment of cells with AICAR (an AMPK activator), rapamycin (an mTOR inhibitor), or mTOR siRNA downregulated c-Myc expression and induced apoptosis to a similar extent to that of MAC. These results suggest that the effect of MAC on apoptosis induction in human leukemia cells is mediated by the inhibition of c-Myc protein synthesis via an AMPK/ mTOR-dependent mechanism.

Biography

Young-Chae Chang is a Professor at the department of cell biology in the Catholic University of Daegu School of Medicine, Korea. He received his BS and MS from Yeungnam University, Korea and obtained his PhD dgree in a cell biology from University of Tokyo, Japan in 1995. He then carried out Postdoctoral training at National Institute of Bio-Science and Human Technology, Japan and University of Vermont college of Medicine, USA for 5 years. He has published more than 120 scientific papers in reputed journals. His lab is currently studying the molecular mechanism of signal transduction in tumorigenesis and metastasis control.

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