Chemotherapeutic activity of mistletoe lectin-II (Viscum album var. coloratum) via activation of c-Jun N-Terminal Kinase1 (JNK1) and caspase cascades in the apoptotic death of human myeloleukemic U937 cells

Myung-Sunny Kim\textsuperscript{1,2}, Jienny Lee\textsuperscript{a}, Chang-Min Park\textsuperscript{1}, Yun-Sook Lim\textsuperscript{1}, Sun-Rock Moon\textsuperscript{1}, Kang-Min Lee\textsuperscript{2}, RaeKil Park\textsuperscript{1,3}

\textsuperscript{1}Department of Microbiology and \textsuperscript{2}Institute of Medical Science, Wonkwang University School of Medicine, Iksan, \textsuperscript{3}Department of Molecular Biology, Chonbuk National University, Chonju 561-756, Korea

Background Mistletoe lectins have been interested as a therapeutically active anti-cancer substance in cancer research fields. Mistletoe lectin-II, a major composition of Korean mistletoe (Viscum album coloratum), is of high biological activity and exerts cytopathic effects. However, the mechanism by which the plant extracts kill tumor cells has still remained to be elusive. We investigated the direct effects of \( \beta \)-galactoside as well as N-acetyl-D-galactosamine specific mistletoe lectin-II to induce apoptotic death of U937 cells.

Methods Cells were incubated with Korean mistletoe lectin-II and analyzed the viability, genomic DNA fragmentation, activity of caspase 3-like protease and its cleavage effects on intracellular biosubstrates.

Results \( \beta \)-galactoside and N-acetyl-D-galactosamine specific lectin-II induced apoptotic cell death in U937 cells, primary acute myelocytic leukemic cells as well as a variety of cell types including Jurkat T cells, RAW 264.7, HL-60, DLD1 cells, but not normal polymorphonuclear leukocytes. Mistletoe lectin-II also induced ladder pattern DNA fragmentation and activation of caspase-3, -8 and -9 of U937 cells, but not caspase-1 protease, in a time and dose-dependent manner. Mistletoe extracts markedly increased the phosphotransferase activity of cJun N-terminal kinase1 (JNK1)/stress activated protein kinase (SAPK) in U937 cells in a time and dose-dependent manner. Consistent with catalytic activation of protease, both poly(ADP-ribose) polymerase (PARP) and protein kinase C-\( \delta \) (PKC-\( \delta \)) are also cleaved in mistletoe lectin-II-treated U937 cells. Catalytic activation of JNK1, caspase 3-like protease, and PARP cleavage as well as DNA fragmentation induced by mistletoe lectin-II was inhibited by the addition of peptide AC-DEVD-CHO but not by AC-YVAD-CHO. In addition, IFN-\( \gamma \) differentiation of U937 cells increases the sensitivity to intracellular signaling pathway in mistletoe lectin-II-induced apoptosis.

Conclusions Taken together, we suggest that Korean mistletoe lectin-II have a potential chemotherapeutic activity via induction of apoptotic cell death.