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Proteasome Inhibitor MG-132 Induces Apoptosis in Human Acute Leukemia Jurkat T Cells through Mitochondria-Dependent Caspase Pathway That is Negatively Modulated in the Presence of Caspase-12 Inhibitor (z-ATAD-fmk) or Caspase-4 Inhibitor (z-LEVD-fmk)

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To understand antineoplstic effect of the proteasome inhibitor, the apoptogenic mechanism underlying MG-132-mediated apoptosis in human acute leukemia Jurkat T cells. Exposure of Jurkat T cells to MG-132 (0.63～2.5 μM) induced apoptotic events including mitochondrial cytochrome c release, activation of caspase-9, -3, -7, and -3, cleavage of Bidand PARP, sub-G_1peak, and DNA fragmentation in a dose-dependent manner without accompanying necrosis. The activation of caspases was detectable 4 h after MG-132 treatment. Whereas overexpression of BcL-xL completelyblocked MG-132-induced apoptotic events, individual pretreatments with caspase-8 inhibitor (z-IETD-fmk), caspase-9 inhibitor (z-LEHD-fmk), caspase-3 inhibitor (z-DEVD-fmk), and pan-caspase inhibitor (z-VAD-fmk), which could block MG-132-mediated apoptosis, failed to influence the caspase-9 activation. Caspase-12 inhibitor (z-ATAD-fmk) suppressed the apoptotic caspase pathway more significantly than did caspase-4 inhibitor (z-LEVD-fmk), but none of these inhibitors influenced the caspase-9 activation. These results indicated that MG-132-induced apoptosis was mediated by mitochondria-dependent caspase pathway composed of caspase-9, -3, -7, and -8, in which caspase-3 activation was augmentedby endoplasmic reticulum stress-mediated activation of caspase-12 and caspase-4, and was thus regulated by Bcl-xL.

Key words: proteasome inhibitor, MG-132, apoptosis, mitochondrial cytochrome c, endoplasmic reticulum stress, caspase cascade, Bcl-xL

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Proteasome inhibitor MG-132 induces apoptosis in human acute leukemia Jurkat T cells through mitochondria-dependent caspase pathway that is negatively modulated in the presence of caspase-12 inhibitor (z-ATAD-fmk) or caspase-4 inhibitor (z-LEVD-fmk)

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