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Functional conversion of Mcl-1 protein from pro-survival to pro-apoptotic by amino acid substitutions

Myeloid cell leukemia 1 (Mcl-1) gene was originally isolated as an immediate-early gene from the human myeloid leukemia cell line, ML-1 during phorbol ester-induced differentiation. Mcl-1 is a pro-survival Bcl-2 family protein, characterized by a short half-life due to the presence of PEST sequence. Kato et al. reported that Mcl-1 degradation proceeds with spontaneous apoptosis of human neutrophils, and cyclic adenosine monophosphate (cAMP) agonist stabilizes Mcl-1 and delays spontaneous neutrophil apoptosis (FEBS Lett. 2006). To elucidate the molecular mechanisms of Mcl-1 stabilization by cAMP agonist, an apoptosis induction system in the human embryonic kidney (HEK) 293 cells treated with tumor necrosis factor-a (TNF-a) and cycloheximide (CHX) was used. Treatment of HEK293 cells with TNF-a plus CHX induced apoptosis accompanied by degradation of Mcl-1, but not other pro-survival proteins, similar to spontaneous apoptosis of human neutrophils. A potent proteasome inhibitor, MG-132 suppressed TNF-a plus CHX-induced degradation of Mcl-1 in HEK293 cells, indicating proteasome-mediated degradation of Mcl-1. It has been shown that proteasomal degradation of Mcl-1 is regulated by phosphorylation and subsequent ubiquitination. Dibutyryl-cAMP (db-cAMP), an analog of cAMP that stimulates cAMP-dependent protein kinase (PKA), inhibited TNF-a plus CHX-induced degradation of Mcl-1 as well as apoptosis in HEK293 cells, suggesting the involvement of PKA. Four amino acid residues (S150, S159, S178, and T266) of the human Mcl-1 polypeptide were predicted to be phosphorylation sites for PKA by the NetPhosK server. Interestingly, transfection of a site-directed phosphorylation-deficient human Mcl-1 mutant/4A led to the detachment of HEK293 cells, indicating the induction of apoptosis. Mcl-1 overexpression has been reported in a variety of human tumors, including haematological and solid cancers. The human Mcl-1 mutant/4A is a potential cancer therapeutic gene.

Keywords: Apoptosis, Mcl-1, cAMP agonist, PKA, Phosphorylation, therapeutic gene

Biography:

Hisakazu Fujita, completed his doctorate in cancer biology at Hokkaido University in 1991. After his training as a post-doctorate at Rockefeller University, he started his career in the Laboratory of Molecular Genetics at Cancer Institute, Hokkaido University in 1992. In 2003, he moved to the National Cardiovascular Center Research Institute as the Chief of the Laboratory. In 2006, he joined the Department of Physiology at Osaka City University as the Senior Lecturer. In 2017, he moved to the Department of Scientific and Linguistic Fundamentals of Nursing, Osaka City University/Osaka Metropolitan University, Graduate School of Nursing as the Associate Professor.

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