*S-10 [17:20~17:50]*

## The Role and Regulation of MCL-1 Proteins in Apoptosis Pathway

Jeehyeon Bae, Ph.D

Stanford University, U.S.A.

Phylogenetically conserved Bcl-2 family proteins play a pivotal role in the regulation of apoptosis from virus to human. Members of the Bcl-2 family consist of antiapoptotic proteins such as Bcl-2, Bcl-xL, and Bcl-w, and proapoptotic proteins such as BAD, Bax, BOD, and Bok. It has been proposed that anti- and proapoptotic Bcl-2 proteins regulate cell death by binding to each other and forming heterodimers. A delicate balance between anti- and proapoptotic Bcl-2 family members exists in each cell and the relative concentration of these two groups of proteins determines whether the cell survives or undergoes apoptosis.

Mcl-1 (Myeloid cell leukemia-1) is a member of the Bcl-2 family proteins and was originally cloned as a differentiation-induced early gene that was activated in the human myeloblastic leukemia cell line, ML-1. Mcl-1 is expressed in a wide variety of tissues and cells including neoplastic ones. We recently identified a short splicing variant of Mcl-1 short (Mcl-1S) and designated the known Mcl-1 as Mcl-1 long (Mcl-1L). Mcl-1L protein exhibits antiapoptotic activity and possesses the BH (Bcl-2 homology) 1, BH2, BH3, and transmembrane (TM) domains found in related Bcl-2 proteins. In contrast, Mcl-1S is a BH3 domain-only proapoptotic protein that heterodimerizes with Mcl-1L. Although both Mcl-1L and Mcl-1S proteins contain BH domains found in other Bcl-2 family proteins, they are distinguished by their unusually long N-terminal sequences containing PEST (proline, glutamic acid, serine, and threonine) motifs, four pairs of arginine residues, and alanine- and glycine-rich regions. In addition, the expression pattern of Mcl-1 protein is different from that of Bcl-2 suggesting a unique role for Mcl-1 in apoptosis regulation.

Tankyrase1 (TRF1-interacting, ankyrin-related ADP-ribose polymerase1) was originally isolated based on its binding to TRF1 (telomeric repeat binding factor-1) and contains the sterile alpha motif (SAM) module, 24 ankyrin (ANK) repeats, and the catalytic domain of poly(adenosine diphosphate-ribose) polymerase (PARP). Previous studies showed that tankyrase1 promotes telomere elongation in human cells presumably by inhibiting TRF1 though its poly(ADP-ribosyl)ation by tankyrase1. In addition, tankyrase1 poly(ADP-ribosyl)ates insulin-responsive amino peptidase (IRAP), a resident protein of GLUT4 vesicles, and insulin stimulates the PARP activity of tankyrase1 through its phosphorylation by mitogen-activated protein kinase (MAPK). ADP-ribosylation is a posttranslational modification that usually results in a loss of protein activity presumably by enhancing protein turnover. However, little information is available regarding the physiological function(s) of tankyrase1 other than as a PARP enzyme.

In the present study, we found tankyrase1 as a specific-binding protein of Mcl-1. Overexpression of tankyrase1 led to the inhibition of both the apoptotic activity of Mcl-1S and the survival action of Mcl-1L in mammalian cells. Unlike other known tankyrase1-interacting proteins, tankyrase1 did not poly(ADP-ribosyl)ate either of the Mcl-1 proteins despite its ability to decrease Mcl-1 proteins expression following coexpression. Therefore, this study provides a novel mechanism to regulate Mcl-1-modulated apoptosis in which tankyrase1 downregulates the expression of Mcl-1 proteins without the involvement of its ADP-ribosylation activity.