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# RING-mutant Mdm2-M459I Confers Anti-apoptotic Effect in Primary Cells

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## Image Article

Recently, we reported that a novel RING-mutation, Mdm2-M459I, greatly impairs its ubiquitin ligase activity. Mdm2-M459I stabilizes glycolytic enzyme PGAM, followed by transformation of mouse embryonic fibrobalsts (MEFs) [1]. Here we addressed a question whether Mdm2-M459I could also affect anti-apoptotic effect, the other hallmark of cancer. We compared three mutants of Mdm2 described in COSMIC database; Y281H and W329G are located in its central domain, while M459I in the RING finger motif (Figure 1A). Primary MEFs transfected with wild type or mutant versions of Mdm2 were exposed to oxidative stress or DNA damage. Noteworthy, only M459I mutation restored the viability of primary MEFs in these conditions (Figure 1B), associated with decrease of cleaved PARP (Figure 2A and B). Thus Mdm2-M459I also plays anti-apoptotic role as oncogene.

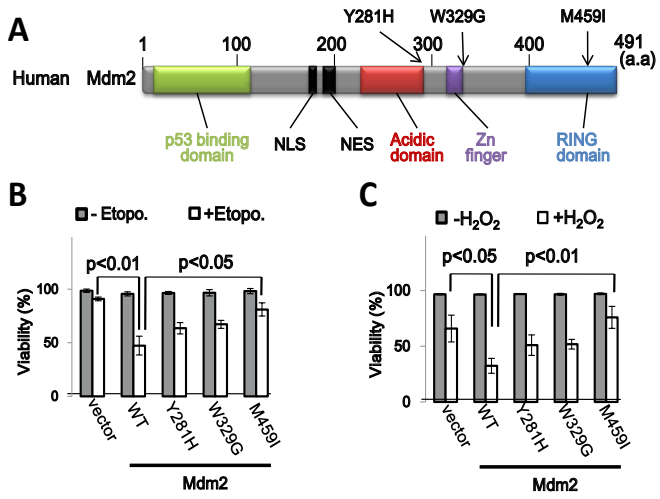


**Figure 1:** (A) Schematic diagram of human Mdm2 and the location of cancer related mutations in Mdm2 according to COSMIC (Catalogue of Somatic Mutations in Cancer) database (http://www.sanger.ac.uk/genetics/CGP/cosmic/). (B and C) Primary MEFs were transfected with various Mdm2 expression vectors or empty vector. Cell viability after exposure to 50 μM Etoposide for 24 hours (B) or exposure to 50 μM $H_2O_2$ for 24 hours (C) as measured by tripan blue stain .Error bar is indicate SE.

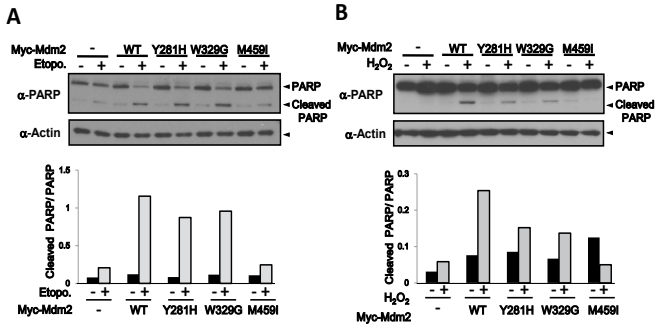


**Figure 2:** (A and B) Various mutant or wild type Mdm2 expressing MEFs were exposed to Etoposide (A) or $H_2O_2$ (B). Apoptotic marker (cleaved PARP) were detected by immunoblotting using anti-PARP antibody (Top), and band intensities were used to assess the level of Cleaved PARP relative to those of full length PARP in each sample (Bottom).

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### Reference

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