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A Decision between DNA Repair and Execution of Cell Death

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Inhibition of DNA repair was required in cells undergoing apoptosis. However, the switching mechanism between DNA repair and apoptosis has been poorly understood. In the present study, a possible mechanism responsible to the inhibition of DNA repair during apoptosis was presented. During the course of apoptosis induced by UV, DNA repair was evaluated by measuring the removal of DNA damages in HeLa cells. DNA repair was elevated by apoptosis inhibitors. The level of DNA repair was higher in the cells over-expressing Bcl-2 or cells treated with inhibitors of caspase, which are known to play crucial roles in the initiation of apoptosis. The proteolytic cleavage of poly(ADP-ribose) polymerase (PARP) occurred in apoptotic cells before the completion of DNA fragmentation has been regarded as a biochemical hallmarker of apoptosis. Data shows that the cleavage of PARP was also inhibited by expression of Bcl-2 and treatment of DEVD-CHO, which is caspase-3 inhibitor. The N-terminal fragment of PARP cleaved by caspase was isolated and inhibition of DNA repair synthesis was observed in a cell-free system in which N-terminal PARP fragment was added to the cell extracts of UV irradiated HeLa cells. The removal of UV damages and UV induced DNA repair synthesis were inhibited by the expression of the exogeneous PARP fragments in HeLa cells with the increased level of apoptosis. The inhibitory effects of Bcl-2 and caspase inhibitors on apoptosis was abrogated in the cells expressing PARP fragments. Increased DNA repair by the inhibition of apoptosis was also reduced by the expression of PARP fragments. It was found that the N-terminal fragment of PARP preferentially bound to DNA strand breaks, while C-terminal fragment inhibits PARP activity. This self-inhibition of PARP by C-terminal fragment seems to be mediated by the irregular dimerization of PARP between its automodification domain. In the present study, we conclude that the cleavage of PARP by caspases stimulates the apoptosis but inhibits DNA repair.