F847 Induction of p21 and apoptosis by C11 in human hepatocarcinoma cells

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C11, a chloride-containing VK3 analog, acts as a mediator of programmed cell death in SK-Hep-1 cell lines, but its molecular mechanisms linked to cell death are not understood. In this study, we investigated the expression of p21 gene and its relationship to apoptosis induced by C11. In SK-hep-1 cells, the addition of C11 resulted in time-dependent growth suppression and DNA fragmentation characteristics of apoptosis. p21 protein was induced during this process, while the protein level of p53 was not changed at the same condition. This apoptotic cell death with p21 induction was also observed in the Hep3B cells lacking functional p53 after treatment of C11. These results suggest that C11-induced apoptosis is associated with up-regulation of p21 protein in p53-independent pathway. Next, in order to confirm whether the p53-independent p21 induction is required for C11-induced apoptosis, we introduced the p21 gene into Hep3B. Overexpression of p21 did not affect the expression of the bcl-2 gene, but DNA fragmentation and PARO cleavage were significantly increased. These data indicate that p21 is involved in C11-induced apoptosis. Although Bcl-2 has been implicated to interfere with an essential signaling molecule involved in the apoptosis pathway, its molecular mechanism and target molecule are poorly understood. To determine the effects of bcl-2 overexpression on apoptosis and to investigate whether Bcl-2 interfers with the p53-independent p21 pathway, we transfected the bcl-2 expression vector into SK- Hep-1 cels. Overexpression of Bcl-2 prevented C11-induced apoptosis. Taken together, C11-induced apoptosis is regulated by p52-independent p21 pathway and bcl-2 may inhibit functional activity of p21, therebe may inhibit the C11-induced apoptosis.