Summary of Results

- PTP-S2 overexpression induced mRNA levels of caspase-1 and its regulator Ipaf in MCF-7 cells in a p53 dependent manner. Ipaf mRNA induction, but not that of caspase-1, was also dependent on p73, a p53 family member.
- Inhibition of Ipaf function using DN-Ipaf inhibited PTP-S2 induced apoptosis in MCF-7 cells. Knockdown of Ipaf gene expression using RNA interference strategy also inhibited PTP-S2 induced apoptosis.
- These results show that Ipaf gene expression is required for PTP-S2 induced apoptosis.
- Caspase-1 expression sensitized MCF-7 cells to doxorubicin-induced apoptosis and this apoptosis was enhanced upon co-expression of Ipaf. Mutant caspase-1 did not enhance doxorubicin-induced apoptosis when co-expressed with Ipaf. shRNA mediated knockdown of Ipaf inhibited doxorubicin induced apoptosis in caspase-1 expressing MCF-7 cells. It also inhibited IL-1β processing by exogenous caspase-1 in response to doxorubicin.
- These results indicate a requirement of endogenous Ipaf in doxorubicin-induced apoptosis mediated by caspase-1.
- Co-expression of caspase-1 with activated Ipaf resulted in caspase-1 activation as well as enhanced apoptosis. This apoptosis, but not caspase-1 processing, was inhibited by co-expression of Bcl-2 and caspase-9s. Doxorubicin induced apoptosis in MCF-7 cells expressing Ipaf and caspase-1 was also inhibited by Bcl-2 and caspase-9s.
- Expression of caspase-1 and activated Ipaf in MCF-7 cells induced proteolytic processing of Bid protein, Bax activation and mitochondrial outer membrane permeabilization. Mitochondrial intermembrane proteins, cytochrome c and Omi were detected in cytosol under these conditions. This release was inhibited by Bcl-2, but not by caspase-9s.
- PTP-S2 induced mitochondrial outer membrane permeabilization was inhibited by co-expression of mutant caspase-1.
- These results reveal an upstream role for caspase-1 and Ipaf in p53 dependent apoptosis induced by PTP-S2 and doxorubicin.
- Doxorubicin treatment induced caspase-3 gene expression in MCF-7 cells in a p53 dependent manner. A p53 binding site was identified in the third intron of caspase-3 gene.