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Intracellular Reactive Oxygen Species enhances the survival of cells under the conditions of ER stress

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An increase in reactive oxygen species (ROS) level in cells that are in a state of stress has been known for a very long time but the underlying functional significance is as yet uncertain. We have addressed this issue by examining the role played by ROS in instances of endoplasmic reticulum (ER) stress in HeLa cells. The treatment of these cells with tunicamycin resulted in sustained increase in intracellular level of ROS that is susceptible to quenching by either N-acetylcysteine(NAc) or dithiolthreitol(DTT), but not by ascorbic acid. The reduction of the availability of folding substrates through inhibition of protein synthesis with cycloheximide resulted in complete absence of tunicamycin-induced phosphorylation of PERK and the splicing of XBP-1, but the increase in ROS level and eIF2α phosphorylation was still observed. The quenching of ROS in tunicamycin-treated cells resulted in partial reduction of eIF2α phosphorylation but otherwise had no effects on the extent of stress-induced inhibition of global protein synthesis, the phosphorylation of PERK and the splicing of XBP. More importantly, significant increase in caspase activities and cell death was observed when tunicamycin was added to cells in the simultaneous presence of NAc or DTT, or to cells that over-expressed catalase to remove intracellular hydrogen peroxide. Our experiments rather unexpectedly reveal that there is a lack of correlation between protein folding and ROS production in ER-stressed cells and that ROS may function to lengthen the period of cellular survival under the condition of continuous stress