

MANGANESE SUPEROXIDE DISMUTASE VS P53: MITOCHONDRIA AT THE CENTER

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Manganese superoxide dismutase (MnSOD) is a nuclear-encoded antioxidant enzyme that localizes to the mitochondria. Expression of MnSOD is essential for the survival of aerobic life and increased expression of MnSOD has been shown to protect against prooxidant conditions leading to normal tissue injury. Using transgenic mice, we have demonstrated that MnSOD modulates tumor formation caused by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) by regulation of cellular proliferation pathways. However, MnSOD deficiency did not lead to an enhanced tumorigenesis because it can also modulate the p53 mediated apoptosis pathways. TPA induces p53 translocation to mitochondria and nucleus, a response, which eventually leads to apoptosis. Rapid mitochondrial translocation preceding nuclear translocation is a general response of p53 to oxidative stress inducing agents in vitro and in vivo. In the mitochondria, p53 interacts with MnSOD, and reduces its superoxide scavenging activity, leading to an amplification of p53-mediated transcriptional responses.

We also demonstrated that translocation of p53 to mitochondria can be prevented by overexpression of nucleophosmin (NPM). The NPM-mediated reduced levels of p53 in mitochondria are associated with an increased stability of p53 suggesting that the absence of p53 in NPM over-expressing cells is not due to NPM-mediated p53 degradation. Stabilization of p53 by NPM enhances the expression of p53 target genes p21 and Bax. However, the increase in Bax level without p53 in mitochondria does not lead to an increase in TPA-induced apoptosis suggesting that the presence of p53 in mitochondria is important for p53-mediated apoptosis. Suppression of NPM by NPM siRNA leads to an increase of p53 levels in mitochondria and apoptosis. Furthermore, suppression of NPM in tumor cells with a high constitutive level of NPM results in p53 translocation to mitochondria and enhances TPA-mediated apoptosis. These results establish that p53 localization to mitochondria plays a critical role in apoptosis even when p53 is present at high levels in the nucleus.