

**Suppression of MIA PaCa-2 Malignant Phenotype By SOD:
Role of MnSOD, CuZnSOD, and EcSOD on cell proliferation,
cell cycle distribution, and tumor invasion.**

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ABSTRACT

K-ras mutations have been identified in approximately 95% of human pancreatic cancers, implying their critical role in the molecular pathogenesis. Since ras over expression leads to increased plasma-membrane generated superoxide, we determined if scavenging the superoxide with superoxide dismutase enzymes (i.e., MnSOD, EcSOD, and CuZnSOD) would suppress growth of a K-ras mutated pancreatic cancer cell line, MiaPaCa-2. Enforced over expression of enzymes involved with superoxide scavenging were shown to decrease pancreatic cancer cell superoxide production as well as slightly increasing cell death and CuZnSOD had the greatest effect on inhibition of growth in cell culture. To further evaluate the tumor suppressive effects of SODs, we performed an *in vivo* study using nude mice with human pancreatic cancer tumor xenografts. Although AdMnSOD, AdCuZnSOD, and AdEcSOD all inhibited pancreatic human tumor growth in mice, AdEcSOD provided the best tumor suppression and longest animal survival. Most importantly, SOD over expression greatly reduced metastatic potential as indicated by Matrigel invasion assays. The reduction in invasiveness correlated well with parameters indicative of angiogenesis inhibition suggesting a role of these SODs in regulating tumor blood vessel formation essential for tumor growth. These observations imply that modulation of intracellular levels of reactive oxygen species in pancreas cancer cells lead to inhibition of tumor growth as well as reducing tumor invasiveness.