Targeting Redox Homeostasis in Malignant Mesothelioma

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Effective therapy is lacking for malignant mesothelioma (MM), a highly aggressive cancer linked to occupational asbestos exposure. Redox-dependent signaling by reactive oxygen species (ROS) plays an important role in cancer pathogenesis, and may represent a therapeutic target in MM. We have explored the role of FOXM1, a redox-dependent transcription factor that regulates resistance to oxidative stress and entry into G2/M in MM cell proliferation and viability. FOXM1 is expressed at higher levels in MM cells and, in contrast to control telomerase-immortalized mesothelial cell line LP9, continues to be expressed in the absence of growth factors. Human MM tumors express more FOXM1 transcript than normal mesothelial tissue, and immunostaining of human MM tissue arrays confirms that FOXM1 is highly expressed in human MM. Studies in vitro show that MM cells constitutively generate approximately twice the level of superoxide, which is predominantly derived from mitochondria. The triphenylmethane gentian violet (GV) and the thiazole antibiotic thiostrepton (TS) inhibit FOXM1 expression, MM tumor cell viability and impede tumor progression in mouse xenograft models of human MM. While GV induces mitochondrial depolarization and inhibits the production of mitochondrial ROS, and TS hyperpolarizes the mitochondria and increases mitochondrial ROS production, both compounds extinguished the expression of FOXM1 mRNA and protein in a dose-dependent manner. TS, but not GV, alters the electrophoretic mobility of the mitochondrial antioxidant enzyme peroxiredoxin 3 (PRX3), possibly by adducting the peroxidatic cysteine, thereby inducing intolerable levels of mitochondrial oxidative stress. Interestingly GV markedly potentiates the effect of TS on PRX3. Taken together, our studies indicate that expression of FOXM1 is tuned to mitochondrial oxidant production, and compounds that target the redox homeostasis of mitochondria may be useful in the treatment of MM.