Investigating p16 Control of Mitochondrial Biogenesis in Melanoma

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Melanoma is the most dangerous type of skin cancer and its incidence has significantly increased in the past decade. Inherited mutations in CDKN2A, which encodes the p16 tumor suppressor, predispose individuals to melanoma. The purpose is to further understand the genetic basis of melanoma in order to provide future advances in prevention and therapy. Cells used are wild-type (WT) fibroblasts, p16-deficient (p16-/-) fibroblasts, and A375, a human malignant melanoma cell line. A375 cells were infected with either the GFP lentivirus or lentivirus overexpressing p16. Western blotting was used to analyze protein expression. Other methods used were a cell migration assay, flow cytometry for determination of mitochondrial mass and ROS, and the MitoStress Test to measure oxygen consumption rates. Increased mitochondrial mass in p16-/- cells was consistent with increased expression of mitochondrial proteins. Increased mitochondrial biogenesis was correlated with increased expression of the PRC (PGC-1-related coactivator) and mitochondrial transcription factor A (TFAM). A375 cells overexpressing p16 showed decreased expression of mitochondrial proteins compared to control cells. p16-deficient cells showed increased cell migration, which was significantly reduced by addition of ROS-quenching agent NAC or the mitochondrial poison CCCP. Overexpression of p16 in A375 cells was also associated with increased respiration capacity. The results indicate that loss of p16 promotes mitochondrial biogenesis, which results in enhanced ROS production and cell migration, and is associated with decreased mitochondrial respiration capacity. Further identification of the mechanisms by which p16 controls mitochondrial function leads to improved treatments or prevention of melanoma in the future.

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