Analysis of the functional integrity of the p53 tumor-suppressor gene in malignant melanoma.

Abstract:
Derogation of the p53 pathway is a hallmark in human malignancies but its implication in melanomas remains unclear. p53 is frequently accumulated in melanomas despite protein stabilizing mutations being rare. For a panel of six melanoma cell lines we performed transcript sequence analysis of the entire coding region and determined p53 protein stability and messenger RNA stability by western blot experiments and quantitative reverse-transcription-PCR, respectively. Transcript levels of p53 modifying genes as well as p53 target genes were investigated after ultraviolet irradiation, interferon-?2b, and chemotherapy (cisplatin or dacarbazine) by quantitative reverse-transcription-PCR. Transcript sequence analysis identified three aberrations in three of six melanomas. Four of six melanomas showed high-constitutive p53 protein levels. p53 transcripts remained stable in four of six melanomas. All p53-expressing melanomas displayed high p53 protein stability. Constitutively, and after ultraviolet irradiation, mouse double min-2 expression was reduced in melanomas. We detected high homeodomain-interacting protein kinase-2 level in melanomas-expressing mutant p53. Most experimental conditions resulted in lower expression of p21, GADD45A, and PUMA, and a higher expression of CDC2 in melanomas. Altogether, accumulation of p53 protein is due to
posttranslational modification or aberrant expression of p53 modifiers. p53 is functionally disrupted although the p53 upstream signaling pathway remains inducible.