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Titel des Beitrags:
Differential effects of genes of the Rb1 signalling pathway on osteosarcoma incidence and latency in alpha-particle irradiated mice.

Abstract:
Osteosarcoma is the most frequent secondary malignancy following radiotherapy of patients with bilateral retinoblastoma. This suggests that the Rb1 tumour suppressor gene might confer genetic susceptibility towards radiation-induced osteosarcoma. To define the contribution of the Rb1 pathway in the multistep process of radiation carcinogenesis, we evaluated somatic allelic changes affecting the Rb1 gene itself as well as its upstream regulator p16 in murine osteosarcoma induced by (227)Th incorporation. To distinguish between the contribution of germline predisposition and the effect of a 2-hit allelic loss, two mouse models harbouring heterozygote germline Rb1 and p16 defects were tested for the incidence and latency of osteosarcoma following irradiation. We could show that all tumours arising in BALB/c×CBA/CA hybrid mice (wild-type for Rb1 and for p16) carried a somatic allelic loss of either the Rb1 gene (76.5%) or the p16 gene (59%). In none of the tumours, we found concordant retention of heterozygosity at both loci. Heterozygote knock-out mice for Rb1 exhibit a significant increase in the incidence of osteosarcoma following (227)Th incorporation (22/24 in Rb1+/− vs. 2/18 in Rb1+/+, p=4×10(-5)), without affecting tumour latency. In contrast, heterozygote knock-out mice for p16 had no significant change in tumour
incidence, but a pronounced reduction of latency (LT(50%) = 355 days in p16+- vs. 445 days in p16+/-, p=8×10(-3)). These data suggest that Rb1 germline defects influence early steps of radiation osteosarcomagenesis, whereas alterations in p16 mainly affect later stages of tumour promotion and growth.