The tumor suppressor role of ARID1A

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ARID1A (BAF250A), a gene participating in the formation of a BRG1 SWI/SNF chromatin remodeling complex, has emerged as a potential tumor suppressor because of its frequent inactivating mutations in gynecological cancer (approximately 50% of ovarian clear cell and 30% of ovarian endometrioid carcinomas). The mutation is associated with loss of protein expression as assessed by immunohistochemistry. In this study, we evaluated ARID1A immunoreactivity in a wide variety of carcinomas to determine the prevalence of ARID1A inactivation in carcinomas. Immunoreactivity was not detected in 36 (3.6%) of 995 tumors. Uterine low-grade endometrioid carcinomas showed a relatively high-frequency loss of ARID1A expression, as 15 (26%) of 58 cases were negative. Mutational analysis showed 10 (40%) of 25 uterine endometrioid carcinomas; none of 12 uterine serous carcinomas and none of 56 ovarian serous and mucinous carcinomas harbored somatic ARID1A mutations. These findings suggest that the molecular pathogenesis of low-grade uterine endometrioid carcinoma is similar to that of ovarian low-grade endometrioid and clear cell carcinoma, tumors that have previously been shown to have a high-frequency loss of expression and mutation of ARID1A. We further studied the functions of ARID1A and found that restoration of wild-type ARID1A expression in ovarian cancer cells harboring ARID1A mutations suppressed cellular proliferation and tumor growth in mice. Gene silencing of ARID1A in non-transformed epithelial cells enhanced cellular proliferation and tumorigenicity. Mutations in ARID1A and TP53 were mutually exclusive in tumor specimens, and knockdown of ARID1A affected multiple p53-regulated genes and pathways, including CDKN1A and SMAD3. The ARID1A/BRG1 complex bound to the promoters and enhanced transcriptional activity of CDKN1A and SMAD3 in a p53-dependent manner. We further showed that p21 mediated, at least in part, the tumor suppressive functions of ARID1A. These results provide new evidence that ARID1A functions as a tumor suppressor by directly modulating transcriptional activity of several p53-regulated genes.