Histone deacetylases (HDAC) reverse the acetylation of histone and nonhistone proteins and thereby modulate chromatin structure and function of nonhistone proteins. Many tumor cell lines and experimental tumors respond to HDAC inhibition. To assess the role of an individual HDAC isoenzyme in physiology and tumor development, HDAC2-mutant mice were generated from a gene trap embryonic stem cell clone. These mice express a catalytically inactive fusion protein of the NH(2)-terminal part of HDAC2 and beta-galactosidase, which fails to integrate into corepressor complexes with mSin3B. They are the first class 1 HDAC mutant mice that are viable although they are approximately 25% smaller than their littermates. Cell number and thickness of intestinal mucosa are reduced. Mutant embryonic fibroblasts fail to respond to insulin-like growth factor I (IGF) by the IGF-I-induced increase in cell number observed in wild-type cells. These data suggest a novel link between HDACs and IGF-I-dependent responses. Crossing of HDAC2-mutant with tumor-prone APC(min) mice revealed tumor rates that are lower in HDAC2-deficient mice by 10% to 100% depending on segment of the gut and sex of the mice. These mice provide evidence that the key functions of HDAC2, although not essential for survival of the organism, play a rate-limiting role
for tumor development in vivo.

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