

B1 Role of polyamine metabolism in neoplastic growth

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In mammals, putrescine is provided predominantly by the action of ornithine decarboxylase (ODC). We have generated transgenic mice that overexpress antizyme (AZ) from the bovine keratin 5 (K5) and 6 (K6) promoter elements. Antizyme is a multifunctional regulator of polyamine metabolism that inhibits ODC activity, stimulates ODC degradation and suppresses polyamine uptake. These mice show a dramatic reduction in susceptibility to two stage carcinogenesis protocols. The K5-AZ line was also much less susceptible to N-nitrosomethylbenzylamine-induced forestomach carcinogenesis. Carcinogenesis is enhanced by feeding a zinc deficient diet which leads to hyperplasia of the forestomach epithelium. This hyperplasia was not seen in the K5-AZ mice. These results indicate that AZ suppresses tumor growth and these mice provide a valuable model system to evaluate the role of ODC and polyamines in tumorigenesis. The K6 promoter was also used to target expression of spermidine/spermine-N1- acetyltransferase (SSAT) to epidermal keratinocytes in the hair follicle of transgenic mice. K6-SSAT transgenic mice showed a remarkable increase in epidermal tumor incidence in response to two stage carcinogenesis protocols and in the number of tumors progressing to carcinomas. These results suggest that activation of polyamine catabolism and/or associated oxidative damage from the SSAT/polyamine oxidase pathway accelerates neoplasia.