

B12 Polyamines as modifiers of genetic risk factors in human intestinal cancers

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Polyamines are downstream mediators of genetic risk factors in human intestinal cancers. The adenomatous polyposis coli (APC) tumor suppressor gene, which is mutated in essentially all human colon cancers, regulates the expression of several e-box transcription factors. These factors, in turn, regulate the transcription of ornithine decarboxylase (ODC), the first enzyme in polyamine synthesis. The Kirsten ras (K-ras) oncogene regulates the expression of several genes, including suppressing the expression of the peroxisomal proliferator activated receptor gamma (PPAR γ). This PPAR, in turn, activates the expression of the spermidine/spermine N¹-acetyltransferase (SSAT), the first enzyme in polyamine catabolism. The nonsteroidal anti-inflammatory drug (NSAID) sulindac induces the transcription of SSAT via activation of PPAR γ . Inactivation of the APC tumor suppressor gene, and activation of the K-ras oncogene, have the combined effect of increasing tissue polyamine contents due to increased synthesis and decreased catabolism of the polyamines. Pharmacological strategies suppressing ODC (e.g. the enzyme activated inhibitor α -difluoromethylornithine) and activating SSAT (e.g. NSAIDs) are potent inhibitors of intestinal carcinogenesis in rodent models. Clinical trials combining these classes of agents, in humans with risk factors for colon cancer, are in progress.