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EXPERIMENTAL STUDIES FOR PREVENTION OF LARGE BOWEL CARCINOGENESIS; A NEW BIOMARKER AND ITS ROLE

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Large bowel cancer is one of the major causes of increasing world-wide cancer mortality. Our group has found a variety of naturally-occurring and synthetic compounds which have chemopreventive potentials against the occurrence of large bowel cancers using animal models. Aberrant crypt foci (ACF) which develop in rodents soon after the carcinogen exposure have been used as a biomarker for screening effective agents for cancer chemoprevention. Very recently, our group demonstrated the presence of probable premalignant lesions with frequent β-catenin gene mutations and accumulations of the corresponding protein by exmination in *en face* preparations and in serial sections after the observation in whole mount preparations of the colon epithelium in rats which received azoxymethane (AOM). These lesions also occur soon after the carcinogen exposure like ACF are lacking ACF appearance. Expression of such β-catenin accumulated crypts (BCAC) was found to be markedly suppressed by COX 2-inhibitors such as celecoxib and enhanced by tumor promoters like cholic acid. We also found that induction of apoptosis being regarded as a mechanism of chemopreventive agents is generated by exposure of sulindac, a NSAID in AOM-induced BCAC in rats. BCAC are suggested to be truly premalignant lesions for large bowel cancers and are considered useful for a beneficial biomarker not only for screening reliable agents to prevent occurrence of cancers but also for investigating mode of actions of chemopreventing agents.