Crucial involvement of tumor necrosis factor in colon carcinogenesis

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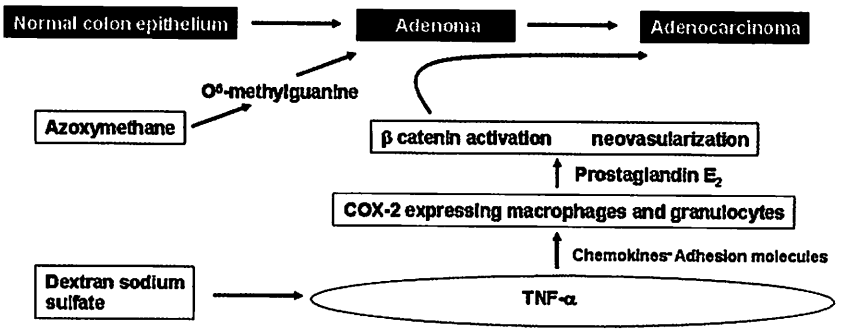
The risk of colon cancer is 20- to 30-fold higher in patients with ulcerative colitis, than in a control population. These observations suggest the crucial contribution of chronic inflammation to colon carcinogenesis. Multiple colon tumors with nuclear accumulation of β-catenin, develop in mice after an intraperitoneal injection of a generator of O^6-methylguanine, azoxymethane (AOM), followed by a repetitive oral intake of dextran sodium sulfate (DSS) solution. This condition mimics colon carcinoma development in patients with ulcerative colitis. Accumulating evidence indicates the crucial role of the activation of a transcription factor NF-κB in this model, although it remains elusive which factor(s) is responsible for NF-κB activation. We examined the role of tumor necrosis factor (TNF), a potent activator of NF-κB, in this model

Treatment with AOM + DSS caused TNF-α expression and TNF-receptor p55 (TNF-Rp55)-expressing inflammatory cell infiltration in lamina propria and submucosal regions of colon, together with enhanced cyclooxygenase (COX)-2 expression. TNF-Rp55-deficient mice developed much less numbers of colon tumors, along with reduced inflammatory cell infiltration and COX-2 expression. COX-2 was expressed mainly by infiltrating granulocytes and macrophages. The analysis using bone marrow chimeric mice revealed that bone marrow-derived cells were mainly responsible for tumor formation. Thus, locally-produced TNF-α is presumed to recruit TNF-Rp55-expressing granulocytes and macrophages, main producers of COX-2, therby contributing to colon carcinogenesis. Administration of etanercept, a specific antagonist of TNF-α, after multiple tumor formation induced by AOM + DSS, markedly reduced the numbers and sizes of tumors and reduced colonic infiltration of granulocytes and macrophages, COX-2 expression, and tumor neovascularization.

These observations identify TNF-α as a crucial mediator of the initiation and progression of colitis-associated colon carcinogenesis.



Reference

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