MUCIN DEPLETED FOCI (MDF) ARE USEFUL BIOMARKERS TO STUDY INFLAMMATION- INDUCED COLON CARCINOGENESIS IN RODENTS

Femia A. Pietro, Dolara Piero, Tarquini Elena, Salvadori Maddalena and Caderni Giovanna

Department of Pharmacology University of Florence, Florence, Italy

Colon carcinogenesis induced in rodents by azoxymethane (AOM) or 1-2 dimethylhydrazine (DMH) evolves through the sequential formation of histopathological lesions similar to those observed in spontaneous carcinogenesis in humans. In this process, preneoplastic lesions, still not endowed of all the alterations proper of more advanced lesions but already showing some of them, can be used as biomarkers in experimental studies aimed the identification of agents able to block or promote colon carcinogenesis. Aberrant crypt foci (ACF), purported preneoplastic lesions identifiable in whole mount preparations of unsectioned colons (1) have been widely used as a short-term assay to predict carcinogenesis, but in the last few years some observations have questioned the use of ACF as reliable biomarkers of carcinogenesis. Recently, we described the formation of dysplastic crypt foci with scant mucin production in rodents treated with DMH or AOM (2). These mucin-depleted foci (MDF) show many characteristic of preneoplastic lesions, such as activation of Wnt signaling, mutations in *β-catenin* and *Apc* gene and good correlation with carcinogenesis (3). Since epidemiological and experimental studies suggest that chronic inflammation (colitis) may promote the development of colorectal cancer (5), we though interesting to study the induction of preneoplastic lesions such as ACF and MDF in a mouse model of colonic inflammation induced by dextran sodium sulphate (DSS). Accordingly, sixteen CD1male mice, aged 4-5 weeks, were treated with AOM (10 mg/kg i.p.) and one week later randomly divided into two groups. DSS group was given 2% DSS in drinking water for 1 week to induce colitis, while Controls received just water. Mice were sacrificed 6 weeks later and ACF and MDF determined as described (2). While the number of ACF/colon was not varied, the number of MDF was significantly higher in the group treated with DSS than in controls (mean number of MDF/colon: 10.1±2.2 (SD) and 1,2±1.6 in DSS and control groups, respectively, $P<0.001$). Since DSS treatment has been demonstrate to induce colon cancers at later time points, these results, showing that DSS induced colitis promote the growth of MDF, further confirm the precancerous nature of these lesions. The results also indicate that this model can be used to study the effect of anti-inflammatory agents in short term tests in which MDF are used as surrogate biomarkers of colon carcinogenesis.

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