CELECOXIB MODULATES THE EXPRESSION OF ADHESION MOLECULES IN COLON CANCER CELLS

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Celecoxib is a selective COX-2 inhibitor approved in 2003 by the EMEA, as an adjunct to surgery and further endoscopic surveillance for reducing the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP). However, the mechanisms of action for the cancer chemoprevention of celecoxib and other COX inhibitors are not fully understood. It has been shown that COX-2 inhibitors can interfere with cellular adhesion machinery. Since intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) can play a role in metastases formation, aim of this work was to study the effect of celecoxib on ICAM-1 and VCAM-1 expression in colon cancer cell line HT29. Celecoxib down-regulated ICAM-1 and VCAM-1 expression in HT29 with a maximum effect observed at 10 μM and after 4 h of incubation. These effects were not produced by rofecoxib suggesting a COX-independent mechanism. To investigate the signalling pathways involved in these effects, we have evaluated the role of mitogen-activated protein kinases (MAPKs) in celecoxib modulation of adhesion molecule expression on HT29. Celecoxib (10 μM) reduced activation of p54 c-Jun terminal NH_2 kinase (JNK) and p38 MAPKs and the pretreatment with the specific inhibitors of these kinases, respectively SP600125 or SB202190, reduced ICAM-1 and VCAM-1 expression. On the contrary, ICAM-1 and VCAM-1 expressions were not affected by PD98059, a p42/44 inhibitor. To evaluate the functional significance of this observation, we performed experiments of HT29 cell adhesion to FCS-coated plastic wells. Celecoxib inhibited HT29 adhesion to FCS-coated plastic wells in a concentration-dependent manner, and cell pretreatment with antibodies blocking ICAM-1 and VCAM-1 had the same effects. All selective MAPK inhibitors decreased HT29 adhesion to plastic. Moreover, we have studied the effects of celecoxib on apoptosis in HT29 demonstrating that this drug induced Bax and BID while downregulated Bcl-2. In conclusion, our results show that celecoxib mediates down-regulation of ICAM-1 and VCAM-1, affecting adhesive proprieties of HT29 in a COX-independent way, inhibiting MAPKs p54 and p38 activation, and activating a proapoptotic pathway.