SUMMARY

Background:

Long-standing ulcerative colitis (UC) has an increased risk of evolving into colorectal cancer (CRC) and upregulated expression of cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS), survivin, telomerase catalytic subunit (TERT), integrin-linked kinase (ILK) and transcription factors c-MYB and TCF-4, has been implicated in the development and progression of sporadic colorectal cancer. Nevertheless much less is known about their role in the process of UC-associated colon carcinogenesis.

Methods:

We analyzed the gene expression of these markers during the transition of colonic mucosa from chronic inflammation to epithelial neoplasia in biopsies of UC patients using quantitative real-time polymerase chain reaction and immunohistochemistry, and compared the expression profiles of this gene panel in samples of patients with CRC and in human tumor xenografts of SW620 malignant colonic cells. Additionally, we determined the expression of these genes in mouse models of sporadic and colitis-associated CRC in A/J and ICR mouse strains using quantitative RT-PCR and laser microdissection.

Results:

The transcript levels of survivin, c-MYB, COX-2, iNOS, and TCF-4 showed statistically significant increase during neoplastic transformation of UC-patient colonic mucosa, whereas TERT and ILK were not elevated. In contrast, the specimens of CRC showed upregulated expression of not only survivin, c-MYB, TCF-4, COX-2 and iNOS but also TERT. Similarly, in human tumor xenografts all transcripts with the exception of c-MYB were upregulated. In both sporadic (A/J mice) and colitis-associated (ICR mice) models of CRC, the levels of TERT, COX-2 and TCF-4 mRNA were higher in microdissected neoplastic cells. Survivin mRNA was up-regulated only in neoplastic cells from A/J mice and ILK mRNA was up-regulated only in neoplastic cells from ICR mice. However, the expression of iNOS mRNA was similar in normal and neoplastic cells in both models and c-MYB mRNA was even down-regulated in neoplastic cells compared with normal cells in both models.

Conclusion:

These results suggest that hTERT and ILK activation occurs during the later stages of CRC progression, whereas upregulation of survivin, c-MYB and TCF-4 is a feature of the early stage development of human colonic neoplasia, and thus, they might serve as early indicators for UC-associated colorectal carcinogenesis.