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Dissertations-Kurzfassung

Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer

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Curcumin is a compound produced by plants in the ginger family, Zingiberaceae (Chun et al., 1999; Surh, 1999). Curcumin has been shown to possess a wide range of therapeutic potential or preventive effects in both *in vitro* and animal models. In clinical trials, treatment with curcumin has improved survival rates in a number of human diseases, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis and Alzheimer's disease (Shishodia et al., 2005; Shishodia et al., 2007). Curcumin interacts with various proteins and modifies their expression and activity, including transcription factors, inflammatory cytokines and factors relating to cell survival, proliferation and angiogenesis. The microRNA miR-21 is overexpressed in many tumors, and promotes progression and metastasis. Therefore, in order to prevent this deleterious event, I have examined the potential of curcumin to regulate miR-21 expression, tumor growth, invasion, and *in vivo* metastasis in colorectal cancer. Using Rko and HCT116 cells, I have identified two new transcriptional start sites of the miR-21 gene and delineated its promoter region. PMA stimulation induced miR-21 expression via motifs bound to AP-1 transcription factors. Curcumin treatment reduced miR-21 promoter activity and expression in a dose-dependent manner by inhibiting AP-1 binding to the promoter, and induced the expression of the tumor suppressor Pdcd4, which is a target of miR-21. Curcumin-treated Rko and HCT116 cells were arrested in the G2/M phase with increasing concentrations. Furthermore, curcumin inhibited tumor growth, invasion and *in vivo* metastasis in the chicken embryo chorionallantoic membrane (CAM) assay. Additionally, curcumin significantly inhibited miR-21 expression in primary tumors generated *in vivo* in the CAM assay using Rko and HCT116 cells ($p<0.00006$ and $p<0.035$, respectively). In conclusion, this is the first study to show that curcumin inhibits the transcription of miR-21 by inhibiting AP-1, suppresses cell proliferation, tumor growth, invasion and *in vivo* metastasis, and stabilizes the expression of the tumor suppressor Pdcd4 in colorectal cancer.