What is the Role of Extra-Renal Vitamin D Hydroxylase Expression and Activity in Normal and Malignant Cells? How Is This Modified By Epigenetic Mechanisms?

Heide S. Cross, Ph.D.
Associate Professor, Department of Pathophysiology
Medical University of Vienna

Evidence is increasing that extra-renally synthesized vitamin D in colon mucosal and in prostate and mammary cells, may provide normalization of growth, differentiation and apoptosis. In particular, this function could be of considerable importance for prevention of cancer incidence as well as of tumor progression. Evaluation of CYP27B1 and the vitamin D receptor (VDR) mRNA and protein expression in colon tumor patients compared with that in non-tumor patients showed that early during tumor progression CYP27B1 and the VDR were strongly upregulated, while expression was diminished in well advanced tumors. The reverse was observed for CYP24 expression.

We demonstrated in cell cultures derived from human tumor tissue at different stages of progression that colonic, prostatic and mammary cells express CYP27B1, the 1 -hydroxylating enzyme, primarily in differentiated cells, whereas the catabolic CYP24, the 24-hydroxylase, is increasingly expressed in undifferentiated cells. Hypomethylation of CpG islands in CYP24 promoter regions may underlie this elevated expression, which would result in prevention of 1,25-$(OH)_2$-D_3 accumulation in extra-renal tissues by enhanced degradation. Interestingly, CYP27B1 expression in colon cells may be epigenetically silenced by hypermethylation during tumor progression, since in undifferentiated colon cells CYP27B1 can be induced by an inhibitor of the DNA (cytosine-5)-methyltransferase (DNMT) that catalyzes the transfer of a methyl group to CpG islands. These data, for the first time, provide evidence that, if properly modulated, the vitamin D system could be harnessed for prevention of tumor progression.