How Do Dietary Calcium, Soy, and Folate Regulate Colonic Vitamin D Synthesis?

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Epidemiological studies have provided some insight into the impact of vitamin D and calcium in prevention of colon tumor progression. Though there is evidence that both nutritional calcium and serum 25-OH-D_3 need to be optimized to be most effective, the cellular-molecular basis for this observation is unknown. We have previously suggested on the one hand that serum levels of 25-OH-D_3 in the upper range (around 80 nmol/l) would provide the prerequisite for extrarenal colonic 1,25-$(OH)_2$-D_3 synthesis. On the other hand the potential exists to optimize expression of vitamin D hydroxylases for enhanced production of the active vitamin D metabolite in colon mucosal cells. We were able to demonstrate that high levels of extracellular calcium not only have a direct antimitotic action in colon cells via the calcium sensing receptor (CaR), but also that, in parallel to proliferating cell nuclear antigen (PCNA) CYP24 expression was decreased in mice fed high nutritional calcium. This would lead to less degradation of 1,25-$(OH)_2$-D_3. Nutritional soy, as well as its primary component genistein, considered a phytoestrogen binding preferentially to the estrogen receptor (ER)- , have a beneficial effect on the vitamin D system as well: similar to 17 - estradiol they elevate expression of CYP27B1, and reduce that of CYP24, both *in vivo* and *in vitro*.

We have demonstrated *in vitro* that both vitamin D hydroxylases are epigenetically regulated, i.e. that CYP27B1 becomes hypermethylated (repressed) during tumor progression, whereas CYP24 is hypomethylated (activated) in advanced tumor cells. Since it is known that folate deficiency results in DNA hypomethylation, and folic acid protects against gastrointestinal cancers, we tested this nutritional substance as a physiological modulator of CYP24 expression. In a mouse model on a diet containing high/low vitamin D, calcium or folate, it was the diet containing high folate, which diminished CYP24 expression most effectively. This suggests that hypermethylation of CYP24 may be a potential molecular target for prevention of tumor progression.