Type 2 cGMP-dependent protein kinase regulates proliferation and differentiation in the colonic mucosa.

Signaling through cGMP has emerged as an important regulator of tissue homeostasis in the gastrointestinal tract, but the mechanism is not known. Type 2 cGMP-dependent protein kinase (PKG2) is a major cGMP effector in the gut epithelium, and the present studies have tested its importance in the regulation of proliferation and differentiation in the mouse colon and in colon cancer cell lines. Tissue homeostasis was examined in the proximal colon of Prkg2(-/-) mice using histological markers of proliferation and differentiation. The effect of ectopic PKG2 on proliferation and differentiation was tested in vitro using inducible colon cancer cell lines. PCR and luciferase reporter assays were used to determine the importance of Sox9 downstream of PKG2. The colons of Prkg2(-/-) mice exhibited crypt hyperplasia, increased epithelial apoptosis, and reduced numbers of differentiated goblet and enteroendocrine cells. Ectopic PKG2 was able to inhibit proliferation and induce Muc2 and CDX2 expression in colon cancer cells, but did not significantly affect cell death. PKG2 reduced Sox9 levels and signaling, suggesting possible involvement of this pathway downstream of cGMP in the colon. The work presented here demonstrates a novel antiproliferative and prodifferentiation role for PKG2 in the colon. These homeostatic functions of PKG2 were reproducible in colon cancer cells lines where...
downregulation of Sox9 is a possible mechanism. The similarities in phenotype between PKG2 and GCC knockout mice positions PKG2 as a likely mediator of the homeostatic effects of cGMP signaling in the colon.