Bile Acids and Fibroblast Growth Factor 19 (FGF19) Is there a Connection to Cancer?

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The Physiological Source of circulating FGF19 is the ileum
Bile acids, once internalized in ileocytes, are able to stimulate the transcription of FGF19 by binding to the nuclear farnesoid X receptor (FXR). Serum FGF19 levels in healthy individuals demonstrate a marked diurnal variation, closely related to postprandial serum bile acid levels (Lundåsen, Gålman, Angelin, & Rudling, 2006). Fasting plasma FGF19 concentrations are prone to large (seven- to ten-fold) interindividual variations (Angelin, Larsson, & Rudling, 2012). It is not known whether FGF 19 is secreted into the portal vein or enters the liver by other routes. In any event, it activates the FGFR4 receptor (a member of the tyrosine kinase family) associated with beta-klotho (a co-receptor also termed KLB) in hepatocytes. Consequently, cytochrome P450 7A1 (CYP7A1), the rate-limiting enzyme of bile acid synthesis is inhibited and the production of bile acid reduced. However, FGF19 performs many other actions, which will be reviewed briefly in the following.

FGF19-a novel Antidiabetic or Tumor Promotor?
Patients with type 2 diabetes have significantly lower serum FGF 19 levels (Roesch et al., 2015). Due to its insulin-like actions, FGF 19 is discussed as a novel treatment for type 2 diabetes (Owen, Mangelsdorf, & Klierwer, 2015). FGF19 downregulates acetyl-CoA carboxylase 2 (ACC2), which reduces levels of malonyl CoA; this is the first committed step in fatty acid synthesis. Malonyl CoA inhibits carnitine acyltransferase, preventing the entry of fatty acyl-CoAs into the mitochondrial matrix. Lowered levels of malonyl CoA increase fatty acid oxidation. ACC2 is one of the prime targets of the antidiabetic drug metformin via stimulation of AMP-dependent protein kinase (Hardie, 2013), (Foretz, Guigas, Bertrand, Pollak, & Viollet, 2014). Transgenic mice expressing FGF19 showed greater metabolic control, lower glucose levels, increased fatty acid oxidation, and improved insulin sensitivity. Consequently, FGF 19 was discussed as a possible treatment for type 2 diabetes. However, in contrast to metformin which clearly exerts cancer-protective activity in humans and animals (Pernicova & Korbonits, 2014), FGF 19 has been a cause of significant concern because the transgenic mice developed hepatocellular carcinoma (Beenken & Mohammadi, 2009) (Zhou et al., 2014).

FGF19 is an Autocrine Tumor Promotor but is also Secreted into the Systemic Circulation in Cancer Patients
The expression of FGF 19 correlates with tumor progression and a poorer prognosis of hepatocellular carcinoma in humans. Apparently, FGF 19 acts as a local autocrine or paracrine tumor-promoting hormone, which was also secreted by the carcinoma; high serum levels of 300 pg/ml fell to less than 40 pg/ml after curative resection (Miura et al., 2012). Similarly, FGF 19 promotes prostate cancer progression (Feng, Dakhova, Creighton, & Ittmann, 2013); serum levels of FGF 19 are higher (median 216 pg/ml) in high Gleason grade patients than in low Gleason grade (median 116.5 pg/ml) patients (Nagamatsu et al., 2015). Evidently, in addition to the physiological controlled release of FGF19 by bile acids from the ileum, some carcinomas employing it as an autocrine hormone, also secrete it in uncontrolled fashion into the systemic circulation.

Are Bile Acids Connected to Cancer Promotion via FGF19?
The question arises as to whether FGF 19 acts as an autocrine growth factor in tumor cells. Can exposure to high circulating physiological concentrations, controlled by increased transileal transport of bile acids, promote the proliferation of cancer cells? This would connect bile acids via FGF19 to cancer. However, several other players are involved in the game, including intestinal microbiota, which determine the composition of bile acid pool. The latter is relevant for the agonistic or antagonistic activity of FXR in the ileum and elsewhere. Nevertheless, the role of bile acids and the composition of its metabolome in prostate and other cancers should be investigated.
References


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