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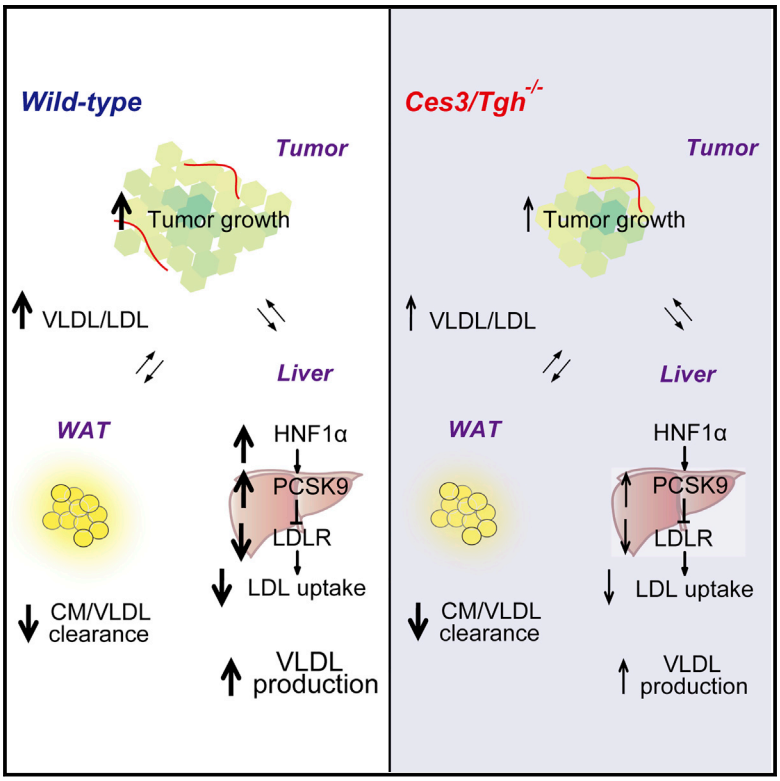
Tumor-Induced Hyperlipidemia Contributes to Tumor Growth

Graphical Abstract



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In Brief

Huang et al. show that the onset of hyperlipidemia in mice caused by tumor-enhanced VLDL production and tumor-impaired VLDL/LDL turnover can be attenuated by genetic ablation of Ces3/TGH in mice, which results in diminished tumor growth by a reduced supply of cholesterol-rich lipoproteins to the tumor.

Highlights

- Lipoprotein cholesterol supports tumor growth
- Tumors increase VLDL/LDL levels
- Ces3/TGH deficiency attenuates tumor-induced hyperlipidemia via inhibition of PCSK9
- Tumor growth was suppressed in *Ces3/Tgh*$^{-/-}$ mice

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Tumor-Induced Hyperlipidemia Contributes to Tumor Growth

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SUMMARY

The known link between obesity and cancer suggests an important interaction between the host lipid metabolism and tumorigenesis. Here, we used a syngeneic tumor graft model to demonstrate that tumor development influences the host lipid metabolism. BCR-Abl-transformed precursor B cell tumors induced hyperlipidemia by stimulating very low-density lipoprotein (VLDL) production and blunting VLDL and low-density lipoprotein (LDL) turnover. To assess whether tumor progression was dependent on tumor-induced hyperlipidemia, we utilized the VLDL production-deficient mouse model, carboxylesterase3/triacylglycerol hydrolase (Ces3/TGH) knockout mice. In Ces3/Tgh$^{-/-}$ tumor-bearing mice, plasma triglyceride and cholesterol levels were attenuated. Importantly tumor weight was reduced in *Ces3/Tgh*$^{-/-}$ mice. Mechanistically, reduced tumor growth in Ces3/Tgh$^{-/-}$ mice was attributed to reversal of tumor-induced PCSK9-mediated degradation of hepatic LDLR and decrease of LDL turnover. Our data demonstrate that tumor-induced hyperlipidemia encompasses a feed-forward loop that reprograms hepatic lipoprotein homeostasis in part by providing LDL cholesterol to support tumor growth.

INTRODUCTION

Dyslipidemia is tightly linked to obesity and is characterized by high levels of triacylglycerol (TG) and low-density lipoprotein cholesterol (LDL-C) as well as low levels of high-density lipoprotein cholesterol (HDL-C) in the bloodstream. Dyslipidimia is also associated with increased human cancer mortality (Calle et al., 2003). This has been functionally validated in experimental models of diet-induced obesity (DIO) that showed poor cancer outcomes (Alikhani et al., 2013; Zhuang et al., 2005). Weight loss intervention has been suggested as an effective cancer prevention strategy and is supported by reductions in cancer incidence and mortality of patients who have had bariatric surgery and dramatic weight loss (Sjöström et al., 2009). However, whether nonsurgical weight loss interventions achieved by calorie restriction, behavioral therapy, and/or pharmacotherapy could also have a beneficial impact on cancer incidence is still unclear. Mechanistic investigations into this relationship have analyzed the potential roles of insulin, insulin-like growth factors (IGFs), sex hormones, and adipokines (e.g., leptin, tumor necrosis factor alpha [TNF-α], and adiponectin). Plasma concentrations of these are often abnormal in obesity (Al-Zoughbi et al., 2014). Onset of insulin resistance and chronic inflammation resulting from excess lipid supply and adipose expansion can distort the normal balance between cell proliferation and differentiation and apoptosis, which eventually contribute to obesity-induced cancer incidence (Bianchini et al., 2002). However, the precise cellular mechanisms that link obesity with cancer incidence, recurrence, progression and death remain largely unexplored. Furthermore, whether dyslipidemia in normal-weight subjects is correlated to tumor incidence is unknown.

Rapidly proliferating tumor cells generally require high amounts of fatty acids (FAs) and cholesterol. Numerous studies have confirmed hyperactivation of de novo lipogenesis in various types of neoplasia. Targeting lipogenesis by inhibiting fatty acid synthase (FASN), stearoyl-CoA desaturase-1 (SCD1), ATP-citrate lyase (ACLY) or sterol regulatory element-binding protein-1 (SREBP1) was effective in tumor suppression (Currie et al., 2013). Cancer cells can also rapidly convert exogenous FAs to lipids required for proliferation and pro-tumorigenic lipid signaling (Arana et al., 2010; Louie et al., 2013). Multiple studies have also demonstrated elevated low-density lipoprotein (LDL) receptor (LDLR) expression and LDL uptake in a wide range of tumors, including glioblastoma (Guo et al., 2011), leukemia (Vitols et al., 1990), pancreatic tumors (Guillaumond et al., 2015), and lung cancer (Vitols et al., 1992). Lipoprotein lipase (LPL), which hydrolyzes TG within chylomicrons (CM) and very low-density lipoprotein (VLDL), was found to be critical for cancer