JCI The Journal of Clinical Investigation

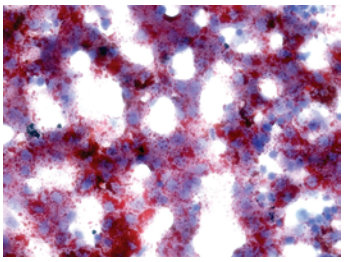
In This Issue

J Clin Invest. 2009;119(2):237-237. https://doi.org/10.1172/JCI38496.

In this issue

Fetal metabolic development affected by mother's diet Maternal obesity is one factor thought to contribute to the rise in the number of children classified as obese and diagnosed with metabolic diseases such as type 2 diabetes and nonalcoholic fatty liver disease (NAFLD). However, McCurdy and colleagues have now found that the offspring of both lean and obese nonhuman primate mothers chronically consuming a high-fat diet (HFD) exhibited an increased risk of developing NAFLD compared with fetal offspring from mothers fed a control diet (pages 323–335). When analyzed early in the third trimester, fetal offspring from both lean and obese HFD-fed mothers showed evidence of NAFLD, including increased levels of hepatic triglycerides. The increased levels of hepatic triglycerides persisted into the postnatal period and were accompanied by an increased percentage of body fat. Importantly, if HFD-fed mothers were reverted to a low-fat diet during a subsequent pregnancy, this fetal offspring exhibited lower, but not normal, hepatic triglyceride levels, even if the mother remained obese. The authors therefore suggest that a developing fetus is highly susceptible to maternal consumption of excess lipids whether or not the mother is obese and that a healthy maternal diet is important for the metabolic health of a developing fetus. No PKCα, no thrombus formation Platelets have a central role in the development of the predominant cause […]

Fetal metabolic development affected by mother's diet

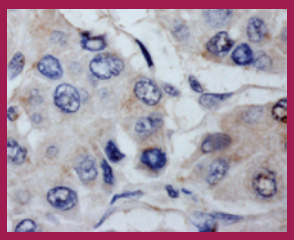


Maternal obesity is one factor thought to contribute to the rise in the number of children classified as obese and diagnosed with metabolic diseases such as type 2 diabetes and nonalcoholic fatty liver disease (NAFLD). However, McCurdy and colleagues have now found that the offspring of both lean and obese nonhuman primate mothers chronically consuming a high-fat diet (HFD) exhibited an increased risk of developing NAFLD compared with fetal offspring from mothers fed a control diet (323–335). When analyzed early in the third trimester, fetal offspring from both lean and obese HFD-fed mothers showed evidence of NAFLD, including increased levels of hepatic triglycerides. The increased levels of hepatic triglycerides persisted into the postnatal period and were accompanied by an increased percentage of body fat. Importantly, if HFD-fed mothers were reverted to a low-fat diet during a subsequent pregnancy, this fetal offspring exhibited lower, but not normal, hepatic triglyceride levels, even if the mother remained obese. The authors therefore suggest that a developing fetus is highly susceptible to maternal consumption of excess lipids whether or not the mother is obese and that a healthy maternal diet is important for the metabolic health of a developing fetus.

Vitamin D3–induced Tregs express TLR9

Interest in harnessing the cytokine IL-10 as a therapeutic for allergy, transplantation, and autoimmunity stems from its potent antiinflammatory effects and ability to inhibit Th1- and Th2-mediated immune responses. Previous studies in Catherine Hawrylowicz's laboratory have shown that IL-10–secreting Tregs (IL-10–Tregs) can be induced by activating human $CD4^+$ T cells in the presence of dexamethasone and the active form of vitamin D3, 1α25VitD3. In this issue (387–398), her laboratory has now shown that TLR9 is highly expressed by IL-10–Tregs induced in vitro by activating both peripheral blood and respiratory tissue $CD3^+$ T cells in the presence of 1α25VitD3 with or without dexamethasone. Importantly, after human volunteers ingested 1α25VitD3, their $CD3^+CD4^+$ T cells showed increased levels of IL-10 and TLR9 expression when analyzed ex vivo. Further analysis revealed the functional consequences of the high levels of TLR9 expression. In vitro stimulation of 1α25VitD3-induced IL-10–Tregs with TLR9 agonists led to decreased IL-10 synthesis and thereby loss of regulatory function. These data lead the authors to suggest that TLR9 could be used to monitor the induction of therapeutic 1α25VitD3-induced IL-10–Tregs. Further, these results have implications for the development of TLR9 agonists for use in cancer therapy and as adjuvants to boost vaccine efficacy.

FHL proteins linked to carcinogenesis



Four-and-a-half LIM (FHL) proteins are known to regulate numerous cellular processes, including proliferation, differentiation, and apoptosis. Although preliminary data have recently linked FHL1 and FHL2 with carcinogenesis, exactly how the cellular functions of these and other FHL proteins influence tumor development and progression has not been determined. In this issue (349–361), Ding and colleagues have now established that FHL1, FHL2, and FHL3 physically and functionally interact with the signaling proteins Smad2, Smad3, and Smad4 in a human hepatoma cell line. These Smad proteins mediate TGF-β signaling, but FHL-mediated regulation of Smad protein activation, which induced TGF-β–like responses, occurred independently of TGF-β and was instead dependent on casein kinase 1δ. Consistent with a potential role for FHL-mediated TGF-β–like responses in tumor development and progression, FHL1–3 inhibited the growth of a human hepatoma cell line both in vitro and when transplanted into mice. Importantly, analysis of samples from patients with hepatocellular carcinoma revealed that expression of FHL proteins is often downregulated and that this correlates with decreased TGF-β–like responses. The authors therefore suggest that FHL proteins might provide a new molecular target for the development of anticancer therapeutics.

No PKCα, no thrombus formation

Platelets have a central role in the development of the predominant cause of heart attack, atherothrombosis — thrombus formation at the site of a ruptured or eroded atherosclerotic plaque. The development of antithrombotic drugs that do not impair other functions of platelets, in particular their role in hemostasis, is therefore of immense interest. As Konopatskaya and colleagues found that mice lacking PKCα exhibited attenuated thrombus formation in vivo but showed no evidence of overt bleeding, they suggest that PKCα is a potential target for antithrombotic therapy (399–407). Detailed in vitro analysis indicated that *Prkca*$^{-/-}$ platelets adhered to both collagen- and fibrinogen-coated surfaces but did not aggregate and form a thrombus in flowing blood. This inability to aggregate was due to a defect in the biogenesis and secretion of dense granules. Consistent with this, addition of ADP (one of the molecules released by dense granules) restored the ability of *Prkca*$^{-/-}$ platelets to aggregate and form a thrombus. These data lead the authors to propose that future studies should determine whether drugs targeting PKCα (e.g., aprinocarsen, an antisense oligonucleotide therapy) are of benefit in the setting of atherothrombosis.