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COMMENTARY

Curcumin adds spice to the debate: lipid metabolism in liver disease

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Activated hepatic stellate cells (HSCs), the major source of the collagens involved in fibrosis and non-alcoholic fatty liver disease (NAFLD), undergo a profound loss of lipid and vitamin A storage capacity, as a consequence of a decline in expression of 'adipogenic' transcription factors such as peroxisome proliferator-activated receptor-γ (PPARγ). By contrast, hepatocytes undergo a micro- and macro-vesicular steatosis, reflecting the accumulation of triacylglycerol, and associated with chronic inflammation and fibrosis. These paradoxical findings are extended in this issue: Kang and Chen demonstrate that while low-density lipoproteins (LDL) can activate HSCs, curcumin can inhibit this process by activation of PPARγ, which not only represses gene expression of *SREBP-2* and *LDLR*, but via induction of expression of *SREBP-1c*, restores the lipid storage capacity characteristic of quiescent HSCs, suggesting that curcumin may be of therapeutic usage in protecting against liver steatosis and fibrosis.
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Abbreviations: C/EBP, CCAAT/enhancer-binding protein; CREB, cAMP responsive element-binding protein; HSC, hepatic stellate cell; LDL, low-density lipoprotein; LXRα, liver X receptor-α; MF, myofibroblastic cells; NAFLD, non-alcoholic fatty liver disease; PPARγ, proliferator-activated receptor-γ; SREBP, sterol regulatory element-binding protein

Hepatic steatosis, characterized by the accumulation of triacylglycerol within hepatocytes, micro- and macro-vesicular steatosis and balloon cell degeneration, is a key feature of non-alcoholic fatty liver disease (NAFLD), triggered by hypercaloric alimentation and obesity, and associated with chronic inflammation and progressive hepatic fibrosis. During this process, hepatic stellate cells (HSCs) within the sinusoid undergo activation and proliferation, producing pro-inflammatory cytokines and chemokines, growth factors, pro-fibrogenic cytokines and metalloproteinase inhibitors, resulting in a collagen-rich extracellular matrix that eventually replaces normal hepatic tissue as fibrosis proceeds (Friedman, 2008). The process of trans-differentiation (activation) of HSC to myofibroblastic cells (MF) is accompanied by loss of 'adipogenic' transcription factors, such as peroxisome proliferator-activated receptor-γ (PPARγ), cAMP responsive element-binding protein (CREB), CCAAT/enhancer-binding protein (C/EBP)α, β and δ, liver X receptor-α (LXRα) and sterol regulatory element-binding protein-1c (*SREBP-1c*). This decline in expression of 'adipogenic' transcription factors is accompanied by loss of vitamin A and lipid storage capacity (Miyahara *et al.*, 2000; Hazra *et al.*, 2004; Tsukamoto, 2005; Tsukamoto *et al.*, 2006). Therefore, as triacylglycerol accumulates within hepatocytes (or parenchymal cells), in response to lipogenic stimuli, HSCs progressively lose their fat-storing ability.

This paradox was highlighted by Tsukamoto *et al.* (Miyahara *et al.*, 2000; Hazra *et al.*, 2004; Tsukamoto, 2005; Tsukamoto *et al.*, 2006), who observed that trans-differentiation of HSC to MF essentially models adipocytes-pre-adipocytic fibroblast de-differentiation: both quiescent HSC and adipocytes exhibit substantive lipid storage capacity, while activated HSC and pre-adipocytic fibroblasts are devoid of this function. Equally, while quiescent HSC and adipocytes express extracellular matrix proteins of the basement membrane, activated HSC and pre-adipocytes produce predominantly interstitial collagens. Factors that induce HSC activation, such as platelet-derived growth factor, tumour necrosis factor-α and transforming growth factor-β, also suppress adipocyte differentiation, while adipocyte differentiation cocktail (insulin, dexamethasone and isobutylmethylxanthine), or ectopic overexpression of PPARγ or *SREBP-1c*, can restore activated HSC to quiescence.

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An intriguing study by Kang and Chen (2009), in this issue of *British Journal of Pharmacology*, extends this argument, clearly showing that low-density lipoprotein (LDL) can be added to the list of factors that induce HSC activation, increasing the expression of αI collagen and α-smooth muscle actin, as well as pro-mitogenic platelet-derived growth factor-β receptor, pro-fibrogenic type I and type II transforming growth factor-β receptors and connective tissue growth factor (CTGF). The link between hypercholesterolaemia and liver steatosis and fibrosis is not clearly defined at present, and is worthy of further investigation, as is the possibility that statin drugs may have some utility in this regard.

Interestingly, Kang and Chen also demonstrate that the activating effect of LDL can be reversed by curcumin ($C_{21}H_{20}O_6$) or diferuloylmethane, one of the active spice principles found in turmeric (*Curcuma longa*). Turmeric has been described in Ayurveda and traditional Chinese medicine for treatment of differing inflammatory disorders for thousands of years (Goel *et al.*, 2008). The hypocholesterolaemic action of curcumin was first reported almost 40 years ago, and numerous studies have indicated that curcumin reduces serum cholesterol concentrations by increasing the expression of hepatic LDL receptors, blocks oxidation of LDL, increases bile acid secretion and faecal excretion of cholesterol, represses the expression of genes involved in cholesterol biosynthesis and protects against liver injury and fibrogenesis in animal models (Peschel *et al.*, 2007; Dou *et al.*, 2008; Fu *et al.*, 2008). Curcumin induces apoptosis, and blocks proliferation, of HSC, and, via activation of PPARγ inhibits extracellular matrix formation and suppresses CTGF expression by inhibiting ERK and NF-κB (Chen and Zheng, 2008). Notably, however, while curcumin activates PPARγ in both hepatocytes and HSC and up-regulates expression of the LDL receptor in hepatocytes (Peschel *et al.*, 2007; Dou *et al.*, 2008), curcumin represses expression of *SREBP-2* and the LDL receptor in HSC (Kang and Chen, 2009). At the same time, induction and activation of *SREBP-1c* restores the lipid-storing capacity of HSC, triggering increases in cellular mass of fatty acids and triacylglycerols characteristic of quiescent HSCs. These findings add a further element to the debate surrounding the 'fat paradox', wherein hepatocytes and HSCs respond in quite distinct ways to identical stimuli.

The molecular mechanisms underlying these diametrically opposing responses, to lipogenic stimuli and to curcumin (above), in hepatocytes and HSCs are not currently understood, although it seems likely that investigations into the crosstalk between these inter-dependent cell types may prove of interest. HSCs were initially characterized as fat-storing cells, by Ito *et al.* in the 1950s, who made the pivotal observation that lipid droplets increased in HSC after exposure to insulin and glucose (reviewed in Tsukamoto *et al.*, 2006). These cells form part of the hepatic sinusoid, being found in the perisinusoidal space of Disse, and numerous in the periportal region of the hepatic acinus. Conceptually, it is possible to hypothesize that HSC, despite representing only 5–8% of hepatic cells, may protect hepatocytes, perhaps by 'buffering' these cells against rapid increases in concentration of fatty acids. However, exposure of HSC to pro-mitogenic or pro-fibrogenic stimuli, or, as in the study by Kang and Chen, to elevated levels of LDL cholesterol, results in loss of 'adipogenic' regulation, and declining fat storage capacity in these cells. In turn, this may lead to damaging increases in the concentrations of fatty acids delivered to hepatocytes, triggering over-accumulation of triacylglycerol within these cells. Curcumin, via activation of PPARγ, down-regulates the expression of LDL receptors, induces *SREBP-1c* and increases the fat-storing capacity of HSC, and may thereby restore this 'protective' functionality, proving of therapeutic usage in preventing liver steatosis and fibrosis.

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