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RESEARCH ARTICLE

The Starbuck stops here: it's a Smad world

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Abstract A recent study by Gressner and colleagues suggested caffeine may block CCN2 expression in hepatic cells. This commentary briefly summarizes these observations.

Keywords CCN2 · Liver fibrosis · Caffeine

Over the past century, the Pacific Northwest has been attractive to new residents for the possibility of a year-round active lifestyle. Perhaps another reason to move to the rainforest of the Pacific Northwest is apparently the propensity of the inhabitants to warm up by drinking copious quantities of espresso. Recent epidemiological studies have suggested that people who drink caffeinated coffee decreased incidence of chronic liver disease (Ruhl and Everhart 2005). The cytokine transforming growth factor β (TGFβ) has long been recognized for promoting fibrosis ability acting through the Smad family of transcription factors (Leask and Abraham 2004). In particular, Smad3 has been shown to be necessary for TGFβ to induce expression of the fibrogenic effector protein CCN2 (Holmes et al. 2001). In an interesting report recently published online in the *Journal of Hepatology*, Gressner et al. (2008) provide the first mechanistic context for the epidemiological studies on coffee drinkers by showing that caffeine may have potent anti-fibrotic capabilities through its ability to antagonize the Smad pathway. In particular, the authors show, using protein and reporter assays in primary rat hepatocytes, that caffeine can decrease SMAD2 protein levels and SMAD1/3-phosphorylation. Consistent with these observations, caffeine also blocked TGFβ-induced CCN2 gene expression in hepatocytes (Gressner et al. 2008). Caffeine also modulated cAMP and PPARγ levels (Gressner et al. 2008).

Limitations of this study were that the authors did not examine whether caffeine affected expression of other key fibrogenic genes such as type I collagen and α-smooth muscle actin. Moreover, the specificity of caffeine was not assessed. For example, whether caffeine affected only pro-fibrotic gene expression or TGFβ signaling was not determined. Genome-wide expression profiling or proteomic signaling arrays would be useful in the future to address these issues. Nonetheless, these data provide a strong support for initiating further in vivo studies addressing whether caffeine can suppress fibrogenesis in animal models. Overall, this intriguing report is consistent with the notion that diet can significantly affect the outcome of fibrotic disease and that perhaps the coffee shop lifestyle may not only provide a good environment to socialize (and write scientific papers!) but also have a significant outcome on physical health.

This commentary also appears online under Newsletter section of the ICCNS Website at http://ccnsociety.com.

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