

The Starbucks stops here: It's a Smad world:

Gressner OA, Lahme B, Rehbein K, Siluschek M, Weiskirchen R, Gressner AM. Pharmacological application of caffeine inhibits TGF-beta-stimulated connective tissue growth factor expression in hepatocytes via PPARgamma and SMAD2/3-dependent pathways. *J. Hepatol.* 2008 Apr 30. [Epub ahead of print]

Over the past century, cities in the Pacific Northwest have 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 (TGF) 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 TGF 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 and colleagues (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 TGF-induced CCN2 gene expression in hepatocytes (Gressner et al., 2008). Caffeine also modulated cAMP and PPARlevels (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 smooth muscle actin. Moreover, the specificity of caffeine was not assessed. For example, whether caffeine affected only pro-fibrotic gene expression or TGF 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 coffeeshop lifestyle may not only provide a good environment to socialize (and write scientific papers!) but also have a significant outcome on physical health.

References

Gressner OA, Lahme B, Rehbein K, Siluschek M, Weiskirchen R, Gressner AM. Pharmacological application of caffeine inhibits TGF-beta-stimulated connective tissue growth factor expression in hepatocytes via PPARgamma and SMAD2/3-dependent pathways. *J. Hepatol.* 2008 Apr 30. [Epub ahead of print]

Holmes A, Abraham, D.J., Sa S, Shiwen X, Black CM, Leask A. (2001). CTGF and SMADs, maintenance of scleroderma phenotype is independent of SMAD signaling. *J. Biol. Chem.* 276: 10594-601.

Leask, A and Abraham, D.J. (2004). The control of TGF signaling in wound healing and fibrosis. *FASEB J.* 18:816-27.

Ruhl C.E., Everhart, J.E. (2005) Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States, *Gastroenterology* **129**,. 1928–1936