

Inflammation-associated suppression of metabolic gene networks in acute and chronic liver disease.

Campos G, Schmidt-Heck W*, De Smedt J, Widera A, Ghallab A, Pütter L, González D, Edlund K, Cadenas C, Marchan R, Guthke R, Verfaillie C, Hetz C, Sachinidis A, Braeuning A, Schwarz M, Weiß TS, Banhart BK, Hoek J, Vadigepalli R, Willy J, Stevens JL, Hay DC, Hengstler JG, Godoy P (2020) Inflammation-associated suppression of metabolic gene networks in acute and chronic liver disease. *Arch Toxicol* 94(1), 205-217.

Details

*equal contribution



Abstract

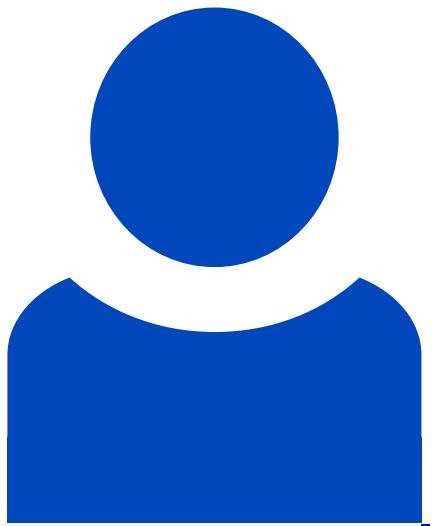
Inflammation has been recognized as essential for restorative regeneration. Here, we analyzed the sequential processes during onset of liver injury and subsequent regeneration based on time-resolved transcriptional regulatory networks (TRNs) to understand the relationship between inflammation, mature organ function, and regeneration. Genome-wide expression and TRN analysis were performed time dependently in mouse liver after acute injury by CCl₄ (2 h, 8 h, 1, 2,

4, 6, 8, 16 days), as well as lipopolysaccharide (LPS, 24 h) and compared to publicly available data after tunicamycin exposure (mouse, 6 h), hepatocellular carcinoma (HCC, mouse), and human chronic liver disease (non-alcoholic fatty liver, HBV infection and HCC). Spatiotemporal investigation differentiated lobular zones for signaling and transcription factor expression. Acute CCl₄ intoxication induced expression of gene clusters enriched for inflammation and stress signaling that peaked between 2 and 24 h, accompanied by a decrease of mature liver functions, particularly metabolic genes. Metabolism decreased not only in pericentral hepatocytes that underwent CCl₄-induced necrosis, but extended to the surviving periportal hepatocytes. Proliferation and tissue restorative TRNs occurred only later reaching a maximum at 48 h. The same upstream regulators (e.g. inhibited RXR function) were implicated in increased inflammation and suppressed metabolism. The concomitant inflammation/metabolism TRN occurred similarly after acute LPS and tunicamycin challenges, in chronic mouse models and also in human liver diseases. Downregulation of metabolic genes occurs concomitantly to induce inflammation-associated genes as an early response and appears to be initiated by similar upstream regulators in acute and chronic liver diseases in humans and mice. In the acute setting, proliferation and restorative regeneration associated TRNs peak only later when metabolism is already suppressed.

Beteiligte Forschungseinheiten

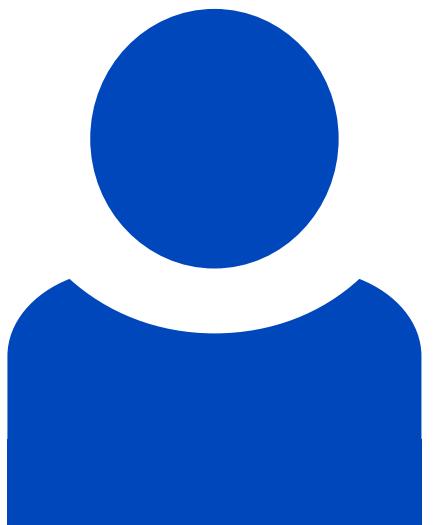
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