Sweet Liver, Careful Liver: The Liver in Health and Stress

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Abstract

The liver is a vital organ responsible for maintaining systemic homeostasis through its diverse metabolic, biosynthetic, detoxifying, immune-regulatory, and endocrine functions. However, in modern life, environmental and dietary challenges, including high-fat diets, drugs, and toxins, impose chronic metabolic burdens that contribute to metabolic dysfunction-associated fatty liver disease (MAFLD). During disease progression, the liver senses and responds to stress-induced injury while attempting self-repair. Understanding how the liver maintains physiological balance and alleviates stress-related damage provides a foundation for developing therapeutic strategies to improve health. We employed a high-content screening platform to identify compounds that reduce lipid droplet accumulation and modulate mitochondrial morphology in hepatocytes, thereby alleviating hepatic steatosis and fibrosis associated with aging. In a lung cancer mouse model, high-fat diet-induced metabolic stress was found to elevate hepatic secretion of C-reactive protein, which alters the pulmonary tumor microenvironment and accelerates cancer progression. During the course of our studies, we further identified a heat shock protein, DNAJB4, as unique and potent stress-responsive protein that enables the live to cope with external challenges; accordingly, a Dnajb4 deficient mouse model was generated by genetic engineering to investigate its physiological and pathological roles. We employed multiple physiological and pathological stimuli to examine its regulatory mechanisms. Under inflammatory stress, we found that DNAJB4 facilitates the activation of Kupffer cells following LPS challenge, promoting the maturation and release of IL-12 and subsequently triggering NK cell-derived IFN-γ production, which exacerbates septic shock. Conversely, the absence of DNAJB4 combined with antibiotic treatment ameliorates this response. In the context of drug-induced stress, particular acetaminophen hepatoxicity, DNAJB4 mitigates liver injury by alleviating ER stress, reducing oxidative burden associated with drug metabolism, and enhancing phase II

detoxification capacity. When exposed to genotoxic induced by DEN, DNAJB4 suppresses the activation of STAT3, thereby limiting compensatory hepatocyte proliferation and decreasing susceptibility to hepatocellular carcinoma. Furthermore, under metabolic stress caused by a high-fat diet, reduced DNAJB4 expression stabilizes HSF1, which in turn activates the SCD1/SIRT1/ATGL signaling cascade to enhance lipolysis alleviate lipid overload, and mitigate obesity-associated metabolic stress. Notably, diminished DNAJB4 expression also appears to promote adipocyte differentiation and thermogenesis, suggesting a potential role in regulating lipid biosynthesis, energy metabolism, and overall body weight homeostasis. Together, these findings provide a comprehensive view from hepatic physiology to disease, elucidating the liver's adaptive mechanisms under stress and identifying potential therapeutic compounds that may support liver protection and metabolic health in the future.