

Ubiquitin-proteasome pathway, alcohol and hepatitis C infection

Abbreviations: HCV, hepatitis C virus; UPS, ubiquitin-proteasome system

Introduction

About 70% of HCV-infected patients develop chronic hepatitis with significant progression to fibrosis, cirrhosis and hepatocellular carcinoma. Numerous attempts to create an efficient vaccine for the prevention of HCV-infection failed due to extremely high mutagenesis of HCV. However, recently, sufficient progress in the treatment of HCV-infection has been achieved with appearance of highly effective direct HCV antivirals as Sofosbuvir and Ledipasvir on the market.^{1,2} Multiple clinical trials are in progress to demonstrate the efficiency of these new medications alone or in a combination with already known ribavirin and interferon alpha. However “the honeymoon period” with the successful treatment by direct antivirals may not be applied to HCV patients that drink alcohol since the pathogenesis of liver

disease progression in these patients is different than in alcohol non-consuming HCV patients and requires the involvement of additional therapeutic strategies.

Ubiquitin-Proteasome System (UPS)

UPS is the most important intracellular system that degrades old, mutated, modified and non-functional host proteins, signal transduction factors and regulates vitally important cell functions as proliferation, cell cycle, quality control of newly synthesized proteins, apoptotic cell death and immune response (antigen presentation). Specifically, a small protein, ubiquitin, is activated and attaches to the substrate protein by cascade reaction of three enzymes, E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme) and E3 (ubiquitin ligase). Ubiquitylated protein is delivered to the degrading enzyme, proteasome that exists in equilibrium of three particles: 26S proteasome, 20S proteasome and the combination. 26S proteasome includes 20S proteolytic core and two regulatory 19S caps. 20S proteasome as a separate particle may degrade proteins without prior ubiquitylation, and accessibility of substrate protein to proteolytic core is regulated by PA28 protein (11S) (reviewed by³).

HCV and UPS

It has been shown that the most of HCV proteins (E2, NS2, NS5A, NS5B, p7, core) are degraded by proteasome and thus, proteasome controls viral propagation.⁴⁻⁷ In addition, HCV proteins affect the enzyme activity: core protein regulate proteasome activity via protein-protein interactions and oxidative stress,⁸ while NS3 protein blocks the activity of IFN-stimulated immunoproteasome (LMP7 subunit) that trims the peptides for antigen presentation in the context of MHC class I to cytotoxic T-lymphocytes.⁹ The best studied effects of UPS on HCV propagation are related to HCV core protein. Ubiquitylated-HCV core protein is processed by 26S proteasome in cytosol, while non-ubiquitylated-core is processed by the 20S proteasome mainly in the nucleus to activate steatosis-regulating genes and thus, to contribute to HCV pathogenesis. In cytosol, HCV core protein is ubiquitylated by E3 ubiquitin ligase, E6AP followed by HCV core degradation, which prevents viral propagation. A nuclear proteasome activator,

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PA28 γ is involved in ubiquitin-independent proteasomal degradation of core protein.¹⁰ Exclusive knockdown of nuclear PA28 γ enhances ubiquitylation of core protein and impairs virus production (but not HCV RNA replication), where as that of E6AP reduces ubiquitylation of core protein and enhances virus production (reviewed by¹¹).

Ethanol and UPS

Ethanol metabolism suppresses proteasome activity and IFN signaling necessary for proteasome activation.¹² Furthermore, in HCV protein-expressing liver cells, ethanol metabolism reverses up-regulating effects of core protein on proteasome and down-regulated the proteasome activity due to induction of higher level of oxidative stress by the combination of mitochondria-associated HCV core and ethanol metabolism.⁸ In addition, ethanol impedes proteasome function by affecting proteasome-interacting proteins in HCV-expressing liver cells. Specifically, when the 26S proteasome was purified from the liver cells of ethanol-fed transgenic HCV core-expressing mice, we observed the reduction of Ecm29, a protein that is responsible for the 26S proteasome stability. The loss in 26S proteasome stability led to a decreased content of the 20S proteasomal particles. In the same hybrid 26S-20S proteasome preparation, we found a decreased content of PA28 α , an activator of 20S proteasome as well as the lower amount of 19S-proteasome-associated deubiquitylase, UCHL5.¹³ These changes in association with the 26S proteasome and proteasome-interacting proteins certainly impair proteasome function and subsequent degradation of ubiquitylated host and viral proteins, which finally explains why ethanol provides negative impact on UPS-regulated HCV propagation, activation of protective signaling pathways and induction of immune response. In fact, we observed defective presentation of foreign peptides-MHC class I complexes in HCV+ hepatocytes isolated from ethanol-fed reduced,¹³ which corroborated the in vitro effects of ethanol on generation of antigenic peptides by immunoproteasome.¹²

Taken together

The combination of HCV proteins and ethanol metabolites induce high levels of oxidative stress, which impairs the 26S

proteasome function, thereby preventing protective effects of UPS on HCV pathogenesis. This suggests that except direct antivirals, the medications that inhibit ethanol-elicited oxidative stress (such as mitoquinone that protects mitochondria) should be used for the treatment of alcoholic patients with HCV-infection.

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Conflicts of interest

Author declares that there is no conflict of interest.

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