

EDITORIAL

Kupffer Cell TLR2/3 Signaling: A Pathway for EGCG Amelioration of Ethanol-Induced Hepatic Injury



Alcoholic liver disease (ALD) affects millions of people worldwide and is a condition associated with high morbidity and mortality. Ethanol-induced liver injury encompasses acute liver injury (alcoholic hepatitis) and chronic liver injury (steatohepatitis, fibrosis, and cirrhosis). Currently, few therapeutic options for ALD are available. Corticosteroids remain the gold standard therapy for severe alcoholic hepatitis. New research has sought to understand the role of immune modulation, gut microbiota, caspase inhibitors, granulocyte colony-stimulating factor, interleukin (IL)-1 receptor antagonists, and farnesoid X receptor agonists in altering the pathophysiology and halting the progression of ALD.

The pathophysiology of ALD involves many processes including cellular damage caused by inflammation and oxidative stress and ultimately cellular death. Research groups have proposed that polyphenol epigallocatechin-3-gallate (EGCG) may be a promising therapy for ALD; however, the mechanism is unclear. EGCG is a catechin within the larger group of polyphenols and is a plant extract found in green tea. It has already been investigated because of its ability to mitigate effects of damage caused by lead and amyloid peptides in human neuronal cells, and having antiatherosclerotic, anti-inflammatory, and antioxidant properties.^{1,2}

In the past 2 decades, immune modulation via toll-like receptors (TLRs) has become a topic of interest as a therapeutic target in ALD. In addition to microbial products, such as lipopolysaccharide, TLRs can also recognize endogenous molecules from damaged cells, tissues, extracellular matrix, and danger signals, termed damage-associated molecular patterns. In ALD, ethanol exposure decreases the strength of gastrointestinal junctions, leading to an increase in microbiota and endogenous molecules seen by the liver and thus able to be presented to TLRs. TLR2 is a receptor for gram-positive bacterial cell wall components, such as lipoproteins, and endogenous ligands, high mobility group B-1, serum amyloid A, antiphospholipid antibodies, hyaluronan, and saturated fatty acids. In hepatocytes, TLR2 deficiency has undefined effects with some studies showing TLR2 deficiency may confer resistance to the effects of ethanol exposure.³ TLR3, located in the intracellular endolysosome, can sense microbial-derived nucleic acids and double-stranded RNA. One study has led to the proposed mechanism that TLR3 activation is protective in ALD as TLR3 stimulation leads to Kupffer and stellate cell activation via enhanced production of IL-10, a liver-protective cytokine.⁴

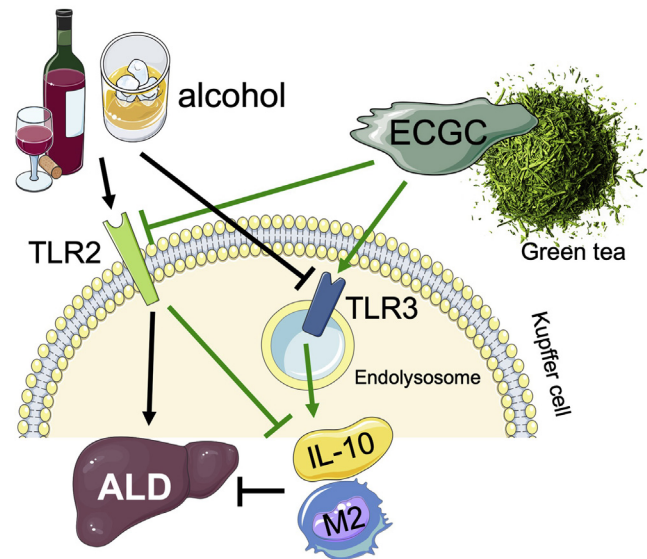


Figure 1. EGCG induces IL-10 production and M2 macrophage polarization to suppress ALD development. Alcohol-induced liver injury is mediated through TLR2 but inhibited by TLR3 signaling. EGCG can effectively suppress alcohol-induced liver injury by inducing IL-10 expression and M2 polarization. The EGCG-mediated inhibitory effect on alcohol-induced liver injury is mediated by activating TLR3 and inhibiting TLR2 in Kupffer cells.

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Luo et al⁵ provide additional evidence that in Kupffer cells, EGCG divergently regulates IL-10 expression by interacting with TLR2 and TLR3 receptors (Figure 1).

This study first provided evidence that ALD injury is decreased with EGCG. In ALD, EGCG decreased all injury and inflammatory markers, such as serum aminotransferase, tumor necrosis factor- α , IL-1 β , IL-6, monocyte chemoattractant protein-1, and hepatic nuclear factor (NF)- κ B phosphorylation, but surprisingly showed increased anti-inflammatory IL-10 levels.

The study then demonstrated that EGCG could induce IL-10 directly from Kupffer cells. This is novel because it incorporated the use of an in vivo model. EGCG was shown to increase IL-10 transcription and translation. Lipopolysaccharide increased p38 MAPK, ERK, NF- κ B p65 phosphorylation, whereas EGCG inhibited p38 MAPK and NF- κ B phosphorylation. In addition, EGCG decreased M1 markers, such as inducible nitric oxide synthase, but increased M2 markers, including Arginase-1. This demonstrated that EGCG contributes to Kupffer cell M2 polarization to protect against ALD.

The effect of EGCG on ALD was further investigated in TLR2^{-/-} and TLR3^{-/-} mice. Supplementation of EGCG in TLR2^{-/-} mice yielded decreased liver injury, whereas in TLR3^{-/-} mice, EGCG supplementation revealed increased liver injury. EGCG was posited to work in a protective manner in the absence of TLR2 stimulation and act to have an opposite effect in the absence of TLR3. These experiments were repeated in IL10^{-/-} mice. EGCG supplementation had decreased protection if IL-10 was knocked out, suggesting that IL-10 is at least one mediator in the protective effects induced by EGCG. In mice with present TLR2/3, IL-10 production yielded liver protection. It remains unknown how mechanistically EGCG interacts with TLR2 and TLR3. Although these experiments were conducted in TLR2 and TLR3 knockout Kupffer cells, the mechanism of Kupffer cell dysfunction and its role in ALD additionally warrants further investigation. Other key mediators among TLR2/3, NF- κ B, and IL-10 remain to be investigated. This experiment is novel in that it demonstrated *in vivo* benefits of EGCG, which could be superior to other treatments including resveratrol, silibinin, N-Acetyl Cysteine, and prednisolone. In this manner, the study was critical in demonstrating strong evidence for a proposed mechanism for EGCG action. This study markedly furthers the understanding of EGCG within the context of ALD pathophysiology and provides a new area of investigation in therapies that may benefit patients suffering from ALD.

TORREY Y. CZECH, BS

School of Medicine, University of California San Diego
La Jolla, California

EKIHIRO SEKI, MD, PhD

Division of Digestive and Liver Diseases, Department of
Medicine
Department of Biomedical Sciences
Cedars-Sinai Medical Center
Los Angeles, California

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Correspondence

Address correspondence to: Ekihiro Seki, MD, PhD, Division of Digestive and Liver Diseases, Department of Medicine, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Davis Research Building, Suite 2099, Los Angeles, California 90048. e-mail: Ekihiro.Seki@cshs.org.

Conflicts of interest

The authors disclose no conflicts.

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