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Spotlight

Altered Cholesterol and Lipid Synthesis Mediates Hyperinflammation in COVID-19

Yahya Sohrabi,[1,2,*] Holger Reinecke,[1] and Rinesh Godfrey[1]

Recent data have revealed that fructose-rich diet triggers inflammation and lipid synthesis. Furthermore, lipid metabolism, cholesterol synthesis and sterol regulatory element binding protein-2 (SREBP-2) activation correlates with coronavirus disease 2019 (COVID-19)-induced cytokine storm. High fructose consumption result in SREBPs activation, altered cholesterol and lipid synthesis and may establish an innate immune memory in the cells, leading to severe COVID-19 in patients with obesity.

A growing number of evidence suggests that obese patients face severe COVID-19 symptoms more frequently and are more likely to experience hospitalisation and intensive clinical care requirements. Current epidemiological data also shows that morbidity and mortality among COVID-19 patients with obesity are significantly higher [1]. Despite many epidemiological studies on the severity of COVID-19 in overweight individuals, molecular mechanisms remain obscure. Recent studies have uncovered interplay between specific metabolic pathways and aggravated immune responses. Over the years, fructose consumption among humans has increased by several thousand folds. An unhealthy level of fructose consumption, through soft drinks or fruit juices, leads to obesity and contributes to non-alcoholic fatty liver disease. A recent paper by Todoric *et al*. reported a vital role of a high-fructose diet (HFrD) in inducing inflammation and enhanced *de novo* lipogenesis (DNL) [2] (see Figure 1).

The authors showed that HFrD, and not corn starch diet (CSD), specifically contributed to hepatosteatosis and hepatocellular carcinoma (HCC) development. Acetyl-CoA, needed to promote DNL, was twofold higher in HFrD- than in CSD-fed mice. Mechanistically, HFrD led to defective *N*-glycosylation-dependent endoplasmic reticulum (ER) stress, which prevented tight junction protein (TJP) transcription (TJPs, occludin and claudins) and transport, leading to the deterioration of the intestinal barrier. Impaired intestinal barrier function promoted endotoxaemia. Higher lipopolysaccharide levels subsequently led to enhanced toll-like receptor-2 (TLR2) and TLR4 expression and activated MyD88 signalling, NLRP3 protein expression, and inflammatory cytokine production, such as IL-1β, TNF-α, and IL-6 [2]. Extended HFrD feeding upregulated MyD88-dependent genes necessary for lipid syntheses, such as SREBP-1, SREBP-2, carbohydrate-responsive element-binding protein (ChREBP), and the SREBP-1-regulated enzymes ACC1 (Acaca) and FAS (Fasn). These data suggest that fructose promotes DNL and contributes directly to hepatosteatosis and HCC. Notably, Abx administration or barrier restoration inhibited endotoxaemia and reduced HFrD-stimulated release of inflammatory cytokines, hepatosteatosis, and liver tumorigenesis [2].

There is a direct connection between the barrier integrity and the increase in the circulating levels of endotoxin. Interestingly, obese individuals were reported to have increased levels of endotoxin in the plasma [3]. The elevated levels of lipids could also promote inflammation by directly binding to TLR2 and TLR4 [3]. Fructose metabolism increases triglyceride levels in the plasma through the SREBP activation-dependent potentiation of triglyceride synthesis. HFrD induces the cholesterol synthesis pathway, and the activation of SREBP-2 promotes lipid and cholesterol synthesis [4]. Our recent study demonstrated that liver X receptor (LXR) activation results in a proinflammatory immune response and innate immune memory development. The data suggest that LXR priming increased cellular acetyl-CoA levels, upregulated SREBP expression, and activated the mevalonate pathway and IL-1β signalling [5].

A recent study reported that SREBP-2 is highly expressed in the severe form of

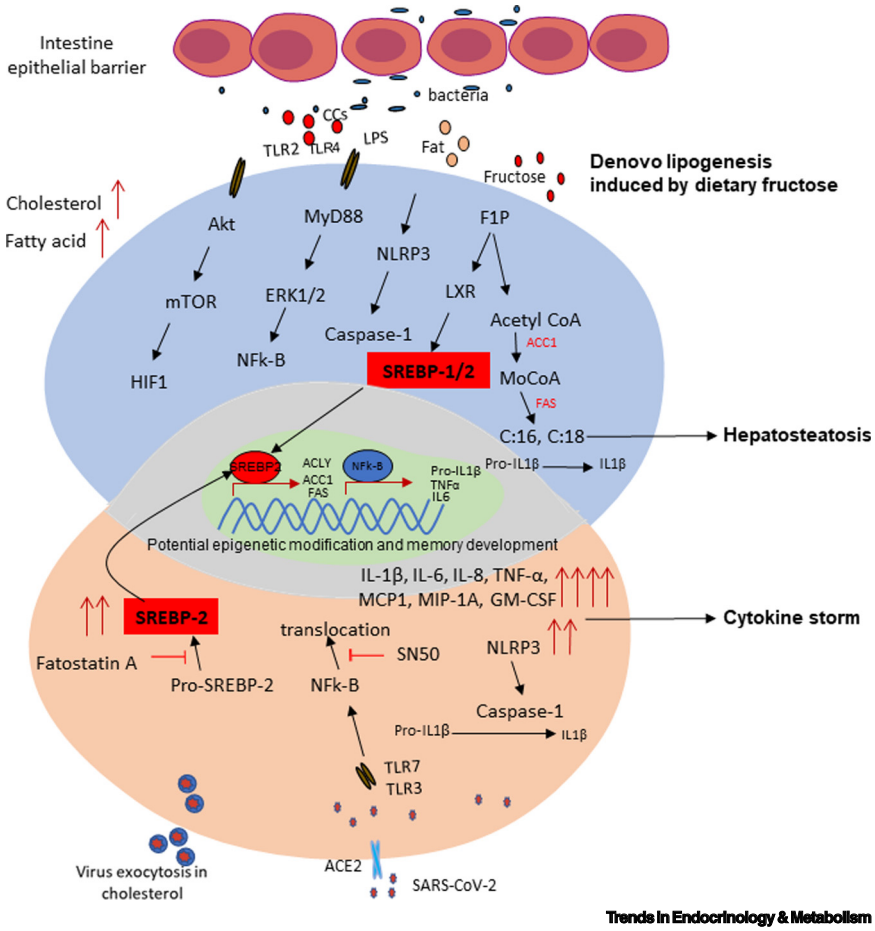

Figure 1. Diet Induced Lipid Metabolism and Cholesterol Synthesis May Contribute to Hyperinflammatory Response Against COVID-19. Fructose-rich diet promotes *de novo* lipid synthesis through SREBP-2 and potentiates a nonspecific inflammatory response in response to an infection. A low dose of endotoxin in the blood due to deterioration of the intestinal barrier, high fat, cholesterol crystals (CCs), and activation of LXR induces development of immune memory in the cells. When an obese person encounters severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), SREBP-2 is highly activated and the expression of fatty acid and cholesterol synthesis genes is upregulated. This leads to NLRP3 inflammasome and NF-kB activation and excessive cytokine production or cytokine storm. Abbreviations: COVID-19, coronavirus disease 2019; LPS, lipopolysaccharide; SREBP-2, sterol regulatory element binding protein-2.

COVID-19 [6], indicating an essential role of the lipid and cholesterol synthesis pathway in COVID-19 pathogenesis. Furthermore, NF-κB, which is known to be a master regulator of inflammatory responses, was also increased with the severity of the disease. There was also a very close association between increased expression of SREBP-2, NF-κB, and the level of inflammatory cytokines such as IL-1β and TNF-α. Interestingly, the pharmacological inhibition of both SREBP2 and NF-κB inhibited the life-threatening cytokine storm [6]. The expression of SREBP cleavage-activating protein (SCAP) and insulin-induced gene 1 (INSIG1) and SIRT1, associated with SREBP-2 stability and maturation, was also inhibited, suggesting the possibility of targeted therapy against abnormal activation of SREBP-2 and NF-κB [6]. Intriguingly, although the SREBP-2 is a regulator of lipid synthesis, the cholesterol levels were lower in the severe form of the disease than the control groups [6] (see Figure 1).

Moreover, the expression of sestrin 1 (SESN1) and proprotein convertase subtilisin/kexin type 9 (PCSK9), known suppressors of lipid biosynthesis, was significantly increased. In contrast, the expression of cholesterol synthesis-related genes, such as 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and low-density lipoprotein receptor (LDLR), did not change, irrespective of the disease severity [6], suggesting that cholesterol synthesis was suppressed, which leads to increased SREBP-2 activity and enhances its role as an inflammatory transcription factor. In line with previous studies on sepsis, the authors detected elevated C-term of SREBP-2 in the bloodstream of those patients with severe COVID-19 [6]. The inhibition of NF-κB and SREBP-2 suppressed inflammatory cytokine production. Recent studies implicate that cellular metabolism and metabolic regulators such as SCAP-SREBP-2 can modulate NLRP3 inflammasome activation [7]. NLRP3, in turn, modulates innate immune response by contributing to the maturation of pro-IL-1β and pro-IL-18. In line with Lee *et al*. [6], the induction of inflammatory response through NLRP3 does not depend on cholesterol homeostasis and was mainly due to the translocation and maturation of SREBP-2, and the inhibition of SCAP-SREBP2 suppressed NLRP3 activation [7]. Interestingly, the TLR4-MyD88-NF-κB axis is also implicated in the SCAP-SREBP2 translocation and expression of SREBP2 target genes. Notably, SCAP-SREBP-2 upregulation by inflammatory cytokines can directly increase the intracellular cholesterol levels by elevating LDLR and HMG-CoA reductase (HMG-CoAR) and this could be attenuated by the down-regulation of MyD88 [8]. This data is in line with Todoric *et al*. [2] and suggests a close crosstalk between cholesterol, lipid synthesis, and inflammatory signalling pathways. It is also known that mTORC1 activates SREBP-2 by reducing cholesterol delivery to the ER [9]. This is a critical observation because mTORC1 is the primary regulator

of memory-like formation, characterised by an enhanced inflammatory response in response to secondary stimuli, a concept named trained immunity [10]. It has become increasingly apparent that interplay between metabolic programming and inflammatory responses leads to epigenetic modifications, implicating long-term phenotypic changes in the cells [10]. High-fat diet, certain metabolites, and cholesterol crystals can induce nonspecific priming of circulating cells and change the epigenetic profile of haematopoietic progenitor cells in the bone marrow.

The current knowledge suggests that low-grade inflammatory conditions due to adipocyte cytokine production and high circulating endotoxin levels might prime immune cells and lung epithelial cells in obese individuals. Besides, specific dietary elements such as high fructose lead to the accumulation of metabolites such as cholesterol or fatty acids and these metabolites prime leukocytes and possibly non-immune cells such as epithelial cells, endothelial cells, and adipocytes. This causes alteration of innate immunity and leads to a long-term memory development in the cells, which potentiates inflammatory responses when encountered with a pathogen such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (see Figure 1). The data also shed light on how the upregulation of lipogenesis-associated signalling molecules could trigger excessive systemic inflammation during infectious diseases. These studies also imply that maintaining a healthy eating habit during COVID-19 pandemic is essential to avoid any possible detrimental hyperactivation of the immune response against the disease.

Declaration of Interests

No interests are declared.

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