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Review Article

Deregulation of Lipid Homeostasis in Metabolic dysfunction–Associated Fatty Liver Disease (MAFLD)

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Metabolic dysfunction–Associated Fatty Liver Disease (MAFLD) affects a quarter of the world's population, with a substantial impact on the quality of life, healthcare system, and economy. The pressing need to identify the underlying etiology and a cure is motivated by years of observation that MAFLD significantly increases the risk for fatal outcomes such as cardiovascular abnormalities, type II diabetes, liver fibrosis, liver cirrhosis, and hepatocellular carcinoma [1-3]. MAFLD is a collective term for a set of progressive disease conditions that begins with the benign accumulation of fat in the liver called steatosis, followed by inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma, with ~10% of patients advancing to progressively worsening pathology [1-3]. Hepatic steatosis is often preceded by reduced disposal of glucose and glycogen synthesis by skeletal muscle, resulting in elevated plasma glucose [4-6]. The elevated glucose levels lead to increased secretion of insulin levels from the beta cells of the pancreas causing hyperinsulinemia. The elevated glucose levels and the ensuing hyperinsulinemia appears to de-sensitize the insulin receptors by locking it in a fully occupied conformation that is less competent for downstream signaling [7,8]. Reduced signaling through the receptors causes failure of Glut4 (Glucose transporter4) translocation to the plasma membrane, reduced glucose uptake, and reduced glycogen synthesis in the skeletal muscle [4, 5, 9, 10]. In the liver, insulin resistance causes excess glucose production leading to fasting hyperglycemia and in the adipose tissue, insulin-resistant adipocytes are unable to suppress the lipolysis of triglycerides into Non-Esterified Free Fatty Acids (NEFA) [4-6]. This is primarily because insulin-resistant adipocytes lose their ability to regulate ATGL and HSL lipases. The NEFA is immediately esterified to lipids upon entry into the hepatocytes. The influx of NEFA from insulin-resistant adipose tissue contributes to about 65% of liver triglycerides in MAFLD [11-13]. Glycerol, another byproduct of adipose tissue lipolysis undergoes phosphorylation into Glycerol-3-kinase (G-3K) in the liver. The G-3K leads to the generation of more glucose from oxoacetate through the actions of PEPCK, one of the rate-limiting enzymes of gluconeogenesis pathway [12,14,15]. Overall, the functions of liver, skeletal muscles, adipose tissue, and pancreas, get adversely affected and precipitates into MAFLD.

In the liver, the insulin-responsive pathway of De-Novo Lipogenesis (DNL) continues unabated despite systemic insulin resistance [16-18]. About 25% of hepatic triglycerides are contributed by de-novo lipogenesis in the liver of MAFLD patients [11]. Hyperinsulinemia is strongly associated with increases DNL in the liver [11,16,17,19-27]. Through substrate labeling studies, it was determined that fructose does not directly contribute to DNL but the gluconeogenic precursors such as lactate and alanine lead to synthesis of lipids [28-30]. Furthermore, excess fructose consumption leads to increased acetate production from the gut microbiota which stimulates hepatic DNL [31]. The lipid accumulation in the liver both by De-Novo Lipogenesis (DNL) and NEFA esterification further suppresses the insulin signaling [32] increasing hepatic glucose production by gluconeogenesis and glycogenolysis. Altogether, a self-stimulating catastrophic cycle of hyperglycemia, hyperinsulinemia, and hyperlipidemia is mobilized in MAFLD [18,22,33].

The dysregulated substrate flux at the cellular level is evident as increased plasma glucose and lipid at the macroscopic organismal level. The substrate flux through various metabolic pathways is regulated by the rate-limiting enzymes, which are effectors of signaling pathways including insulin, and glucagon. The anabolic processes such as triglyceride, cholesterol, glucose, and nucleic acid syntheses are favored more in the MAFLD compared to healthy livers [11,12,34]. Accordingly, downstream effectors of Insulin signaling such as mTORC2 (mammalian target of rapamycin complex2), and PKB (Protein kinase B), increase the expression of full-length Srepb1c and Srebp2 and their downstream targets in MAFLD liver [27,35,36]. Srebp1c activates the expression of a number of rate-limiting enzymes in the triglyceride synthesis pathways such as Fasn, Acc1, Scd1, Dgat1/2, and Gpat1 while Srebp2 increases the expression of HMGCS1 and HMGCR, two rate-limiting enzymes in the cholesterol synthesis pathway [37-39]. The increased lipid accumulation contributes to reduced insulin sensitivity in the liver and skeletal muscle due to diacylglycerol-dependent inactivation of the insulin Receptor beta subunit [40-42] and/or continuous Insulin-mTORC1 signaling which negatively feedbacks to reduce the insulin-signaling output [43,44]. Despite these observations, it seems counter-intuitive that these insulin-dependent pathways remain active in the MAFLD liver despite an insulin-resistant state in the liver. A possible explanation is that a high-energy state (increased glucose, lipids, or both) increases the expression of genes that activates lipogenesis in the hepatocytes but are

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normally expressed at low levels. One such factor could be Dyrk1b (dual specificity tyrosine phosphorylation regulated kinase 1b), which is increased in the liver of the high calorie fed mice and also in the human liver biopsies from MASH patients [32]. Dyrk1b induces lipogenesis by directly activating mTORC2, the central regulator of lipogenesis, in the fasting liver, when endogenous insulin signaling is minimal [32]. The gain of function mutations in Dyrk1b was previously associated with metabolic syndrome in humans in multiple large families in southwest Iran and in the United States [45]. We showed that Dyrk1b increases lipogenesis in an insulin-resistant liver providing direct relevance to the human disease condition [32].

The concurrent existence of type II diabetes and MAFLD indicates shared metabolic pathways that could be targeted therapeutically by drugs that achieve glycemic control. However, glucose-reducing drugs such as metformin, Sglt2 inhibitors, and PPAR agonists have been unsuccessful in reducing hepatic steatosis, inflammation, and fibrosis [46-55]. Several other therapeutic targets that were deduced rationally from metabolic pathways that trigger steatoses such as Acc1, DGAT1, and Scd1 [56, 57], bile acid analogs [58] that prohibit liver steatosis by transcriptional activation of Fgf19 [59], and Fgf21 analogs [60-62] have not been successful either. This is either due to non-specific targeting of unintended pathways, and/or compensatory activation of feedback pathways resulting in diminished efficacy. The field needs a therapeutic modality that can be delivered specifically to the hepatocytes and targets the intended molecule very specifically resulting in reduced hepatic steatosis, and inflammation without any non-specific effects. Further, to treat advanced pathologies such as fibrosis and cirrhosis, novel solutions and a meta-analysis of intercellular and inter-organ signaling networks is imperative. A recent FDA-approved agonist for gut hormone GLP-1 (glucagon-like peptide-1) has been very popular in reducing obesity by up to 22% [63]. Considering that reduction in body weight is an approved first-line recommendation for MAFLD [64], liver steatosis was improved in patients administered with semaglutides [47,51]. However, advanced MAFLD pathologies may necessitate a different therapeutic intervention. Another promising drug that has reached phase III is the Thyroid hormone beta-agonist which is specifically directed to the liver where it stimulates mitochondrial respiration and promotes the breakdown of lipids [65,66]. Altogether, the emerging therapies are promising and offer possibilities of a cure for MAFLD in the near future.

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