Cell Metabolism
Perspective

The Problem of Establishing Relationships between Hepatic Steatosis and Hepatic Insulin Resistance

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Excessive deposition of fat in the liver (hepatic steatosis) is frequently accompanied by hepatic insulin resistance. Whether this correlation is due to a causal relationship between the conditions has been the subject of considerable debate, and the literature abounds with conflicting data and theories. Here we provide a perspective by defining the problem and its challenges, analyzing the possible causative relationships, and drawing some conclusions.

The Problem

With more obesity in the developed world, the prevalence of hepatic steatosis, or fatty liver, has increased. An estimated ~1/3 of the population in the United States is obese (BMI > 30) and ~40% have type 2 diabetes or prediabetes (http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf). In response to overtaxed adipose tissues, human livers attempt to compensate as a storage depot for triglycerides (TGs). This has resulted in an epidemic of nonalcoholic fatty liver disease (NAFLD), with a prevalence of up to 30% in the United States (Lazo and Clark, 2008). Unfortunately, excessive fat in the liver is associated with organ pathology, including nonalcoholic steatohepatitis (NASH) and cirrhosis, which can lead to liver failure.

In humans, hepatic steatosis is often accompanied by hepatic insulin resistance (IR). This raises an important question: Does hepatic steatosis cause hepatic IR? Or, is the correlation between these two phenomena due to a common underlying molecular pathophysiology? Alternatively, does IR cause hepatic steatosis?

In this perspective, we outline some of the challenges to solving this problem, analyze issues of causality, and draw some conclusions.

Some Background

Hepatic steatosis, the excessive accumulation of lipids in the liver, usually refers to the build-up of neutral lipids, such as TGs or cholesterol esters, in lipid droplets of hepatocytes. The bulk of the evidence suggests that inert lipids, such as TG, contained within lipid droplets are not toxic. Besides neutral lipids, other lipids, including diacylglycerols (DAGs), ceramides, fatty acids, and their metabolites, often accumulate. These lipids are potentially bioactive and could therefore interfere with hepatocyte function and particularly with the ability of hepatocytes to respond to changes in insulin levels.

The failure of hepatocytes to respond to insulin contributes to the development of glucose intolerance and, ultimately, to fasting hyperglycemia and type 2 diabetes. In the liver, insulin normally acts through cell-surface receptors to suppress glycogenolysis and gluconeogenesis and to promote glycogen synthesis and lipogenesis. Hepatic IR usually refers to the impaired ability of insulin to suppress hepatic glucose production. Failure of the insulin system under such circumstances is usually not due to reduced levels of the hormone, since in obesity and diabetes-associated systemic IR, circulating insulin levels are often elevated. Instead, insulin signaling is impaired in insulin-resistant hepatocytes. More precisely, the insulin-stimulated signal transduction pathway that suppresses hepatic glucose production does not function normally. This signaling pathway includes the insulin receptor, IRS proteins, PI 3-kinase, Akt/protein kinase B (PKB), FoxO1, and presumably other downstream mediators (Haas and Biddinger, 2009; Leavens and Birnbaum, 2011). In steatosis-associated IR, defects in this signaling pathway are thought to occur at specific signaling steps, manifesting as defects in FoxO1 phosphorylation and increases in gluconeogenesis (Gross et al., 2009).

While these aspects of insulin's action on the hepatic gluconeogenic pathway are impaired, insulin's signaling to hepatic SREBP-1c and the lipogenic pathway (e.g., via atypical PKCs and possibly other PKCs) are thought to remain intact or to even be hyperstimulated (Farese and Sajan, 2010; Shimomura et al., 2000), thus promoting hepatic lipid synthesis and steatosis. Specific resistance to insulin's effects on suppressing hepatic glucose production, but not lipogenesis, is referred to as selective IR (Brown and Goldstein, 2008). Thus, in insulin-resistant states of obesity and type 2 diabetes, hepatic lipid production is increased paradoxically in concert with increased hepatic glucose production.

Challenges to Solving the Problem

Addressing the relationship between hepatic steatosis and IR presents considerable challenges. First, our view of insulin signaling in the liver is likely incomplete. A recent study of the

phosphoproteome of mouse livers treated with insulin showed hundreds of changes in phosphorylation in cellular proteins, many of which had not been described as parts of the insulin-signaling network (Monetti et al., 2011b). Thus, most studies that measure one or a few changes in the canonical pathway of insulin signaling likely ignore other important effects of the hormone, some of which may affect the development of IR. Second, it is impossible to study the accumulation of a specific lipid in isolation. Any change in a lipid metabolic pathway induced by an experimental intervention will almost assuredly result in compensatory changes in other pathways affecting discrete lipid pools. Moreover, analyses of lipids in livers are most often incomplete. Only some lipids are measured, frequently by different assays in different laboratories, and usually only general classes are measured, without differentiation of individual lipid species or their concentration within specific subcellular compartments. Third, the liver is influenced by multiple hormonal and neural inputs and is itself a complex tissue with several cell types, including hepatocytes, macrophage-related reticulo-endothelial cells, and stellate cells. Studies of cultured liver cells reduce the complexity of the problem, but most hepatocytes in culture lose insulin responsiveness, so fail to model the in vivo situation. Finally, the assessment of hepatic IR is not standardized. Many different assays are employed, including measurements of hepatic insulin signaling factors (by either phosphorylation states, enzyme activities, or enzyme amounts within membrane compartments), systemic measurements of glucose metabolism, or hyperinsulinemic-euglycemic insulin clamp studies. The latter method—considered the gold standard test in humans—presents significant technical and standardization challenges in mice (McGuinness et al., 2009). A lack of standardized criteria for measuring hepatic IR contributes to confusion in the literature with regard to the role of steatosis in its development.

Does Hepatic Steatosis Cause Insulin Resistance?

Many studies report a correlation between development of hepatic IR and accumulation of tissue lipids (e.g., TG, DAG, ceramides, or fatty acyl CoAs). But does the accumulation of specific lipids cause hepatic IR, or are both phenomena consequences of another condition? Problems of causality can be considered by addressing questions of sufficiency and necessity. Establishing causality is difficult: although consistent experimental results support or establish a theory, even a single contradictory result can refute it.

Is there a specific lipid, which upon accumulating to excessive levels in the liver, that invariably ("if and only if") causes hepatic IR? The available data indicate not. Steatosis normally refers to the accumulation of neutral lipids, such as TG or cholesterol esters. Numerous murine models accumulate TGs in the liver without accompanying IR. These include models with altered fatty acid synthesis (Chakravarthy et al., 2005), storage (Monetti et al., 2007), mobilization (Brown et al., 2010; Hoy et al., 2011; Minehira et al., 2008; Wu et al., 2011), and oxidation (Monsenego et al., 2011). Also, numerous studies of humans with mutations or genetic variations in genes that cause or contribute to hepatic TG accumulation, such as *ATGL*, *CGI58*, or *PNPLA3*, are not associated with IR (Cohen et al., 2011; Hooper et al., 2011). Thus, since TG accumulation is not invariably associated with hepatic IR, it cannot be considered as sufficient.

Numerous other lipids, including DAGs, ceramides, and fatty acyl CoAs, have been associated with hepatic IR (Nagle et al., 2009; Samuel et al., 2010; Summers, 2010). Excessive accumulation of these molecules might interfere with insulin signaling to regulate glucose production. In particular, DAGs activate conventional (classical) and novel protein kinase Cs, and ceramides activate atypical protein kinase Cs and c-Jun N-terminal kinases (JNK). Both classes of kinases might then interfere with insulin signaling by phosphorylation of key signaling molecules, such as the insulin receptor or IRS proteins (Morino et al., 2006; Vallerie and Hotamisligil, 2010). In many instances, the accumulation of these lipids in the liver is associated with hepatic IR (Cohen et al., 2011; Nagle et al., 2009; Samuel et al., 2010; Summers, 2010). Thus, it is reasonable to implicate these molecules as sufficient for causing or promoting hepatic IR.

DAG has been suggested as a unifying mediator (Samuel et al., 2010), although its role in causing hepatic IR has recently been debated (Jornayvaz et al., 2011; Monetti et al., 2011a; Monetti et al., 2007). Several studies in murine models and humans found normal hepatic insulin sensitivity in the setting of steatosis with elevated DAG levels (Brown et al., 2010; Minehira et al., 2008; Monetti et al., 2007; Voshol et al., 2003), refuting the hypothesis that liver DAG levels per se are causative. This does not exclude, however, the possibility that a particular DAG species is sufficient for driving hepatic IR in some models. DAG refers to a class of lipid molecules, and DAG species differ in the position and types of fatty acid side chains. Evidence suggests that only specific DAG species (i.e., *sn*-1,2-diacylglycerols) are potent activators of PKC enzymes (Boni and Rando, 1985). Moreover, measurement of total organ DAG levels, the method employed by most groups to date, may obscure elevations of DAG levels within a specific subcellular compartment that could activate PKC (e.g., at the plasma membrane). Such events may be required for DAG to serve as a mediator of insulin resistance. At present, there are few data addressing DAG species or DAG localization in models of hepatic steatosis associated with hepatic IR, although one recent study correlated DAG content in lipid droplets, as well as total liver DAG content, with plasma indices of IR (Kumashiro et al., 2011). This study was correlative in nature, however, and did not directly address causation. More studies are needed on both DAG species and compartmentalization with respect to sufficiency for causing hepatic IR. Similar arguments can be made for other lipids, including fatty acyl-CoAs and ceramides, which in excess are sometimes, but not always, associated with hepatic IR (Summers, 2010) and do not fulfill strict criteria for sufficiency arguments.

The available data indicate that most lipids fail the criteria of sufficiency for causing hepatic IR. What about their necessity for hepatic IR? The data show that hepatic IR can arise as a result of conditions other than lipid accumulation in the liver. For example, a murine model with hepatocyte-specific deletion of the insulin receptor exhibits marked IR but lacks hepatic steatosis (Biddinger et al., 2008). Moreover, humans with mutations in the insulin receptor are insulin resistant, but also lack hepatic steatosis (Semple et al., 2009). Thus, steatosis is not a strict requirement for developing hepatic IR.

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