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Insulin Resistance and Other Metabolic Risk Factors

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Introduction

Coinciding with the increased incidence of hepatocellular carcinoma (HCC), worldwide and in the United States^{1, 2, 3}, there has been a significant increase in the global incidence of obesity and diabetes, the two major risk factors for non-alcoholic steatohepatitis (NASH). In this context, 15%–50% of patients with HCC have no specific identifiable risk factors, such as hepatitis B (HBV) or hepatitis C virus (HCV) infection, and are labeled as having ‘cryptogenic cirrhosis’⁴. A recent study of 105 patients with HCC of whom 29% carried a diagnosis of ‘cryptogenic cirrhosis, found that 50% had non-alcoholic fatty liver disease (NAFLD)- related cirrhosis⁵.

Obesity and HCC

Overweight (body mass index [BMI; calculated as the weight in kilograms divided by height in meters squared, ie, kg/m²] between 25 and 30) and obesity (BMI of 30 or higher) have been identified as independent risk factors for various cancers including postmenopausal breast cancer, endometrial cancer, colorectal cancer, renal-cell and adenocarcinoma of the esophagus⁶. There is also a possible association between obesity and gallbladder, pancreas, thyroid and hematologic malignancies⁶. With regard to HCC, data suggest that there is a 1.5 to 4-fold increased risk among obese individuals^{6–8}. In a large prospective study involving 900,000 United States adults initially free from cancer and followed for 16 years, obese men and obese women, respectively, had a 14% and 20% increased incidence of cancer-related death, after controlling for other risk factors⁶. In the morbidly obese (BMI >40), the death rate from cancer was 52% higher in men and 62% higher in women, respectively, compared to those of normal weight⁶. The relative risk of liver cancer among obese individuals in this population was 2.0 to 4.0 fold, as seen in other studies. A large Danish study of 43,965 obese individuals found an overall 16% increased incidence of cancers in general and a relative risk of 1.9 for liver cancer, compared to non-obese individuals⁷. Similarly, in a study in Sweden of over 28,000 obese individuals, Wolk and colleagues⁸ found an almost threefold increased risk of HCC as in slim counterparts. Regimbeau and colleagues⁹ analyzed 19,271 explanted liver specimens for HCC; after controlling for confounding variables such as age and gender, there was a slightly higher prevalence of HCC in obese than in non-obese patients. Furthermore, obesity was also an independent risk factor for HCC in patients with alcoholic and cryptogenic cirrhosis, but not among those with viral hepatitis, primary biliary cirrhosis or metabolic liver diseases. A meta-analysis of 11 cohort studies confirmed that overweight and obese individuals had a 17% and 89% increased risk of liver cancer, respectively, compared to those with normal weight; moreover, the relative risk was significantly higher for men than for women¹⁰. The investigators estimated that

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overweight or obesity was a risk factor for HCC in 28% of men and 27% of women, respectively¹⁰.

The mechanism that links obesity and cancer is not clear. It is hypothesized that dysregulation of adipokines and insulin resistance may both contribute to tumorigenesis¹¹. Both adipose tissue excess and adipose tissue deficiency (ie lipodystrophy) are associated with features of the metabolic syndrome¹². Adipose tissue is no longer considered a passive reservoir for energy storage but is currently viewed as an essential and active endocrine organ, as it secretes adipocyte-specific proteins called adipocytokines and other hormones that exert a wide range of physiologic effects and may also contribute to obesity-related complications¹³. The adipocytokines, which include tumor necrosis factor (TNF)- α , resistin, leptin, and adiponectin among others, act at both the local (autocrine/paracrine) and systemic (endocrine) levels to create a milieu that results in inhibition of apoptosis, increased cellular proliferation, angiogenesis and worsened insulin resistance^{12,14}. Adipose tissue also expresses molecules like vascular endothelial growth factor (VEGF) which exert a direct effect on cellular metabolism and proinflammatory pro-oncogenic proteins such as TNF- α , interleukin (IL)-6, and IL-1¹⁵.

Diabetes Mellitus and HCC

Patients with cirrhosis frequently develop impaired glucose tolerance or overt diabetes mellitus (DM) making it difficult to assess whether a direct relationship exists between DM and HCC. Results of a several studies have convincingly shown that DM is an independent risk factor for the development of HCC¹⁶⁻¹⁹. In a large prospective study among United States veterans, which included 173,643 patients with and 650,620 patients without DM, a twofold increase in the relative risk of HCC was reported in DM patients,¹⁶ after adjustment for confounding factors such as HBV, HCV and alcoholic cirrhosis. Adami and colleagues¹⁷ reported an overall fourfold increase in primary liver cancer in a cohort of 153,852 diabetics in Sweden who were followed for 1 to 24 years; after excluding patients with concomitant diseases such as cirrhosis, alcoholism and hepatitis, the increased HCC risk persisted and was approximately threefold. Similarly, in a study from Denmark, standardized incidence ratios (SIRs) were estimated for primary liver cancer at 4.0 in males and 2.1 in women, in a cohort of 109,581 diabetics¹⁸. Finally, investigators using Surveillance, Epidemiology and End-Results (SEER) registries identified and compared 2061 patients with HCC with noncancer controls¹⁹. DM was reported in 43% and 19% of subjects with HCC and controls, respectively; after adjusting for other HCC risk factors (HBV, HCV, alcoholic liver disease, and hemochromatosis), DM was associated with a threefold increase risk of HCC.

NAFLD has now emerged as the most common chronic liver disease in western countries with approximately 20% to 30% of the general population affected. Furthermore, the prevalence of NAFLD is likely to increase given the rising incidence of obesity and DM^{20,21}. NAFLD is closely linked to the metabolic syndrome, which includes obesity, DM, hyperlipidemia and insulin resistance^{22,23}. Approximately 10% of patients with NAFLD are likely to progress to NASH and 8% to 26% of individuals with NASH progress to cirrhosis, which is an independent risk factor for HCC^{24,25}. Although the exact factors that influence the progression of NAFLD to the more severe NASH are not clear, BMI and DM are independent risk factors for progression of fibrosis²⁶. Moreover, the association of NASH with other components of the metabolic syndrome increases the risk for developing chronic liver disease and cirrhosis, and subsequently HCC²⁷.

In a recent review of 4406 HCC patients who were identified from a claims database, 59% had NAFLD/NASH as the underlying etiology followed by DM (36%) and HCV infection (22%)²⁸. In another study of 195 patients with NASH cirrhosis and 315 patients with HCV

cirrhosis, who were followed for a mean period of 3.2 years, HCC was identified in 12.8% and 20.3% of NASH and HCV patients, respectively. The yearly cumulative incidence of HCC was 2.6% in NASH cirrhosis compared with 4.0% in HCV cirrhosis, respectively. NASH-cirrhotic individuals who drank alcohol were at higher risk of developing HCC than nondrinkers²⁹. Similarly, comparing NASH-associated cirrhosis to HCV-associated cirrhosis in Japanese subjects during a 5 year follow up period, the incidence of HCC was 11.3% versus 30.5% in these 2 respective groups³⁰. In contrast to these many positive associations, it is not clear why Hui and colleagues,³¹ in Australia, found that HCC did not develop in patients with NASH cirrhosis compared with a 17% prevalence in age-matched and gender-matched HCV-cirrhosis controls.

Although the mechanism of carcinogenesis in patients With NAFLD/NASH remains uncertain, it is plausible that insulin resistance and oxidative stress are contributing factors, as is now discussed.

Oxidative Stress, Reactive Oxygen Species and HCC

Insulin resistance leads to increased hepatocyte lipogenesis, decreased hepatic secretion of very-low-density lipoproteins and increased hepatic uptake of circulating free fatty acids (FFA) that come from peripheral lipolysis^{23, 32}. The resulting liver phenotype is characterized by increased hepatic triglyceride accumulation and macrovesicular steatosis, with varying degrees of necroinflammation and fibrosis³³.

Increased production of TNF- α from adipose tissue and oxidative stress results in an up-regulation of suppressors of cytokines signaling (SOCS 1 and 3) which bind to tyrosine Janus kinases (JAK) and inhibit phosphorylation of signal transducer and activator of transcription (STAT) proteins, resulting in inhibition of insulin signaling pathways that leads to hepatic insulin resistance^{34,35}. Oxidative stress also stimulates production of reactive oxygen species (ROS) in the liver,³⁶ which increases the expression of the cytokines transforming growth factor (TGF)- β and IL-8, and generates lipid peroxidation products, such as 4-hydroxynonenal (4-HNE). These molecules are chemoattractants for neutrophils and likely contribute to the neutrophil infiltration and inflammation in the fatty liver³⁷. ROS activate fibrogenesis by stimulating hepatic stellate cells^{36, 38}. ROS also impair mitochondrial respiration, deplete mitochondrial cytochrome *c* and cause oxidative damage to the mitochondrial genome, thereby activating the apoptosis cascade³⁹. Furthermore, other products of lipid peroxidation (such as malondialdehyde) can cause DNA mutations. *trans*-4-Hydroxy-2-nonenal, another major by-product of lipid peroxidation, likely plays a major role in the pathogenesis of HCC, due to mutations induced in the tumor protein *p53* gene⁴⁰. Downstream targets of *p53* include *p21/Waf1*, and growth arrest DNA damage gene (GADD) 45 and 14-3-3, which mediate G2/M arrest⁴¹. *P53* protein also has apoptotic properties due to its action on *Bax*⁴². Furthermore, activation of activating protein (AP)-1 and nuclear factor kappa B (NF-KB) by oxidative stress causes either cellular proliferation or apoptosis depending on the cellular redox state. Oxidative stress has also been shown to cause decreased expression of the nuclear respiratory factor (*Nrf1*) gene; *Nrf1*L knock-out mice show increased susceptibility to oxidative stress, increases in intracellular ROS, development of fatty liver with inflammation, hepatic cell death, fibrosis and ultimately liver cancer⁴³.

Insulin resistance and HCC

Insulin resistance is characterized by reduced sensitivity to insulin and, as a result, impaired ability of insulin to suppress glucose production and stimulate peripheral glucose elimination. To overcome insulin resistance and maintain normal metabolic functions,

insulin secretion is increased, leading to a state of compensatory hyperinsulinemia⁴⁴. The liver also secretes Insulin-like growth factor (IGF)-1. IGF-1 is one of the most potent activators of cellular proliferation via the Akt (also called protein kinase B, [PKB]) signaling pathway, and is an inhibitor of apoptosis (Figure 1).⁴⁵ Chronic hyperinsulinemia has been associated with a variety of cancers. Changes in the expression of the IGF axis, which consists of IGF-1 and IGF-2, its receptors IGF1R and IGF2R, and IGF-binding proteins (IGFB1–6), have been observed in rodent models of HCC and in human HCC cell lines^{46, 47}.

Insulin resistance and compensatory hyperinsulinemia promote increased phosphorylation and activation of downstream pathways resulting in inhibition of apoptosis and increased mitogenesis, which thereby promotes tumorigenesis. Insulin resistance may also directly accelerate hepatocarcinogenesis via the stimulation of hepatic neovascularization⁴⁸. Insulin causes upregulation of hepatic growth hormone (GH) receptors, and GH is the principal stimulus for IGF-1 activation. IGF-1, like insulin, promotes cell proliferation, upregulates endothelial growth factor, and inhibits apoptosis⁴⁹. Hyperinsulinemia further reduces liver synthesis and blood levels of IGFBP1 and IGFBP2, which lead to increased bioavailability of IGF-1⁵⁰. IGF signaling in HCC has been shown to increase production of IGFs, IGFBPs, IGFBP proteases, and IGF receptor expression⁵⁰. IGF-1 also has mitogenic effects on a variety of cancer cell lines and activates mitogen-activated protein kinase (MAPK) and increases expression of the c-fos and c-jun protooncogenes in cultured HCC cells^{51, 52}. IGF-2 may also be over-expressed as result of a reduced expression of IGFBP in cirrhotic patients⁵⁰. IGF-2 promotes proliferation, survival and migration in HCC cells through binding to its IGF type 1 receptor. This receptor, as well as its main substrates insulin receptor substrate (IRS)-1 and IRS-2 are overexpressed in HCC and in experimental models of liver carcinogenesis⁵³.

Hyperinsulinemia and the activated insulin receptors cause phosphorylation of IRS-1, a key protein involved in cellular proliferation that transmits insulin signals through two main pathways: phosphatase and tensin homolog (PTEN)/P13K/Akt and MAPK kinase (MAPKK),⁵⁴ which is also referred to as MEK (MAP kinase or extracellular signal-related kinase [ERK] kinase). PTEN/P13K/Akt, an important pathway in cellular proliferation and apoptosis, also plays an important role in the pathogenesis of HCC⁵⁵. PTEN is a tumor suppressor gene, and its activity is reduced by mutations or deletions in a number of malignancies^{56, 57}. Loss of PTEN results in activation of downstream effector Akt⁵⁸. Akt is also activated by insulin and IGF-1. Activated Akt promotes cell survival by inhibiting pro-apoptotic protein Bcl-2 family member BAD⁵⁹. Under normal circumstances BAD interacts with Bcl-XL and causes apoptosis. Phosphorylation of BAD by Akt prevents its binding to Bcl-XL and thereby suppresses apoptosis. Activated Akt thereby plays an important role in promoting cell growth and survival, and also inhibits apoptosis. The central role of Akt in insulin signaling is shown in Figure 2.

However, despite these compelling circumstantial data linking hyperinsulinemia to cancer, a 10-year prospective study from Korea of 1,298,385 patients showed that cancer risk was influenced by fasting blood glucose in a dose dependent manner rather than insulin resistance, which challenges a supposed direct action of insulin on promotion of cancers⁶⁰.

Leptin and HCC

Hyperleptinemia is noted in both obesity and in type 2 diabetes. The link between hepatic fibrosis and leptin, and its profibrogenic and angiogenic properties, suggests that this protein may be a risk factor for the development of HCC⁶. Male mice treated with simultaneous carbon tetrachloride and/or leptin had significant leptin-enhanced hepatic

necroinflammatory and fibrotic changes.⁶¹ The *db/db* mouse - a model of obesity, diabetes and dyslipidemia that is caused by homozygous genetic hepatic leptin receptor deficiency - when fed a diet deficient in methionine and choline (MCD diet) develops insulin resistance and hyperleptinemia, and a picture that mimics severe human NASH⁶² with liver fibrosis. By comparison, leptin-deficient obese, diabetic and genetically leptin-deficient *ob/ob* mice fed an MCD diet; do not develop liver fibrosis, suggesting that leptin has an important role in hepatic fibrogenesis. Furthermore in a NASH rat model, Kitade and colleagues⁶³ were able to demonstrate increased leptin-mediated neovascularization in the liver with progression of NASH, while leptin inhibition mitigated both fibrogenesis and hepatocarcinogenesis.

Leptin, the product of the obese (*Ob*) gene, is an adipokine predominant in adipose tissue. Leptin acts centrally in the hypothalamus and decreases appetite, regulates food intake and increases energy expenditure.⁶⁴ Of the six isoforms of leptin receptors (*ObRa* through *ObRf*), *ObRb* is the most important mediator of the biological effects of leptin⁶⁴. Obesity in humans is frequently associated with elevated leptin levels, suggesting that leptin resistance may be present.⁶⁵ Failure of elevated leptin to mediate weight loss in this setting is likely caused by mechanisms that attenuate leptin signaling including inhibition of SOCS3 by adenosine monophosphate (AMP)-activated protein kinase (AMPK) due to leptin resistance.^{64, 66}

In liver disease, serum leptin levels are substantially elevated; patients with alcohol and viral cirrhosis may have a twofold increase in leptin as compared to controls.⁶⁷ Leptin is upregulated by cytokines such as IL- 1, TNF α , and insulin, which are often elevated in patients with cirrhosis.^{68–70} Circulating free leptin levels are also significantly higher in NASH patients and in HCC patients than in healthy controls.^{71, 72} Wang and colleagues⁷² evaluated 36 HCC specimens and corresponding adjacent non-tumorous liver tissue, and found that adjacent liver cells expressed higher levels of leptin and its receptor than adjacent HCC cells, suggesting that leptin acts as a growth factor to hepatocytes and may have a role in initiation and progression of HCC.⁷⁵

Leptin binds to its receptors, and causes phosphorylation of JAK2 and the downstream STAT3. The JAK/STAT signaling pathway then triggers a signaling cascade involving activations of PI3K/Akt and MEK 1/2 (Figure 3).⁷³ These signal pathways increase cyclin D1 protein expression, resulting in proliferation of hepatocytes and HCC cells.⁷⁴ Inhibition of any of these signal pathways blocks the action of leptin. Leptin also inhibits TGF- β 1-induced apoptosis by down-regulating proapoptotic Bax expression.⁷⁴ Therefore, by increasing cellular proliferation and decreasing apoptosis, leptin may function as a growth factor for HCC cells. Activation of these pathways also results in increase in methionine adenosyl transferase (*MAT*) 2A and *MAT2beta* gene expression, markers of liver cell growth and differentiation.

Leptin may also contribute to hepatic fibrogenesis via TGF- β and activation of hepatic stellate cells (HSCs).⁷⁵ HSCs are liver specific, and are involved in wound healing and development of fibrosis in the setting of chronic liver disease.⁷⁶ HSCs regulate inflammation and promote angiogenesis via secretion of various cytokines, including chemokines, by acting through several pathways including ERK/Akt, nuclear factor kappa B (NFkB) and hypoxia-inducible factor 1 (HIF-1).⁷⁷ Activated HSCs proliferate and secrete collagen and other extracellular matrix components, which ultimately results in liver fibrogenesis.⁷⁶ Increased expression of has been observed in the areas surrounding HCC and hepatic metastases secondary to activation of HSCs via cyclooxygenase (COX)-2 dependent prostaglandin (PG)E₂.⁷⁸ VEGF upregulation creates a proangiogenic microenvironment, which leads to progression of liver fibrogenesis and possibly cancer.⁷⁸ The role of leptin in

carcinogenesis may be more complex. As mentioned earlier, because leptin expression was shown to be increased in adjacent noncancerous liver tissues but markedly decreased in the cancerous lesions, it is possible that leptin may be associated with angiogenesis but not with the proliferation of HCC cells.⁷²

Furthermore, Ellinav and colleagues⁷⁹ reported that administration of leptin in a murine model of HCC resulted in a significant reduction in tumor size and improved survival.

In summary, leptin remains a reasonable candidate for promotion of cancer via effects on angiogenesis and other pathways; the presence of leptin resistance in obesity suggests a possible relation between altered regulation of this pathway and liver cancer.

Adipocytokines and HCC

The plasma concentration of adiponectin, a hormone exclusively secreted by adipose tissue, is markedly decreased in obesity, Type 2 DM and atherosclerosis.⁸⁰ Obesity is associated with a state of low grade chronic inflammation characterized by up-regulation of TNF- α , IL-6 and other proinflammatory cytokines, which inhibit expression of adiponectin.⁸¹ Maeda and colleagues⁸² have shown that adiponectin knock-out mice had high levels of plasma TNF- α , and TNF- α mRNA in adipose tissue. These mice developed severe insulin resistance, had increased atherogenesis, and significant endothelial dysfunction in response to vascular injury. Administration of adiponectin to these mice resulted in improvement of insulin resistance. Similarly, a rhesus monkey model of obesity and Type 2 DM is characterized by low levels of adiponectin.

Adiponectin has several beneficial effects. The anti-inflammatory effects of adiponectin can be linked to stimulation of the anti-inflammatory cytokines and inhibition of proinflammatory markers, including TNF- α and IL-6, the NF κ B pathway, and chemokines.⁸¹ Adiponectin exerts atheroprotective properties by inhibition of monocyte adhesion to endothelial cells, macrophage cytokine production, lipid accumulation in macrophages and phagocytosis.⁸⁴ There are convincing data showing an inverse relationship between serum adiponectin concentration and inflammatory markers such as C-reactive protein, and development of features of the metabolic syndrome.⁸⁵ Low adiponectin levels have also been strongly implicated in the development of insulin resistance.⁸⁶ Adiponectin-induced AMPK up-regulates glucose transporter (GLUT)-4 gene expression and inhibits transcription of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase, which regulate hepatic gluconeogenesis.⁸⁷ Insulin resistance and chronic hyperinsulinemia result in reduced synthesis of IGFBP1 and IGFBP2, and increased bioavailability of IGF1, which promotes cellular proliferation, up-regulates EGF, and inhibits apoptosis, thereby promoting carcinogenesis.⁸⁸ Insulin reduces the expression of AdipoR1 and AdipoR2 via a PI3K/Forkhead boxO1-dependent pathway in cultured hepatocytes.⁸⁹ Patients with insulin resistance and type 2 DM have significantly reduced adiponectin levels, which increase upon administration of insulin-sensitizing drugs, such as the thiazolidinediones (TZDs).⁸⁵ Missense mutations in adiponectin genes have been identified in subjects with Type 2 DM and hypoadiponectinemia.⁹⁰ These data suggest that hyperinsulinemia may negatively regulate adiponectin.

Low levels of adiponectin have been implicated in many common cancers including breast, colorectal and prostate in men, and breast and endometrial cancer in women.^{91–94} Mouse NASH models that have low levels of adiponectin demonstrate increased progression of hepatic fibrosis, whereas administration of adiponectin reduces inflammation and steatosis. Moreover, these animals also had accelerated tumorigenesis, suggesting that adiponectin probably contributes to NASH cirrhosis and HCC.⁹⁵ Similarly, patients with HCC had lower levels of plasma adiponectin as well as an inverse relationship between adiponectin

expression and tumor size.⁹⁶ Saxena and colleagues⁹⁷ showed that HCC cells overexpress AdipoR1 and R2 leading to increased adiponectin-binding capacity, while adiponectin treatment inhibited HCC tumorigenesis *in vivo* by inhibition of cellular proliferation and induction of apoptosis.

AdipoR1 is expressed mainly in skeletal muscle but is also present in endothelial cells and other tissues, whereas AdipoR2 is predominantly expressed in the liver.⁹⁸ These receptors mediate the cellular function of adiponectin by activating two main downstream signaling pathways: AMPK and peroxisome proliferator-activated receptor (PPAR)- α . AMPK activation by novel small molecules appear to show promise for the treatment of diabetes and metabolic syndrome via effects on glucose and lipid metabolism.⁹⁹

The antiproliferative and proapoptotic effect of adiponectin is mediated by AMPK, which has been shown to cause cell cycle arrest in HepG2 cells via p53 phosphorylation of tuberous sclerosis protein (TSC)2, phosphorylation and inhibition of translation elongation factor (TEF)2 (EF2), and/or suppression of mammalian target of rapamycin (mTOR), thereby decreasing protein synthesis and cell growth.¹⁰⁰ mTOR pathway activation via phosphatidylinositol (PI) 3-kinase and PKB/Akt signaling plays an important role in activation of cell growth and proliferation (Figure 4). mTOR stimulates cell growth by activating ribosomal protein S6 kinase (S6K1) and by increasing phosphorylation of elongation factor-4E binding protein 1 (4E-BP1) resulting in protein synthesis.¹⁰¹ In addition, activated AMPK positively regulates 2 important proteins for the control of growth arrest and apoptosis, namely p53 and p21.¹⁰² In addition, c-Jun N-terminal kinase (JNK) and STAT3 are important downstream effectors of adiponectin. JNK regulates cell proliferation and apoptosis while STAT3 stimulates cell proliferation and prevents apoptosis.¹⁰³ Adiponectin has been shown to stimulate JNK and suppress STAT3 in HepG2 cells. Thus, adiponectin may play a pivotal role in the pathogenesis of HCC via JNK/STAT3 signal pathway (See Figure 4).

In summary, the beneficial effect of adiponectin on tumorigenesis is probably multifactorial and likely involves the effect of adiponectin on insulin resistance, a direct effect on tumor cells and suppression of endothelial cell proliferation, migration and survival thereby inhibiting neovascularization.

Summary

There are many causes of HCC, and NAFLD/NASH is now emerging as a leading risk factor owing to the epidemic of obesity and type 2 DM. The mechanisms leading to HCC in obesity and type 2 DM likely involve interactions between several signaling pathways, including oxidative stress, inflammation, oncogenes, adiponectins, and insulin resistance associated with visceral adiposity and diabetes. Understanding the molecular signaling pathways involved in the pathogenesis of HCC will aid in the development of molecular therapies targeting specific receptors and/or signaling proteins for the prevention and treatment of HCC. In addition, a better understanding of the role of insulin and leptin resistance and adiponectin deficiency in these pathways may provide greater awareness of dietary, lifestyle and pharmacologic interventions.

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Figure 1.

Schematic diagram illustrating the canonical insulin signaling pathway. The insulin receptor (IR) phosphorylates itself as well as Insulin Receptor Substrate (IRS). PI3 kinase (PI3K) phosphorylates 3-phosphoinositides, which produce binding sites for PIP3 dependent kinase (PDK) and Akt via their PH domains. Akt is phosphorylated by PDK and Mammalian Target Of Rapamycin (mTOR)-Rictor, which lead to active Akt kinase activity and its pleiotropic effects. P denotes key phosphorylation events. Reprinted from: *Endocr Rev.* 2008 Jun;29(4):381–402. Epub 2008 May 1. © The Endocrine Society; with permission

Figure 2. Insulin is the major hormone controlling critical energy functions such as glucose and lipid metabolism. Insulin activates the insulin receptor tyrosine kinase (IR), which phosphorylates and recruits different substrate adaptors such as the IRS family of proteins. Tyrosine phosphorylated IRS then displays binding sites for numerous signaling partners. Among them, PI3K has a major role in insulin function, mainly via the activation of the Akt/PKB and the PKC ζ cascades. Activated Akt induces glycogen synthesis, through inhibition of GSK-3; protein synthesis via mTOR and downstream elements; and cell survival, through inhibition of several pro-apoptotic agents (Bad, Forkhead family transcription factors, GSK-3). (Pathway diagram reproduced *courtesy* of Cell Signaling Inc. www.cellsignal.com)

Figure 3.

Schematic diagram for the role of Methionine Adenosyl Transferase (MAT) genes and s-Adenosyl Methyl Transferase (SAMe) in leptin-induced mitogenic response in HepG2 cells. Upon leptin interaction with its receptor, Ob-RL, activation of Janus kinase 2 (JAK2) occurs via trans-phosphorylation of the receptor as well as subsequent phosphorylation of the Signal Transducer and Activator of Transcription (STAT) proteins. This leads to a series of downstream events including activation of Extracellular Signal-Related Kinase (ERK)/Mitogen-Activated Protein Kinase (MAPK) and PI3-K/AKT survival pathways in HepG2 cells. Leptin signaling induces MAT2A and MAT2_β genes via activation of these survival pathways, which further leads to enhanced cell proliferation. The MAT2A-encoded protein induces leptin's mitogenic response by raising intracellular s-adenosylmethionine (SAMe) levels, leading to polyamine biosynthesis and growth. The MAT2_β gene interacts with leptin signaling components and modulates cell growth. Pharmacological doses of SAMe and Metastasis-Associated (MTA) proteins act as inhibitors of leptin signaling and growth in HepG2 cells. (From Ramani K, Yang H, Xia M, et al. Leptin's mitogenic effect in human liver cancer cells requires induction of both methionine adenosyltransferase 2A and 2beta. *Hepatology* 2008;47(2):521–31; Copyright © 2007 American Association for the Study of Liver Diseases. Wiley and Sons; with permission.)

Figure 4.

Many potential signaling pathways for adiponectin in endothelial cells. Both isoforms of the adiponectin receptor (AdipoR1 and AdipoR2) are expressed in endothelial cells, but mRNA for the AdipoR1 receptor, with a higher affinity for Globular Adiponectin (gAd), is more abundant. As in metabolically responsive tissues, one of the major signaling effects of adiponectin in endothelial cells is activation of AMP kinase. AMP kinase, in turn, activates Endothelial Nitric Oxide Synthase (eNOS) via a pathway that also appears to be dependent on Akt activation, which is linked upstream to phosphatidylinositol 3-kinase (PI-3K) signaling. Both eNOS activation and Akt activation contribute to the effects of adiponectin on angiogenesis. Adiponectin also inhibits oxidized Low Density Lipoprotein (oxLDL)-induced superoxide production, possibly through inhibition of cellular NAD(P)H oxidase activity. Reduced ROS generation may enhance (Nitric Oxide) NO production and diminish cell proliferation by adiponectin by ameliorating the suppression of eNOS activity and NO quenching by Reactive Oxygen Species (ROS) and by blocking oxLDL-induced MAPK activation, respectively. Adiponectin can also lead to endothelial apoptosis via upstream caspase activation. The *solid arrows* and *dotted lines* reflect stimulatory and inhibitory effects, respectively. (From Goldstein BJ, Scalia R. Adiponectin: A novel adipokine linking adipocytes and vascular function. *J Clin Endocrinol Metab* 2004;89(6):2563–68; @ The Endocrine Society; with permission.)