effective exercise is in reversing perturbed insulin sensitivity and oxidative capacity and (2) that because exercise activates Ca^{2+}, AMPK, SIRT1, and PGC1-α, the possibility of targeting the adiponectin/adipoR1 pathway as a therapeutic is tangible. It must be emphasized, however, that discovering any single pharmacological agent that will mimic the broad range of exercise-related health benefits is indeed remote, and, alas, we should not put our joggers into mothballs just yet! However, identifying and targeting specific common biochemical and molecular components of the exercise response are likely to lead to viable drug therapies and prove beneficial in the battle against such pathophysiologies as mitochondrial dysfunction in obesity and insulin resistance.

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Autophagy: A Potential Link between Obesity and Insulin Resistance

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Dysregulation of autophagy contributes to aging and to diseases such as neurodegeneration, cardiomyopathy, and cancer. The paper by Yang et al. (2010) in this issue of *Cell Metabolism* indicates that defective autophagy may also underlie impaired insulin sensitivity in obesity and that upregulating autophagy can combat insulin resistance.

Autophagy is responsible for the turnover of long-lived proteins and of intracellular structures that are damaged or functionally redundant. The process is essential for the maintenance of cellular homeostasis and is activated by starvation (to supply ATP-producing substrates, e.g., amino acids) and other stress-inducing conditions. Its dysregulation is involved in many disorders and in aging (Meijer and Codogno, 2009). In this issue of *Cell Metabolism,* Yang et al. (2010) now show that hepatic autophagy is defective in obesity and diabetes and that its upregulation improves insulin sensitivity.

During autophagy, part of the cytoplasm is surrounded by a double membrane, presumably formed from the endoplasmic reticulum (ER), to form an autophagosome that then fuses with lysosomes, after which the sequestered material is degraded. This process requires the participation of autophagy-related (ATG) proteins (see Meijer and Codogno, 2009 for review).

Autophagy is inhibited by the insulin-amino acid-mTOR signaling pathway via both short-term and long-term regulation mechanisms. Short-term inhibition can be produced by the mammalian target of rapamycin (mTOR) complex 1, which causes phosphorylation and the inhibition of ULK1 (the human homolog of yeast ATG1). Long-term regulation occurs via the transcription factors FoxO1 and FoxO3 (Liu et al., 2009), which control the transcription of *atg* genes and become phosphorylated and inhibited by insulin-induced activation of protein kinase B (Figure 1).

Recent evidence indicates that dysregulation of autophagy is implicated in obesity (characterized by ER stress, insulin resistance, and glucose intolerance; Hotamisligil, 2010) and in diabetes. Mice fed a high-fat diet (HFD) have reduced hepatic autophagy (Liu et al., 2009). However, autophagy, which is essential for maintaining the structure and function of β cells, is increased in β cells during this period of HF feeding (Ebato et al., 2008). In contrast, the

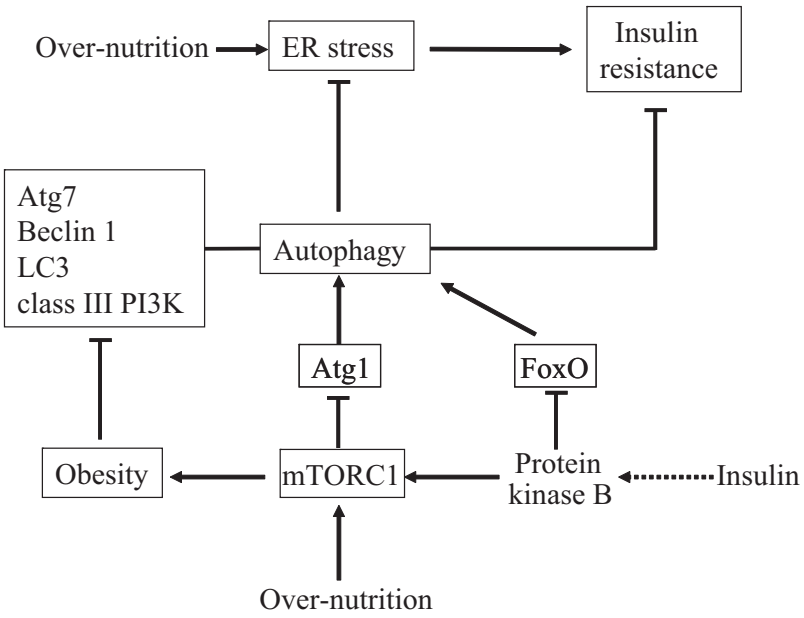

Figure 1. Autophagy and Insulin Resistance
Autophagy is controlled by insulin-amino acid-mTOR signaling. Overfeeding causes chronic ER stress, which results in the downregulation of several of the proteins required for autophagy. This reinforces ER stress and leads to insulin resistance. Overactivation of mTOR complex 1 (mTORC1) activates lipogenesis and thus contributes to obesity.

destruction of insulin production in β cells by streptozotocin (STZ) increases autophagy in the liver (Liu et al., 2009). Likewise, autophagy is also increased in β cells derived from human subjects with type-2 diabetes (Masini et al., 2009).

Yang et al. (2010) demonstrate that, not only is hepatic autophagy severely depressed in dietary (HFD for 16–22 weeks) and genetic (ob/ob, db/db) models of murine obesity and diabetes (as indicated by the severe downregulation [>90%] of the ATG proteins LC3, BECLIN1, ATG5, and ATG7), but also that this process may underlie the impaired insulin sensitivity in these models. Thus, the suppression of hepatic ATG7 using shRNAi (using an adenovirus-mediated approach) in lean control mice resulted in insulin resistance and ER stress. Similarly, suppression of ATG7 or ATG5 in in vitro cell models caused defective insulin signaling. Conversely, restoration of hepatic autophagy in HFD-fed or in ob/ob mice, by means of adenovirus-directed overexpression of ATG7, diminished ER stress, counteracted insulin resistance, improved hepatic fat metabolism, decreased gluconeogenesis, and increased peripheral glucose disposal, effects that could all be blunted by the expression of dominant-negative ATG5. The latter observation makes it unlikely that the effect of ATG7 overexpression on insulin sensitivity can be ascribed to some unknown function of ATG7 that is unrelated to autophagy. Assuming that food intake had remained unchanged under these conditions, these data clearly demonstrate that defective autophagy and insulin resistance are closely linked.

At first sight, it is surprising that autophagy can be restored by increasing the expression of ATG7 alone, amidst many other severely depressed ATG proteins. Surprisingly, the expression of ATG7 alone also appeared to enhance the expression of BECLIN 1, ATG 5, ATG12, and LC3 protein. The inhibition of calpain 2 at least partially restored ATG7 levels, suggesting that this Ca^{2+}-dependent protease is responsible for the decrease in ATG7 protein and other ATG proteins in the liver of ob/ob mice. The intimate mechanism of this effect remains to be explored.

In order to rule out the possibility that the chronic high insulin levels in ob/ob mice were responsible for the reduced levels of ATG proteins, STZ was administered to the animals but did not restore the hepatic levels of ATGs (in contrast to what happened in lean mice, in which STZ increased hepatic autophagy (Liu et al., 2009; see above). Likewise, hepatic levels of ATGs in db/db mice, in which insulin levels were already very low, were also severely depressed. These findings indicate that it is the chronic obesity-related ER stress rather than the high insulin levels that is responsible for the low levels of ATGs in the livers of these mice. An additional contributing factor is that, in obesity, mTOR in the liver is overactivated, presumably as the result of increased amino acid concentrations (Newgard et al., 2009). This activates lipogenesis and decreases fatty acid oxidation (Li et al., 2010), which exacerbates the negative effects of the high fat content of the diet.

Insulin inhibits autophagy, so one would expect insulin resistance to disinhibit autophagy in order to protect cells against oxidative stress (Meijer and Codogno, 2009). In the case of β cells, autophagy does indeed increase during the initial period of HFD feeding, presumably in order to protect the β cells and allow them to boost their insulin production in order to deal with the increased plasma glucose concentrations. In contrast, hepatic autophagy declines in obesity. However, it may be that during the first few weeks of HFD feeding, autophagy increases before it starts to decline as a result of continued stress. In the study by Yang et al. (2010), autophagy was unchanged after 7 weeks of HFD feeding but declined thereafter; earlier time points were not analyzed.

One may conclude that simply increasing autophagy, e.g., by pharmacological means, would be sufficient to improve insulin sensitivity in obesity. Unfortunately, metabolism is more complicated because autophagy is also required for adipocyte differentiation; it is the inhibition, rather than the stimulation, of autophagy in adipocytes that gives them a brown-fat-cell-like appearance that favors fatty acid oxidation and increases insulin sensitivity (Zhang et al., 2009; Singh et al., 2009).

Yang et al. (2010) stress the many parallels between pathologies associated with obesity and the age-related impairment of metabolism. During aging, autophagy declines, and insulin resistance can develop (Meijer and Codogno, 2009). The best way to increase autophagy in vivo is by restricting calorie intake.

Though it has been known for decades that calorie restriction is an effective way to combat obesity-related insulin resistance (and also aging), the present study reveals a mechanism for these effects.

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Chronic Kidney Disease and GWAS: "The Proper Study of Mankind Is Man"

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Genome-wide association studies (GWAS) have been applied to complex diseases such as diabetes and hypertension, successfully uncovering strong gene associations of potential pathophysiologic significance. Recently, two studies (Köttgen et al., 2010; Chambers et al., 2010) have been applied to uncover genes relevant to the pathophysiology of chronic kidney disease (CKD).

Chronic kidney disease (CKD) is defined as an irreversible reduction in glomerular filtration rate (GFR), the first process of urine production that often progresses to end stage renal disease (ESRD), whereby the level of GFR falls below the minimal level to sustain life. The final common pathway to ESRD, achieved regardless of the initiating event, is characterized by glomerular sclerosis, interstitial fibrosis, and inflammation and loss of kidney function. The burden of ESRD worldwide is growing, and as much as 13% of the United States population is at risk (Coresh et al., 2007). Animal studies have focused on the profibrotic and inflammatory roles of the renin-angiotensin system (RAS) (Chevalier et al., 2009), and inhibition of this system is the focus of current therapy. This approach has proven only partially successful, as such treatment delays rather than prevents ESRD. Thus, the need to identify better targets to prevent ESRD is urgently needed. Genome-wide association studies (GWAS) have been widely used since 2005 (Klein et al., 2005) to understand the underlying genetic component(s) of complex phenotypes, i.e., phenotypes that do not exhibit classical Mendelian inheritance resulting from a single gene alteration (Lander and Schork, 1994). More than any other approach, these studies have reproducibly associated closely linked genetic loci, identified by single nucleotide polymorphisms (SNPs), to these traits. At best, they have led to the delineation in many parts of the human genome of sequences showing association with common disease traits, e.g., diabetes, obesity, hypertension, etc. and have also been used to find association with normal physical traits such as height, hair, and eye color (Hindorff et al., 2010). GWAS require the study of the DNA from several thousands of individuals with and without a demonstrable and measurable phenotype. SNPs associated with these characteristics are identified by hybridization with known SNP arrays. An international project has developed a haplotype map (HapMap; http://hapmap.ncbi.nlm.nih.gov/) of the genome, which identifies variable regions of the human genome and associated genetic variation. Once the associated areas of DNA have been located, there follows a search in the region to find candidate genes potentially involved in the pathologic physiology responsible for susceptibility to the trait or disease under investigation. In most GWAS, each discovered DNA variant usually has only a small impact on the increased risk of the disease, as was predicted 50 years ago by D.S. Falconer (1960), and that is also the case in two