FFA concentrations between the 2 groups [McQuaid S et al. *Diabetes* 2011]. A systematic literature review and comparison of patients from the Oxford Biobank found no relationship between body mass index (BMI) and FFA concentrations [Karpe F et al. *Diabetes* 2011]. Additionally, an analysis of several large studies found that hyperinsulinemia was associated with a decreased release of FFA from adipose tissue [Karpe F et al. *Diabetes* 2011]. In fact, adipose tissue in obese (and insulin resistant) individuals almost invariably supply less FFA per unit fat mass than in lean individuals.

Prof. Karpe and fellow researchers investigated whether excess fat deposition in non-adipose tissue is due to excess fatty acid delivery from adipose tissue or to impaired adipose tissue fat storage [McQuaid S et al. *Diabetes* 2011]. Using stable-isotope fatty acid tracers to assess FFA delivery over a diurnal cycle, they found that the FFA Ra (rate of appearance) was significantly higher in abdominally obese versus lean men ($p=0.009$), but when the data were normalized per lean body mass, the difference disappeared. When expressed per total fat mass, the obese men had significantly lower FFA Ra compared with lean men ($p=0.029$). It therefore appears that adipose tissue in obese individuals down-regulate FFA supply to the systemic circulation as part of an adequate metabolic adaptation despite an element of insulin resistance.

In the same study, lean men had a progressive increase in meal fat deposition into adipose tissue with each meal (13%, 35%, and 47%, first to third meal; $p<0.001$). Abdominally obese men did not have a significant increase in adipose tissue fat storage with sequential feeding (6%, 25%, and 18%, first to third meal; $p=0.12$). The difference was statistically significant for the last meal ($p=0.001$). As the up-regulation of fat storage is an insulin-sensitive process, it therefore seems that obese individuals have a defect in immediate fat storage. The transcriptional signature of adipose tissue from the obese men was consistent with impaired fat storage function. Klimcakova and colleagues demonstrated that lipolysis, lipogenesis, glycolysis, and mitochondrial genes are highly downregulated in obese adipose tissue [Klimcakova E et al. *J Clin Endocrinol Metab* 2011].

According to Prof. Karpe, analysis of available evidence shows that adipose tissues and organs do not oversecrete FFA but instead adapt extremely well to obesity. Adipose tissue can be insulin resistant but in terms of regulation of lipolysis, this is balanced by hyperinsulinemia. Human adipose tissue adapts to obesity, hyperplasia, and hyperinsulinemia by down-regulating metabolic processes. Increased release of FFA is not an obvious feature in the development of insulin resistance, while adipose tissue fat storage is decreased in obese individuals leading to ectopic fat deposition, with the liver as the prime target.

PPAR-Mediated Mechanisms of Skeletal Muscle Insulin Resistance

Written by **Nicola Parry**

Skeletal muscle is the major site for insulin-dependent glucose utilization, and insulin resistance in skeletal muscle is thought to be integral in the pathogenesis of type 2 diabetes mellitus (T2DM). Kyong Soo Park, MD, PhD, Seoul National University, Seoul, South Korea, discussed some emerging insights into the molecular basis of skeletal muscle insulin resistance, highlighting the role of peroxisome proliferator activated receptor–gamma (PPAR-γ), a nuclear transcription factor.

PPAR-γ is implicated in the regulation of fat metabolism in skeletal muscle, and is activated by the binding of specific ligands, including thiazolidinediones (TZDs), such as troglitazone, rosiglitazone, and pioglitazone, which are used for the treatment of T2DM [Chung SS et al. *Mol Cell Biol* 2009]. Although PPAR-γ is mostly expressed in fat tissue where it is critically involved in lipogenesis and adipocyte differentiation, low levels are also expressed in skeletal muscle where it enhances insulin sensitivity [Chung SS et al. *Biochem J* 2011].

Oxidative stress plays a central role in the pathogenesis of insulin resistance, T2DM, and its vascular complications. Production of reactive oxygen species is increased in T2DM, and antioxidant activity is simultaneously reduced. TZDs, however, have been shown to prevent oxidative stress-induced insulin resistance in skeletal muscle. They activate PPAR-γ, stimulating glutathione peroxidase 3 (GPx3) gene expression leading to reduction of extracellular hydrogen peroxide (H_2O_2) levels that contribute to insulin resistance in skeletal muscle cells. Since inhibition of GPx3 expression prevents this TZD-induced antioxidant effect, GPx3 is thought to be essential for the regulation of PPAR-γ-mediated antioxidant activity. And since lower GPx3 levels have also been demonstrated in patients with T2DM and in diabetic diet-induced obese mice, the antioxidant effect of PPAR-γ is considered to be completely mediated by GPx3 [Chung SS et al. *Mol Cell Biol* 2009].

More recently, the function of PPAR-γ has been shown to be regulated by various posttranslational modifications, including SUMOylation, which involves binding of a small ubiquitin-like modifier (SUMO) protein to target proteins. SUMOylation is catalyzed by SUMO-specific proteases (SENPs). In one study of C2C12 cells in a primary line of mouse myoblasts, the critical role of SENP2 in lipogenesis as a desumoylating enzyme was demonstrated. SENP2 effectively removed SUMO from PPAR-γ–SUMO conjugates, while also increasing PPAR-γ transcriptional activity. In

addition, SENP2 overexpression selectively enhanced the expression of the PPAR-γ target genes FABP3 (fatty-acid-binding protein 3) and CD36 (fatty acid translocase), in the presence and absence of rosiglitazone, but had no effect on ADRP (adipose differentiation-related protein) [Chung SS et al. *Biochem J* 2011].

Prof. Park emphasized the important role that GPx3 plays in regulating oxidative stress, and its potential as a therapeutic target for both insulin resistance and T2DM. In addition, he also noted the potential for SENP2 as a potential therapeutic target to deal with excess fatty acids in skeletal muscle.

Thermogenesis-Based Obesity Interventions

Written by Nicola Parry

Yangha Kim, PhD, Ewha Woman's University, Seoul, South Korea, reviewed the role of thermogenic agents in the management of cardiometabolic risk. The global obesity pandemic represents a major public health problem, in particular since overweight and obesity are well-known risk factors that predispose patients to cardiovascular disease (CVD) and type 2 diabetes [Seale P, Lazar MA. *Diabetes* 2009]. Indicators of abdominal adiposity, specifically waist circumference and waist-to-hip ratio have been shown to be associated with coronary heart disease (CHD) risk in middle-aged women [Rexrode KM et al. *JAMA* 1998].

The search for strategies to stimulate thermogenesis in obesity management represents a current focus of significant attention. Brown adipose tissue is important in thermogenesis and contributes to energy expenditure, and studies have shown its activity significantly affects body weight in mice [Seale P, Lazar MA. *Diabetes* 2009].

Cells in brown adipose tissue contain large numbers of mitochondria, the organelles where respiration and thermogenesis occur. Mitochondria also contain uncoupling proteins (UCPs) that function as transporters to control the coupling between cell respiration and phosphorylation of ADP. UCP1 is expressed predominantly in brown adipose tissue, UCP2 is expressed in various body tissues, and UCP3 is expressed in high levels mainly in skeletal muscle and brown adipose tissue. Although UCP2 and UCP3 do not play direct roles in thermogenesis, they can contribute when fully stimulated by certain environmental factors, and skeletal muscle plays an important role in energy expenditure by activation of uncoupling proteins. In one study, long-term high-fat feeding resulted in increased fat storage in mice lacking UCP3 [Costford SR. *Am J Physiol Endocrinol Metab* 2008], suggesting it protects against fat gain on high-fat diets. Skeletal muscle UCP3 gene expression was also increased by dietary fish oil and docosahexaenoic acid.

Research is ongoing to identify agents to exploit thermogenesis, specifically in the areas of increasing lipolysis, uncoupling protein expression, and body temperature:

- Various compounds have been shown to stimulate lipolysis, including green tea epigallocatechin-3-gallate [Lee MS et al. *Phytother Res* 2009], polyunsaturated acid (eicosapentaenoic acid; EPA) [Lee MS et al. *Genes Nutr* 2008], capsaicin [Lee MS et al. *Phytother Res* 2011], and L-carnitine [Lee MS et al. *J Med Food* 2006].
- Upregulation of UCP2 has also been described in studies in which rodents were fed capsaicin [Ann JY et al. *J Food Sci Nutr* 2011]. Prof. Kim reviewed recently published data from an *in vitro* study, demonstrating that EPA and DHA directly control UCP3 gene expression in muscle cells [Lee MS et al. *Nutrients* 2013].
- Increased body temperature, reduced body weight, and white adipose tissue weight were reported in high-fat diet-induced obese mice supplemented with epigallocatechin-3-gallate [Lee MS et al. *Ann Nutr Metab* 2009]. Increased energy expenditure has also been demonstrated in people following capsinoid ingestion.

It is suggested that these agents target the AMP-activated protein kinase pathway. This pathway is important in cellular energy homeostasis, in particular through inhibition of fat synthesis and promotion of thermogenesis [Lee MS et al. *Nutrients* 2013]. Manipulating these mechanisms may therefore provide novel ways to harness the body's thermogenic potential for the development of new therapies for millions of obese or diabetic patients.

Management of Cardiovascular Risk Factors in Asymptomatic Patients With Hypertension

Written by Brian Hoyle

Hyuk-Jae Chang, MD, PhD, Severance Cardiovascular Hospital, Seoul, South Korea, presented the results of the **C**ardiovascular **R**isk factors manag**E**ment in **A**symptoma**t**ic hypertens**IVE** **S**ubjects (CREATIVES) study. CREATIVES was a prospective, observational study conducted between January 2010 and May 2011.

National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) risk stratification that is based largely on the low-density lipoprotein cholesterol (LDL-C) level can overlook many patients with acute