Insulin resistance is defined as reduced insulin action in metabolic and vascular target tissues. Whereas it is widely recognized that insulin resistance is a key pathogenic factor in the development of diabetes and cardiovascular disease (CVD), its etiology remains elusive. In this short report, we will summarize our research efforts toward establishing the potential mechanisms responsible for promoting insulin resistance in key metabolic tissues.

**Inflammation as a cause of insulin resistance**

While obesity-linked diabetes and CVD are known to be chronic inflammatory disorders, the underlying mechanisms by which inflammation promotes these metabolic diseases remain poorly understood. Studies in my laboratory identified inducible nitric oxide synthase (iNOS) as a key inflammatory mediator in obesity, causing insulin resistance in skeletal muscle [1-4] (Figure 1) and impairing insulin action in the liver through inhibition of adiponectin secretion by adipose tissue [5] (Figure 1). Studies by other groups have confirmed the role of iNOS in obesity-linked insulin resistance [6-8] and further indicated that iNOS induction in blood vessels is also involved in mediating vascular dysfunction in obesity [8]. The underlying cause of inflammation in obesity remains poorly understood, but one theory is that it lies within the origin of fat cells. Indeed, metabolic and immune pathways have evolved to be closely linked and interdependent. The finding that obesity is characterized by macrophage accumulation in adipose tissue [9, 10] and that macrophages and fat cells share the expression of multiple genes has added another dimension to our understanding of the development of adipose tissue inflammation in obesity. The role of immune cells in promoting inflammation in obesity has also recently been confirmed in humans [11-13]. What remains to be determined is how obesity promotes an inflammatory process not only in adipose tissue, but also in skeletal/cardiac muscles and liver. In this regard, recent studies point toward hypoxia as a key triggering event in the development of an inflammatory state in obesity [14-16]. However, this remains to be confirmed and better characterized, especially in human obesity.
Recent studies by our group and others suggest that nutrient satiation promotes insulin resistance by activating the protein kinase mTOR pathway, a sensing complex that integrates nutrient and hormonal signals [17-21]. We first proposed that mTOR operates a negative feedback loop by phosphorylating the first substrate of the insulin receptor, IRS-1, on multiple serine residues, uncoupling IRS-1 from the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, two effectors of insulin’s metabolic actions [20] (Figure 1). This metabolic feedback loop has been found in myocytes [20, 22], adipocytes and hepatocytes [17, 23] as well as in liver and muscle tissues of rats [17], suggesting that the mTOR pathway plays a major role in the regulation of glucose homeostasis. Importantly, we and others have shown that mTOR and its effector S6K1 are “overactivated” in skeletal muscle, liver and adipose tissue of both genetic and dietary animal models of obesity-linked insulin resistance [17, 24]. We have further shown that the mTOR pathway negatively modulates insulin’s metabolic actions in skeletal muscle and adipocytes of healthy subjects [17, 22]. We have also recently identified that serine 1101 in the IRS-1 protein is a molecular target of S6K1 in the liver of obese animals and in skeletal muscle during infusion of human subjects with amino acids [25]. Whether increased activation of S6K1 is a common feature of human obesity and insulin resistance through the mTOR pathway promotes insulin resistance

Nutrient sensing through the mTOR pathway promotes insulin resistance

Recent studies by our group and others suggest that nutrient satiation promotes insulin resistance by activating the protein kinase mTOR pathway, a sensing complex that integrates nutrient and hormonal signals [17-21]. We first proposed that mTOR operates a negative feedback loop by phosphorylating the first substrate of the insulin receptor, IRS-1, on multiple serine residues, uncoupling IRS-1 from the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, two effectors of insulin’s metabolic actions [20] (Figure 1). This metabolic feedback loop has been found in myocytes [20, 22], adipocytes and hepatocytes [17, 23] as well as in liver and muscle tissues of rats [17], suggesting that the mTOR pathway plays a major role in the regulation of glucose homeostasis. Importantly, we and others have shown that mTOR and its effector S6K1 are “overactivated” in skeletal muscle, liver and adipose tissue of both genetic and dietary animal models of obesity-linked insulin resistance [17, 24]. We have further shown that the mTOR pathway negatively modulates insulin’s metabolic actions in skeletal muscle and adipocytes of healthy subjects [17, 22]. We have also recently identified that serine 1101 in the IRS-1 protein is a molecular target of S6K1 in the liver of obese animals and in skeletal muscle during infusion of human subjects with amino acids [25]. Whether increased activation of S6K1 is a common feature of human obesity and insulin resistance through the mTOR pathway promotes insulin resistance

Nutrient sensing through the mTOR pathway promotes insulin resistance

Recent studies by our group and others suggest that nutrient satiation promotes insulin resistance by activating the protein kinase mTOR pathway, a sensing complex that integrates nutrient and hormonal signals [17-21]. We first proposed that mTOR operates a negative feedback loop by phosphorylating the first substrate of the insulin receptor, IRS-1, on multiple serine residues, uncoupling IRS-1 from the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, two effectors of insulin’s metabolic actions [20] (Figure 1). This metabolic feedback loop has been found in myocytes [20, 22], adipocytes and hepatocytes [17, 23] as well as in liver and muscle tissues of rats [17], suggesting that the mTOR pathway plays a major role in the regulation of glucose homeostasis. Importantly, we and others have shown that mTOR and its effector S6K1 are “overactivated” in skeletal muscle, liver and adipose tissue of both genetic and dietary animal models of obesity-linked insulin resistance [17, 24]. We have further shown that the mTOR pathway negatively modulates insulin’s metabolic actions in skeletal muscle and adipocytes of healthy subjects [17, 22]. We have also recently identified that serine 1101 in the IRS-1 protein is a molecular target of S6K1 in the liver of obese animals and in skeletal muscle during infusion of human subjects with amino acids [25]. Whether increased activation of S6K1 is a common feature of human obesity and insulin resistance through the mTOR pathway promotes insulin resistance

Nutrient sensing through the mTOR pathway promotes insulin resistance

Recent studies by our group and others suggest that nutrient satiation promotes insulin resistance by activating the protein kinase mTOR pathway, a sensing complex that integrates nutrient and hormonal signals [17-21]. We first proposed that mTOR operates a negative feedback loop by phosphorylating the first substrate of the insulin receptor, IRS-1, on multiple serine residues, uncoupling IRS-1 from the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, two effectors of insulin’s metabolic actions [20] (Figure 1). This metabolic feedback loop has been found in myocytes [20, 22], adipocytes and hepatocytes [17, 23] as well as in liver and muscle tissues of rats [17], suggesting that the mTOR pathway plays a major role in the regulation of glucose homeostasis. Importantly, we and others have shown that mTOR and its effector S6K1 are “overactivated” in skeletal muscle, liver and adipose tissue of both genetic and dietary animal models of obesity-linked insulin resistance [17, 24]. We have further shown that the mTOR pathway negatively modulates insulin’s metabolic actions in skeletal muscle and adipocytes of healthy subjects [17, 22]. We have also recently identified that serine 1101 in the IRS-1 protein is a molecular target of S6K1 in the liver of obese animals and in skeletal muscle during infusion of human subjects with amino acids [25]. Whether increased activation of S6K1 is a common feature of human obesity and insulin resistance through the mTOR pathway promotes insulin resistance

Nutrient sensing through the mTOR pathway promotes insulin resistance

Recent studies by our group and others suggest that nutrient satiation promotes insulin resistance by activating the protein kinase mTOR pathway, a sensing complex that integrates nutrient and hormonal signals [17-21]. We first proposed that mTOR operates a negative feedback loop by phosphorylating the first substrate of the insulin receptor, IRS-1, on multiple serine residues, uncoupling IRS-1 from the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, two effectors of insulin’s metabolic actions [20] (Figure 1). This metabolic feedback loop has been found in myocytes [20, 22], adipocytes and hepatocytes [17, 23] as well as in liver and muscle tissues of rats [17], suggesting that the mTOR pathway plays a major role in the regulation of glucose homeostasis. Importantly, we and others have shown that mTOR and its effector S6K1 are “overactivated” in skeletal muscle, liver and adipose tissue of both genetic and dietary animal models of obesity-linked insulin resistance [17, 24]. We have further shown that the mTOR pathway negatively modulates insulin’s metabolic actions in skeletal muscle and adipocytes of healthy subjects [17, 22]. We have also recently identified that serine 1101 in the IRS-1 protein is a molecular target of S6K1 in the liver of obese animals and in skeletal muscle during infusion of human subjects with amino acids [25]. Whether increased activation of S6K1 is a common feature of human obesity and insulin resistance through the mTOR pathway promotes insulin resistance

Nutrient sensing through the mTOR pathway promotes insulin resistance

Recent studies by our group and others suggest that nutrient satiation promotes insulin resistance by activating the protein kinase mTOR pathway, a sensing complex that integrates nutrient and hormonal signals [17-21]. We first proposed that mTOR operates a negative feedback loop by phosphorylating the first substrate of the insulin receptor, IRS-1, on multiple serine residues, uncoupling IRS-1 from the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, two effectors of insulin’s metabolic actions [20] (Figure 1). This metabolic feedback loop has been found in myocytes [20, 22], adipocytes and hepatocytes [17, 23] as well as in liver and muscle tissues of rats [17], suggesting that the mTOR pathway plays a major role in the regulation of glucose homeostasis. Importantly, we and others have shown that mTOR and its effector S6K1 are “overactivated” in skeletal muscle, liver and adipose tissue of both genetic and dietary animal models of obesity-linked insulin resistance [17, 24]. We have further shown that the mTOR pathway negatively modulates insulin’s metabolic actions in skeletal muscle and adipocytes of healthy subjects [17, 22]. We have also recently identified that serine 1101 in the IRS-1 protein is a molecular target of S6K1 in the liver of obese animals and in skeletal muscle during infusion of human subjects with amino acids [25]. Whether increased activation of S6K1 is a common feature of human obesity and insulin resistance through the mTOR pathway promotes insulin resistance
resistance is currently unknown, but IRS-1 (Ser-1101) and S6K1 (Thr-389) may represent future diagnostic tools in order to predict and design therapeutic treatments.

**AMPK: turning on metabolism while turning off insulin resistance**

AMPK is a member of a metabolite-sensing protein kinase family that acts as a fuel gauge monitoring cellular energy levels [26, 27]. When AMP kinase “senses” decreased energy stores, it acts to switch off ATP-consuming pathways and switch on alternative pathways for ATP regeneration. AMPK is activated by exercise/muscle contraction [28] but also by several classes of drugs that are currently used for treatment of diabetes and CVD, including thiazolidinedione (TZD), and that activate proliferator-activated receptor gamma (PPARg). We have recently reported that PPARg agonists inhibit iNOS induction in macrophages, myocytes and adipocytes through activation of AMPK [29] (Figure 1). These studies indicate that AMPK is a master switch that turns on metabolic pathways while turning off inflammation in insulin target tissues and macrophages. Interestingly, AMPK may also improve insulin sensitivity by blunting the activation of the mTOR/S6K1 pathway (Figure 1). Indeed, activation of AMPK by the pharmacological activator AICAR or by the anti-diabetic drug metformin inhibits mTOR/S6K1 in various cell types [30, 31]. AMPK may therefore represent a key therapeutic target since its activation can blunt both inflammation and nutrient sensing signals believed to play a key role in promoting insulin resistance in obesity.

**SHP-1: a new target for the treatment of insulin resistance?**

Because tyrosine phosphorylation is key to insulin signal transduction, protein tyrosine phosphatases (PTPs) are prominent candidates to negatively regulate insulin action. Previous studies have shown that the PTPs PTP1B and LAR (leukocyte related-antigen) are negative regulators of the insulin receptor kinase in liver and peripheral insulin target tissues [32-34]. PTP1B-deficient mice are leaner, exhibit increased energy expenditure and are protected from insulin resistance in the liver and skeletal muscle [35, 36]. Neuron-specific PTP1B KO also increased leptin sensitivity and improved glucose homeostasis, suggesting that PTP1B regulates body mass and adiposity primarily through actions in the brain [37].

We have recently identified the PTP SHP-1 as a novel inhibitor of insulin receptor signalling in liver and skeletal muscle [38]. We found that mouse models with a functionally deficient SHP-1 protein are remarkably glucose tolerant and insulin sensitive for glucose metabolism as a result of increased insulin signalling to the IRS/PI3K/Akt pathway in both liver and muscle tissues. These findings indicate that SHP-1 plays an important role in the regulation of insulin signalling in liver and muscle. Preliminary data also demonstrates that SHP-1 is expressed in adipose tissue and modulates lipid metabolism and adiposity (A. Marette, unpublished data) but the mechanisms involved remain poorly understood. It will be important in the near future to clarify the role of SHP-1 in controlling insulin sensitivity in insulin-resistant states and investigate whether this PTP is a potential target for anti-diabetic drugs.

**Concluding remarks**

Given the prevalence of obesity worldwide and the increase in associated health complications such as diabetes and CVD, the need for a mechanistic understanding of obesity-related insulin resistance remains a major research priority. We also need to speed up the discovery of new biological markers and diagnosis tools to assess insulin resistance and predict its development in populations at risk.
Finally, it is critical to find novel therapeutic targets to improve the pharmacotherapy of obese diabetic subjects, which is a crucial measure when lifestyle modifications (e.g., physical activity, diets) fail to achieve the therapeutic goals.

References