

# Postes pour Étudiants au Doctorat en Recherche sur le Diabète et la Résistance à l'Insuline

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Deux postes pour étudiants au doctorat sont disponibles pour étudier les mécanismes complexes impliqués dans la résistance à l'insuline et le diabète de type 2. Les candidates terminant une maîtrise et hautement motivées sont encouragées à poser leurs candidatures. Les projets sont décrits comme suit:

## 1. The role of iNOS in inflammation as a cause of insulin resistance

This project aims to analyze the contribution of different inflammatory factors and the implication of IKK/NF- $\kappa$ B and JNK pathways in inducible nitric oxide synthase (iNOS) induction and insulin resistance. Furthermore, we want to evaluate the effect of a conditional, tissue-specific invalidation of iNOS on systemic insulin resistance and glucose tolerance.

A major contribution of our group has been to show the novel role of nitric oxide (NO) in modulating glucose transport and insulin action in skeletal muscle. We were among the first to show that muscle expresses NOS enzymes and that NO directly modulates insulin-mediated glucose transport in skeletal muscle cells. We also found that obesity and other inflammatory conditions induce the expression of iNOS and that cytokines reduce insulin's ability to enhance glucose transport in myocytes by inducing iNOS (1-3). We published in Nature Medicine that iNOS is overexpressed in several models of obesity and obese mice lacking iNOS are protected from developing whole-body and skeletal muscle insulin resistance (1). NO signaling results from its interactions with biological targets via redox and additive chemistry such as formation of S-nitrosothiol adducts (S-nitrosylation) which have been shown to affect IR, IRS-1 and Akt in the insulin signaling pathway (4, 5). Furthermore, NO reacts with superoxide to form the highly reactive oxidant peroxynitrite (ONOO) leading to oxidative protein modifications and to nitration of tyrosine residues. Interestingly, the NF- $\kappa$ B pathway, which is necessary for iNOS induction is also subject to S-nitrosylation thus suggesting that iNOS induction affects its own expression though it is not clear yet whether this is a stimulatory or an inhibitory mechanism. Recent studies from our lab show that iNOS knock-out mice are protected from insulin resistance after acute lipid infusion and from inhibitory tyrosine nitration of IR, IRS-1, IRS-2 and Akt (5). Thus, the current project will focus on the evaluation of the effects of NO and ONOO on the insulin signaling pathway and a possible stimulation or inhibition via the NF- $\kappa$ B pathway. Moreover, the role of iNOS in different insulin target tissues (muscle, liver, adipose tissue) will be studied using tissue specific iNOS knock-out models which are now available in the laboratory.

1. Perreault, M. and Marette, A. (2001), Nature Medicine 7,1138-1143
2. Pilon, G. et al. (2004) J. Biol. Chem. 279, 20767-20774
3. Dallaire, P. et al. (2008), Diabetes 57, 1999-2011
4. Charbonneau, A. and Marette A. (2010), Diabetes 59, 861-871
5. White, J.W., et al. (2010), Am. J. Physiol. Endocrinol. Metab., 299. E868-E878

## 2. The role of the protein tyrosine phosphatase SHP-1 in the development of insulin resistance

After having recently identified SHP-1 as a novel inhibitor of insulin signaling (1) we now want to clarify the exact role of SHP-1 in insulin sensitivity and glucose and lipid homeostasis in physiological and insulin-resistant states, and to investigate whether it is a potential target for anti-diabetic drugs.

The protein tyrosine phosphatases (PTPs) PTP1B and LAR modulate the metabolic actions of insulin in liver, skeletal muscle and fat. The PTP SHP-1 is a well-known inhibitor of activation-promoting signaling cascades in hematopoietic cells but its potential role in insulin target tissues is much less known. Recently, we have shown that SHP-1 is expressed in mouse liver and

skeletal muscle. Viable motheaten mice (mev) bearing a functionally-deficient SHP-1 protein have a lower fasting glycemia and are remarkably glucose tolerant as compared to wild-type littermates (1). Results of insulin tolerance tests, hyperinsulinemic-euglycemic clamps, and in vitro glucose uptake studies further revealed that mev mice are markedly insulin sensitive for glucose metabolism in liver and muscle and show increased tyrosine phosphorylation of the insulin receptor and enhanced induction of the IRS/PI3K/Akt pathway in both tissues (1). Adenoviral overexpression of a catalytically inert mutant of SHP-1 (C453S) in liver of normal mice was also associated with increased insulin receptor signaling to IRS/PI3K/Akt and improved glucose tolerance. Also, tyrosine phosphorylation of CEACAM1, a recently identified modulator of hepatic insulin clearance, insulin sensitivity and lipid metabolism (2), was markedly increased in liver of mev mice and following hepatic adenoviral expression of the SHP-1(C453S) mutant. Accordingly, insulin clearance was augmented in mice expressing the SHP-1(C453S) mutant in liver. In vitro dephosphorylation assays confirmed that both, the insulin receptor and CEACAM1, are direct substrates of SHP-1 (1). These findings demonstrate an important role for SHP-1 in the regulation of glucose homeostasis and indicate that SHP-1 subserves this role by modulating insulin signaling in liver and muscle as well as hepatic insulin clearance. Nevertheless, the target of SHP-1 downregulation has been the liver meaning that SHP-1 has been downregulated in hepatocytes as well as in Kupffer cells. Since SHP-1 plays an important role in the immune system we have now used a tissue specific knock-out of SHP-1 directed to hepatocytes only. The current project will focus on the metabolic functions of hepatocyte SHP-1 and CEACAM1 in vivo on energy balance, systemic insulin action and glucose and lipid metabolism.

1. Dubois, M.J. et al. (2006), Nature Med. 12, 549-556
2. Xu, E. (2009), Endocrinology 150, 3503-3512

S.V.P., envoyez votre candidature accompagnée d'une lettre de motivation, de votre Curriculum vitae et une liste complète de publications.

Envoyez vos documents par courriel à:

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