Séminaire présenté par le Pr. C. Ronald Kahn

Chief Academic Officer, Joslin Diabetes Center,
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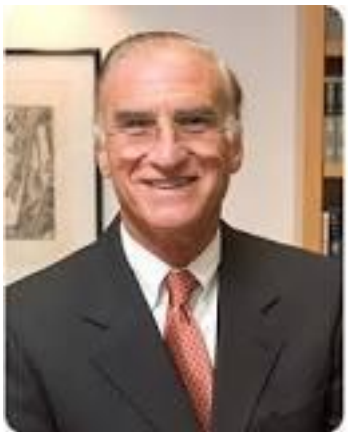
Boston MA, USA
le mardi 18 Avril 2017 à l'Institut du Thorax, Nantes



Le Pr. C. Ronald Kahn est un expert reconnu au niveau mondial dans le domaine du diabète et de l'obésité. Il est directeur académique au Joslin Diabetes Center (Harvard Medical School, Boston, MA, USA) et y dirige le laboratoire de « Physiologie Intégrative et Métabolisme ». Il est particulièrement connu pour ses travaux sur la signalisation de l'insuline et ses altérations dans le diabète de type 2. Il a révélé que l'insuline transmettait son message *via* l'activation de la tyrosine kinase intrinsèque du récepteur de l'insuline ; ce qui a représenté la première étape dans la connaissance de la cascade de signalisation. D'autres découvertes importantes de son laboratoire incluent l'identification de substrats intracellulaires du récepteur de l'insuline et de plusieurs intermédiaires de la voie de signalisation. Ses travaux ont permis de définir l'action spécifique de l'insuline dans les différents tissus (foie, muscle, cœur, vaisseau…). Le Pr C. Ronald Kahn et ses collègues ont aussi été les premiers à définir les altérations de la signalisation de l'insuline dans les états d'insulino-résistance tels que le diabète de type 2 et l'obésité. Ces études ont établi les bases sur lesquelles reposent notre compréhension actuelle de la pathogénie de la résistance à l'insuline.

Titre: "Regulation of Adipose Tissue Turnover and Its Communication with Other Tissues"

Rendez-vous à 11h30, à l'Amphi Denis Escande (IRS-UN)
8 quai Moncousu
44007 Nantes

Abstract – C. Ronald Kahn, MD

"Regulation of Adipose Tissue Turnover and Its Communication with Other Tissues"

Both obesity and lipodystrophy are associated with insulin resistance and inflammatory changes in the adult adipose tissue. Adipose tissue is also involved in control of metabolism through secretion of a number of adipokines. To investigate the physiological role of adipose tissue in insulin resistance, we have established two new classes of experimental mouse model of lipodystrophy. In the first, we have created mice with inducible knockouts of the insulin receptor (FindIRKO), IGF-1 receptor (FindIGKO) or both (FindIGIRKO) using the tamoxifen-inducible Cre-ERT2 transgene under control of the adiponectin promoter. Both FindIRKO and FindIGIRKO, but not FindIGKO, mice show acute, severe insulin resistance with marked hyperglycemia and hyperinsulinemia, marked glucose intolerance, and severely impaired insulin tolerance tests as early as 2 days after induction of recombination. Both also show significant decreases in size of white and brown adipose depots without evidence of inflammation in adipose tissue, inability to maintain body temperature during cold exposure and marked hepatosteatosis. Within 3 days these mice also exhibit marked hyperplasia of pancreatic β-cells. Surprisingly, 9 days after treatment, these mice start to recover normal serum glucose and insulin levels, and by 4 weeks display normal glucose tolerance, recovery from fatty liver and reduced islet hyperplasia. This was associated with an increase in the number of adipose progenitor cells and regeneration of adipose tissues. Interestingly, this whole syndrome could be reproduced again by a second round of tamoxifen and again largely remitted after 10 days. This new model demonstrates the critical role of adipose tissue in systemic insulin resistance, independent of adipose inflammation. This model also demonstrates the presence of an adipose homeostatic mechanism which stimulates regeneration of adipose tissue from new adipocyte precursor cells. In the second model, we have created a novel form of lipodystrophy by knockout of the miRNA processing enzyme Dicer in adipose tissue. This model is designed to mimic changes of Dicer and miRNA processing observed in adipose tissue of normal mice with aging and also in humans with HIV lipodystrophy. This also results in insulin resistance, but also significant reductions in levels of multiple circulating miRNAs. These latter data demonstrate that adipose tissue is a source of circulating miRNAs. The miRNAs may also act as a novel form of adipokine modulating the insulin resistance associated with changes in adipose tissue mass and function.