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Type 2 Diabetes Mellitus: Focusing on Insulin Action from a Cellular Perspective

BY MINNA WOO, M.D., PH.D.

The incidence of type 2 diabetes mellitus (T2 DM) is increasing at an alarming rate.¹ The human genome has evolved to include sophisticated genes that enable us to store fuel in a highly efficient manner. Only those ancestors with this genetic make-up survived during conditions when the nutrient supply was poor. However, in less than half a century, these genetic "jewels" now haunt our existence because of the advent of excess fuel (ie, food) and technology that encourages immobility. These champion genes, which have evolved over time, must now be examined in the context of an environment of abundance. This issue of *Endocrinology Rounds* examines the genetics of T2 DM and focuses on the effects of insulin resistance in traditional and nontraditional insulin target tissues that were elucidated using knockout animal models and the cre-loxP system.

Genetics

It is well accepted that T2 DM is a polygenic disorder with environmental and gene interactions playing a critical role in its pathogenesis (Table 1).² The difficulties in identifying the genes involved in T2 DM are related to the intimate gene/environmental interactions required for the disease to manifest. Moreover, T2 DM becomes increasingly more prevalent with aging, making it more difficult to identify genes. The importance of genetics in diabetes is supported by the high concordance rates of disease in twins, the significance of family history in disease development, and the high occurrence of diabetes in distinct ethnic groups. Additionally, infants who are small for gestational age are at risk for diabetes later in life.^{3,4} One hypothesis for this scenario is that there is placental compromise in the mothers of these infants – likely due to macrovascular disease arising from insulin resistance and diabetes – resulting in poor fetal nutrient supply. These women give birth to small babies that have the same genetic predisposition towards obesity and T2 DM that is, at least, inherited from their mothers.

Many of the culprit genes thought to play a role in T2 DM fall into 1 of 2 categories: they are involved in insulin action or insulin secretion.² Some of these specific genes are discussed in this issue of *Endocrinology Rounds*. Strong evidence to support the multigenic nature of T2 DM comes from animal studies in which models of diabetes were reconstructed from mutations in more than one gene when mutations in a single gene alone were insufficient to manifest disease.

Clinical spectrum

T2 DM comprises a disease spectrum that is bracketed by insulin resistance at one end and vascular complications at the opposite end of the spectrum. Despite the lack of a clear distinction between these two entities, clinicians use these categories as a way to characterize and manage individual patients within the wide spectrum of presentation.



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St. Michael's Hospital
6121-61 Queen St. E.
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Fax: (416) 867-3696

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Table 1: Genetics of Type 2 Diabetes

- polygenic disorder
- high concordance rate amongst twins
- high degree of environment/gene interplay
- genes involved in insulin action
- genes involved in insulin secretion

The insulin resistance syndrome consists of different clinical manifestations, with obesity, visceral adiposity, hypertension, acanthosis nigricans, dyslipidemia, dysglycemia, and hyperuricemia encompassing some of the features. The strict criteria for diagnosis and management of this syndrome is still the subject of much debate. Furthermore, an individual patient is given the diagnosis of T2 DM when their fasting or non-fasting blood glucose levels are above a given level and they have concurrent hyperglycemic symptoms. After a patient has been diagnosed with T2 DM and after, or along with, lifestyle modification, insulin sensitizers are recommended, followed by oral insulin secretagogues, and finally insulin when necessary to maintain euglycemia. Furthermore, vigorous surveillance for the complications of diabetes is recommended. Much evidence supports the benefit of strict glycemic control to decrease the incidence of diabetic complications. Whether treatment modalities should differ at the various stages of diabetes spectrum is a topic of conjecture.

Defects in insulin action in traditional target organs

Much research into the pathogenesis of T2 DM has revealed defects in fuel storage and glucose handling, largely due to defects in physiological insulin action and insulin secretion.⁵ Following a meal, insulin facilitates the majority of blood glucose to be disposed of in skeletal muscle. In the liver, insulin promotes fuel storage by inhibiting hepatic glucose production and permitting glycogen synthesis. In adipose tissue, insulin stimulates fat storage in the form of triglycerides and, to a smaller extent, stimulates glucose uptake in fat. The major role of insulin as an anabolic hormone is to prevent lipolysis and the breakdown of protein in muscle.

In T2 DM, defects in insulin action are evident in liver, fat, and muscle. These tissues are considered the traditional peripheral targets of insulin action. Defects

in insulin action are often referred to as “peripheral insulin resistance” and include:

- an inability to suppress hepatic glucose production in the liver
- a disruption of glucose disposal in muscle
- the loss of inhibition of lipolysis and stimulation of lipogenesis in fat
- the development of β cell hyperplasia to compensate for peripheral insulin resistance
- the loss of some aspects of β cell function, such as first phase insulin secretion, in early T2 DM.

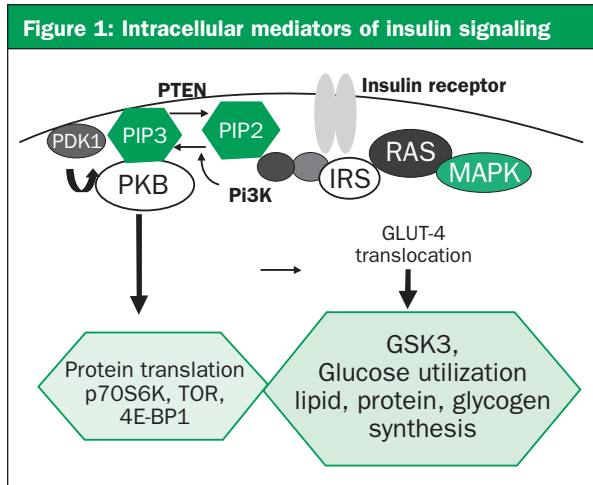
To better understand the defects in insulin action in these organs, molecular signaling of insulin action has been an intense area of research for the last few decades.

Insulin action from a molecular perspective

Despite the vast differences in insulin response in different insulin target tissues, much of the signaling machinery is surprisingly similar.⁵ Indeed, insulin receptors exist in all of the tissues of the body. Furthermore, the same intracellular signaling machinery is used in response to other growth factors within the same cell, such as insulin-like growth factor-I (IGF-I)-mediated signaling. IGF-I and insulin share some degree of affinity to the other ligand’s receptor.⁶ For these reasons, studying the role of a given growth factor can be challenging; however, recent technology has allowed us to dissect the complexity of the signaling pathway with respect to specific molecules within specific tissues.

Insulin action is initiated when it binds to the insulin receptor (IR).⁵ The IR belongs to one of the major groups of receptors known as “receptor tyrosine kinase.” The receptor is made of two α and two β subunits. When binding of insulin at the cell surface occurs, the IR undergoes a conformational change that leads to phosphorylation and it then acquires the ability to phosphorylate other proteins.⁷ This leads to recruitment of docking proteins, insulin receptor substrates (IRSs). IRSs are the major substrates that become phosphorylated by the IR, leading to activation of the PI3 kinase (PI3K)-mediated signaling pathway, one of the major signaling pathways in insulin signaling. For the purposes of this discussion, other signaling pathways of insulin signaling (eg, the mitogen-activated [MAPK] pathway) will not be discussed.

Activation of PI3K leads to phosphorylation of Akt/PKB, one of the molecules involved in the transmission of insulin signaling. Active PKB then phosphorylates a number of substrate proteins that lead to



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PKB = protein kinase B; IRS = insulin receptor substrate; MAPK = mitogen-activated protein kinase; GLUT-4 = glucose transporter 4, PIP = phosphatidylinositol phosphate

the execution of a vast array of cellular processes, including proliferation, survival, and differentiation. For example, in muscle cells, a series of phosphorylation events leads to the translocation of the glucose transporter 4 (GLUT-4) to the cell surface for transport of glucose into muscle cells (Figure 1). In liver, these events lead to activation of glycogen synthase for synthesis of glycogen. In addition, the activation of these molecules in response to growth factors (eg, insulin and IGF-1) also promotes growth, cell division and, in some cases, cancer formation in certain cell types.

Insulin action: an ancestral perspective

Many of the molecules in the insulin signaling pathway, including the insulin receptor itself, Akt/PKB, and forkhead proteins (substrates of PKB), are present in lower organisms, including the fruit fly *Drosophila melanogaster*, the round worm *Caenorhabditis elegans*, and metazoan marine sponges.⁸ In these lower organisms, the insulin signaling pathway determines fuel metabolism and body size. Interestingly, inhibiting insulin signaling in these lower organisms also leads to enhanced longevity. All of these parameters have parallel findings in mammals (Table 2), raising an interesting question about whether the increased mortality observed in T2 DM is partially related to hyperinsulinemia in association with insulin resistance.

As higher organisms evolved, these same key molecules also evolved to undertake different cellular functions and acquire cell-specific functions that are regulated in a tissue-specific manner. Molecular evolution has enabled the tissue or organ to tailor its needs within the context of a highly specialized cellular function.

Table 2: Intracellular signaling molecules

- Many are highly conserved through evolution
- *Caenorhabditis elegans*: Insulin signaling pathway controls
 - longevity
 - metabolism
 - development
- Mammals
 - proliferation
 - differentiation
 - cell size
 - metabolism
 - longevity

Tissue-specific actions of insulin

Gene knockout (KO) strategies in mice have been instrumental in defining the essential function of a given gene in a living organism. Using this technology, IR KO mice were generated to define the role of insulin in the whole body. Not surprisingly, IR KO mice died during the early neonatal period because of ketoacidosis, thus confirming the vital function of insulin in an organism.⁹

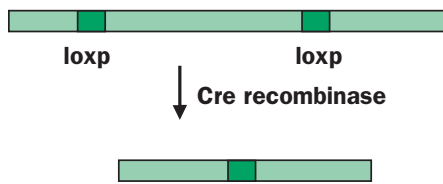
Although this information was valuable in highlighting the metabolic function of insulin in the whole body, this model was unable to characterize insulin action in different tissues. For this purpose, another recently discovered technology was used to study gene function in a tissue-specific manner in living organisms. This technology is referred to as the “cre-loxP system” (Figure 2) and has allowed deletion of genes specifically in one cell or tissue type of interest.¹⁰

Cre is a recombinase that recognizes a specific genetic sequence referred to as a loxP site. A segment of a given gene that is flanked by loxP sites will, in the presence of cre, be recombined, thus causing excision of the gene segment. Cre can be expressed in the tissue of choice by linking it to different tissue-specific promoters. Therefore, by constructing a gene of interest flanked by loxP sites, and combining it with cre expression in a tissue of choice, one has the versatility to knockout the gene of interest in a tissue of choice.

This powerful experimental tool allows us to study the essence of a given gene in a given tissue in the living organism. Such models allow direct examination of the tissue-specific role of a given gene without confounding factors such as compensatory effects that often occur in the field of metabolism. Using cre-loxP technology, the insulin receptor has been knocked-out in numerous tissues. These studies are discussed in

Figure 2: Cre-LoxP System

- Cre is a recombinase that recognizes loxP sites
- Used in mouse model system for tissue specific gene targeting



the following sections to highlight the importance of insulin action, not only in traditional insulin target tissues, but also in other tissues that were previously thought to be insulin-insensitive (eg, the brain, pancreatic β cells, and the endothelium).

Revisiting the traditional metabolic actions of insulin

Using cre-loxP technology, the IR was first deleted in skeletal muscle.¹¹ Given that the majority of glucose disposal following a glucose load occurs in muscle and that defects in glucose disposal in muscle are one of the early signs of T2 DM, it was expected that when the IR was “knocked-out” in muscle, a profound defect in glucose handling and severe glucose intolerance would occur. However, much to the surprise of the investigators, glucose tolerance and glucose disposal was quite normal in mice lacking the insulin receptor in muscle.

IR KO in liver led to severe glucose intolerance after a glucose challenge, despite normal fasting blood glucose levels.¹² Although basal glucose production rates were normal, insulin was not able to suppress hepatic glucose production. Interestingly, the mice with IR KO in liver eventually developed hepatic failure with low albumin and hepatic mass. These results highlight the importance of insulin, not only in the metabolic function of the liver, but also in hepatic synthetic function and maintenance of organ mass.

IR KO in fat led to protection from age-dependent obesity and obesity-related glucose intolerance and insulin resistance.¹³ These mice exhibit low fat mass and an altered relationship between plasma leptin levels and body weight. Interestingly, these mice also demonstrate increased longevity.¹⁴

Insulin action in non-classic metabolic tissues

Since insulin receptors exist in all tissues and most cell types, the role of insulin action in other tissues was also examined using cre-loxP technology. These non-classic metabolic tissues also appear to play a critical role in whole body fuel metabolism. Surprisingly, IR KO in pancreatic β cells had a profound effect on glucose handling and on both β cell function and β cell mass.¹⁵ This study definitively demonstrated that β cells are not only the sole source of insulin, but are also a critical target of insulin action. Following this study, several other studies revealed the critical role of intracellular molecules involved in insulin signaling in determining β cell mass and function.

IR KO in the brain has also displayed some interesting findings.¹⁶ Insulin receptors exist in select areas of the brain, including the olfactory bulb, the hypothalamus, and the pituitary. Previous studies have shown that insulin signaling in the brain regulates food intake and neuronal growth. IR KO in the brain results in an increase in body weight, fat mass, and insulin resistance. Interestingly, decreased luteinizing hormone, leading to a decrease in spermatogenesis and ovarian follicular maturation, was also found in these mice. These findings support the hypothesis that insulin signaling in certain parts of the brain is important for maintaining insulin sensitivity and fertility.

Lastly, insulin action in the vascular endothelium is complex, with effects on traditional endothelial function, as well as glucose metabolism.¹⁷ On the one hand, insulin has been shown to protect the vasculature by promoting anti-apoptosis, relaxation of vascular smooth muscles by producing of nitric oxide, and amelioration of the processes involved in atherosclerosis.^{18,19} On the other hand, insulin has been shown to play a deleterious role in vascular biology by activating strong angiogenic and vasoconstricting factors, such as vascular endothelial growth factor (VEGF) and endothelin-1 (ET-1).²⁰ Furthermore, insulin resistance is associated with hypertension, which can be thought of as a disease of the vascular endothelium. Some studies have demonstrated that insulin action on the endothelium plays a role in glucose homeostasis. These latter effects may be due to direct glucose uptake in the endothelium or via vasodilation in the vascular

bed of skeletal muscle. IR KO in the endothelium does not display any abnormality in the vasculature, although there are some effects on glucose homeostasis in association with high salt load.²¹

Summary

Insulin action in the various organs of the body is highly complex, both at a physiological level and at a molecular level. Exploring the intracellular molecular mediators of insulin action reveals a common platform of signaling machinery. This platform dates back to early evolution. These critical molecules have now evolved to meet the challenges of a highly complex organism.

Characterization of insulin action in all the tissues of the body was a difficult task, given the intricate inter-relationships that exist. A lack of experimental tools in the past limited exploration of the role of insulin action in a given tissue. However, the new cre-loxP technology has allowed scientists to explore the role of insulin in a given tissue in the context of the entire organism. This powerful tool has indicated that unexpected tissues play a critical role in fuel metabolism.

Given the importance of the action of insulin in all of the tissues and systems, and given that defective insulin action underlies the spectrum of T2 DM disease, we may need to reconsider the clinical classifications that often lead to distinct treatment modalities within the spectrum of T2 DM. Perhaps a more unifying approach to disease mechanism may help us examine T2 DM in a different way. Further understanding the global action of insulin can only bring us closer to clarifying the complexity of T2 DM.

Minna Woo, MD, FRCPC, PhD, is a staff endocrinologist at St. Michael's Hospital. She is a Clinician Scientist with a research interest in the molecular mechanisms of islet biology in diabetes.

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Abstracts of interest

Heritability of insulin secretion, peripheral and hepatic insulin action, and intracellular glucose partitioning in young and old Danish twins.

POULSEN P, LEVIN K, PETERSEN I, CHRISTENSEN K, BECK-NIELSEN H, VAAG A. GENTOFTE, DENMARK.

The etiology of type 2 diabetes is multifactorial, including genetic as well as pre- and postnatal factors that influence several different defects of glucose homeostasis, primarily in muscle, beta-cells, and liver. In the present twin study, we report heritability estimates (h²) for measures of insulin secretion, insulin resistance, hepatic

glucose production (HGP), and intracellular glucose partitioning using gold standard methods (euglycemic-hyperinsulinemic clamp technique, tritiated glucose infusion, indirect calorimetry, and intravenous glucose tolerance testing) among 110 younger (22-31 years of age) and 86 older (57-66 years of age) twins. To obtain a valid estimate of beta-cell function, insulin secretion was adjusted for the individual degree of insulin action (disposition index). In both age-groups there was a major genetic component in the etiology of insulin secretion that was statistically significantly higher among older twins (young $h(2) = 0.75$ [0.55-0.86] and old $h(2) = 0.84$ [0.69-0.92], $P < 0.05$). The heritability estimates for peripheral insulin sensitivity (young $h(2) = 0.53$ [0.28-0.71] and old $h(2) = 0.55$ [0.20-0.76]) and nonoxidative glucose metabolism (young $h(2) = 0.50$ [0.32-0.64] and old $h(2) = 0.48$ [0.04-0.72]) were similar in younger and older twins, supporting the notion of both genetic and environmental etiological factors in the control of insulin action and nonoxidative glucose metabolism. The results suggested that HGP was predominantly controlled by nongenetic factors in both young and old twins. In conclusion, we provide further evidence for a role of genes in controlling insulin secretion, insulin action, and nonoxidative glucose metabolism. The relative contribution of genes versus environment on in vivo insulin secretion exhibited an age dependency with a slightly greater relative impact of genes among older as compared with younger twins. *Diabetes* 2005 Jan;54(1):275-83.

Low birthweight and Type 2 diabetes: a study on 11 162 Swedish twins.

ILIADOU A, CNATTINGIUS S, LICHTENSTEIN P.
STOCKHOLM, SWEDEN.

BACKGROUND: To investigate the association between low birthweight and diabetes in a population-based Swedish twin sample. Method A cohort of 11 162 same-sexed Swedish twins born between 1906 and 1958 was used in order to investigate the risk of developing Type 2 diabetes between and within twin pairs by utilizing random effects linear models.

RESULTS: Between pairs there was a significant increase in risk of developing Type 2 diabetes for a 1-kg increase in their mean birthweight (odds ratio [OR] = 2.13; $P < 0.01$), adjusted for age, sex, body mass index (BMI), and smoking status. The corresponding risk within pair was 2.03 ($P = 0.07$) for monozygotic twins and 1.15 ($P = 0.71$) for dizygotic twins. The test of the heterogeneity of the within and between effects showed no significant difference between the estimates.

CONCLUSIONS: The study suggests that reduced fetal growth increase the risk of Type 2 diabetes due to an in utero programming effect possibly caused by intrauterine malnutrition. However, it does not exclude the possibility of a common genetic mechanism.

Int J Epidemiol 2004;33(5):948-53; discussion 953-4.

Knockout models are useful tools to dissect the pathophysiology and genetics of insulin resistance.

MAUVAIS-JARVIS F, KULKARNI RN, KAHN CR.
PARIS, FRANCE.

OBJECTIVE: The development of type 2 diabetes is linked to insulin resistance coupled with a failure of pancreatic beta-cells to compensate by adequate insulin secretion.

DESIGN: Here, we review studies obtained from genetically engineered mice that provide novel insights into the pathophysiology of insulin resistance.

RESULTS: Knockout models with monogenic impairment in insulin action have highlighted the potential role for insulin signalling molecules in insulin resistance at a tissue-specific level. Polygenic models have strengthened the idea that minor defects in insulin secretion and insulin action, when combined, can lead to diabetes, emphasizing the importance of interactions of different genetic loci in the production of diabetes. Knockout models with tissue-specific alterations in glucose or lipid metabolism have dissected the individual contributions of insulin-responsive organs to glucose homeostasis. They have demonstrated the central role of fat as an endocrine tissue in the maintenance of insulin sensitivity and the development of insulin resistance. Finally, these models have shown the potential role of impaired insulin action in pancreatic beta-cells and brain in the development of insulin deficiency and obesity.

Clin Endocrinol (Oxf) 2002;57(1):1-9.

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