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Review

The Genetic and Metabolic Determinants of Cardiovascular Complications in Type 2 Diabetes: Recent Insights from Animal Models and Clinical Investigations

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ABSTRACT

Cardiovascular complications (CVC) are the most common causes of death in patients with type 2 diabetes (T2D). However the pathophysiological determinants and molecular mechanisms involved in the progression of CVC in T2D are poorly understood. We have undertaken the challenging task of identifying some of the genetic and clinical determinants of CVC through a unique multidisciplinary approach involving Canadian and Finnish investigators. We are studying novel animal models combining atherosclerosis, diet-induced obesity and T2D to understand the molecular basis of CVC in obesity-linked T2D. We are also conducting clinical studies to identify key determinants of CVC in T2D patients and to determine whether a lifestyle modification program targeting loss of visceral adipose tissue/ectopic fat could be associated with clinical benefits in these patients. Together, we strongly believe that we can fill some gaps in our understanding of the CVC pathogenesis in T2D and identify novel therapeutic targets and hope that this new knowledge may be translated into the design of effective clinical interventions to optimally reduce cardiovascular risk in T2D subjects.

RÉSUMÉ

Les complications cardiovasculaires (CCV) sont les causes les plus fréquentes de mortalité chez les patients ayant le diabète de type 2 (DT2). Cependant, les déterminants physiopathologiques et les mécanismes moléculaires impliqués dans la progression des CCV liées au DT2 sont mal compris. Nous avons entrepris de cerner quelques déterminants génétiques et cliniques des CCV par une approche multidisciplinaire unique impliquant des investigateurs canadiens et finlandais. Nous étudions les nouveaux modèles animaux combinant l'athérosclérose, l'obésité induite par l'alimentation et le DT2 pour comprendre les bases moléculaires des CCV du DT2 lié à l'obésité. Nous menons également des études cliniques pour cerner les principaux déterminants des CCV chez les patients ayant le DT2 et pour déterminer si un programme de modification du mode de vie ciblant la perte de tissu adipeux viscéral et de graisse ectopique pourrait être associée à des avantages cliniques chez ces patients. Ensemble, nous croyons fermement que nous pourrons combler certaines lacunes en matière de compréhension de la pathogenèse des CCV liées au DT2 et trouver de nouvelles cibles thérapeutiques, et nous espérons que ces nouvelles connaissances pourront mener à l'élaboration d'interventions cliniques efficaces destinées à réduire de manière optimale le risque cardiovasculaire chez les sujets ayant le DT2.

Introduction

It has long been established that type 2 diabetes (T2D) is associated with a myriad of metabolic disorders and with preferential accumulation of adipose tissue in the abdominal region (1–3).

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Today, despite several decades having passed since these seminal observations, what are the key drivers of increased cardiovascular disease (CVD) in obese T2D patients still largely remains an unanswered question. The constellation of complications that are considered as features of the MetS that accompanies T2D are now well characterized and include insulin resistance, hyperinsulinemia, hypertension, obesity, hypertriglyceridemia and low HDL (4). It is also well recognized that the low-grade chronic inflammation found among patients with T2D subjects likely contributes to their elevated cardiometabolic risk (5,6). Moreover, whereas T2D correlates positively with an increased risk of cardiovascular disease, careful analysis of clinical data suggests there is no single clear disease profile (7). In addition, despite recent advances in therapy that have resulted in a reduction in cardiovascular mortality, this decrease is not evident in individuals with T2D (8–11). However, we now have at our disposal advanced resources in biochemical, genetic and clinical research that have provided us with most powerful tools to help us identify novel therapeutic targets, customizing treatments and personalized medicine approaches. This narrative review will present convergent findings from these diverse research approaches.

Cardiovascular complications of type 2 diabetic animal models

Tissue-specific genetic manipulation of the insulin receptor itself has provided only limited information and not necessarily reflect a true state of T2D with its constellation of pathologies and secondary health effects. In addition, while hepatic disruption of the insulin receptor alone is sufficient to produce a diabetic state, disruption in other tissues have generated mixed phenotypes. The use of genetically modified or diet-induced animal models of diabetes (summarized in Table 1) has undoubtedly provided some of the most important findings in the field of metabolic diseases. However, it has been difficult to find an adequate model combining both insulin resistance and cardiovascular pathologies in which detailed studies of the CVC of T2D could be carried out. One of the more commonly used models, the db/db mouse results from a genetic disruption of the leptin receptor and exhibits severe obesity and diabetes that gets progressively worse with aging (12). Yet this model, which also exhibits an altered inflammatory profile, dyslipidemia and left ventricular cardiac hypertrophy, remains limited. Because of its extreme nature, it is difficult to identify the effects of these different mechanisms on any single phenotype.

Other models of T2D, brought about by dietary intervention usually on a C57BL/6 background, have also been extensively used and provide a very useful alternative (13). However, the literature remains highly controversial as to the precise phenotype of these animals since even small variations in diet or study conditions have resulted in a wide range of phenotypes (14). In addition, because of the very different way rodent models handle lipids, extrapolating back to human dyslipidemic profiles can be problematic. Some general conclusions common to most study models can nevertheless be drawn. On the C57BL/6 background, diets very high in fat, both with and without the addition of cholesterol, have generally been shown to bring about obesity and at least a modest hyperglycemia. The addition of a large amount of sucrose or fructose to a high fat content diet further exacerbates the phenotype to full blown insulin resistance (15). Nevertheless, atherosclerosis does not develop easily from dietary intervention alone in these models and modest plaque formation can only be seen after the animals have been fed a cholesterol and cholate-supplemented Paigen diet for extended periods of time (16).

Another important limitation of common murine models for the study of atherosclerosis is the different way in which they handle dietary lipids, secreting the bulk of cholesterol in a nonatherogenic HDL fraction. True atherosclerosis in the mouse thus often requires some degree of genetic manipulation. Both the apoE$^{-/-}$ and the LDL receptor (LDLr)$^{-/-}$ mouse models exhibit severe atherosclerosis and CVC; but this is not usually accompanied by progression toward a full blown diabetic state unless dietary intervention is also applied (17,18). In addition, the apoE-/- model is complicated by the fact that whole body knockout occurs in bone marrow-derived macrophages that may affect atherosclerosis progression (19). Thus, despite these models being readily available and having the

Table 1
Some well-established mouse models used for the study of type 2 diabetes

Mouse model	Reference(s)	Phenotype	Drawbacks
db/db	(12)	Severe obesity and diabetes that becomes progressively worse with aging; altered inflammatory profile dyslipidemia and left ventricular cardiac hypertrophy	Extreme nature, dependent on leptin receptor mutation, difficult to identify the effects of these different mechanisms on any single phenotype
C57BL/6 with high-fat diets	(13)	More coherence with normal physiology of the development of diabetes Development of insulin resistance is dependent on experimental conditions	No or modest hyperglycemia, pre-diabetic model, wide range of phenotypes caused by variable experimental conditions
C57BL/6 with high fat, high sucrose/fructose diets	(15)	More coherence with normal physiology of the development of diabetes Obesity and insulin resistance	Moderate hyperglycemia, wide range of phenotypes caused by variable experimental conditions
C57BL/6 with high-cholesterol or Paigen diet	(16)	Atherosclerosis model	No or modest hyperglycemia. Dietary cholesterol varied metabolic effects depending on experimental context. Only long-term intake can lead to significant lesion development.
ApoE-/-	(17)	Develop vascular lesions	Does not develop diabetes ApoE is expressed in many cell types and affect macrophage functions
LDL receptor knockout LDLr-/-	(18)	Develop vascular lesions if combined with dietary intervention. Lipid profile different than human	Does not develop diabetes Less prone to diet-induced obesity than wild-type animals
LDLr-/-ApoB100/100	(20)	Develop vascular lesions Circulating lipid profile closer to human	Does not develop diabetes Less prone to diet-induced obesity than wild-type animals
LDLr-/-ApoB100/100 X IGF-II	(20)	Develop vascular lesions Circulating lipid profile closer to human Develop diabetes Develop aortic calcification Develop cardiac hypertrophy	Less prone to diet-induced obesity than wild-type animals