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Review

Genomic regulation of type 2 diabetes endophenotypes: Contribution from genetic studies in the Goto-Kakizaki rat

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ABSTRACT

The inbred Goto-Kakizaki (GK) rat strain is a unique model of spontaneous type 2 diabetes mellitus caused by naturally occurring genetic variants that have been selectively isolated from an outbred colony of Wistar rats. Genetic and genomic studies in experimental crosses and congenic strains of the GK have shed light on the complex etiopathogenesis of diabetes phenotypes in this model. Diabetes-related phenotypes in the GK are under polygenic control and distinct genetic loci regulate glucose tolerance, insulin secretion, β-cell mass and plasma lipids. Metabolome and transcriptome profiling data in GK crosses and congenics, combined with GK genome resequencing, have resulted in a comprehensive landscape of genomic regulations of metabolism that can disentangle causal relationships between GK variants and diabetes phenotypes. Application of systems biology and systems genetics in the GK has contributed to improve our understanding of the fundamental mechanisms regulating metabolism. The wealth of physiological, genetic and genomic information in this strain makes it one of the most powerful model systems to improve our understanding of genetic regulations of metabolism and for testing therapeutic solutions for diabetes.

Contents

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1. Introduction

Genome wide association studies (GWAS) of type 2 diabetes mellitus and relevant endophenotypes have shed new light on the complex etiology of the disease and underscored the multiple molecular mechanisms involved in the pathogenic processes leading to hyperglycemia [1]. Even though these studies have successfully mapped many diabetes risk genetic loci that could not be detected by linkage analysis, the risk single nucleotide polymorphisms (SNP) have small effect sizes and generally explain little of disease heritability estimates [2]. The poor contribution of risk loci to diabetes inheritance suggests a prominent role of environmental factors (eg. diet, physical activity, lifestyle), gene × environment interactions and epigenetic mechanisms in the pathological processes leading to the deterioration of glycemic control [3,4].

These limitations support the increasing need of experimental systems to characterize the fundamental biological mechanisms responsible for diabetes inheritance and the function of risk genes. In the context of diabetes pathogenesis, *in vitro* systems are useful but often limited, in particular to assess glucose tolerance, insulin sensitivity, islet architecture and function and diabetes complications. The laboratory mouse provides a wide range of experimental models for diabetes gene discovery and for *in vivo* post-GWAS studies of diabetes that develops either spontaneously or following gene editing [5]. The laboratory rat is also a powerful system to implement phenotyping methods required to record biological variables relevant to common chronic diseases. The rat is the preferred model to perform phenotyping procedures that are often technically challenging in mice or require the collection of large volumes of blood or organs. For these reasons, rat models of type 2 diabetes or hypertension have been successfully used to localise in the genome genes controlling endophenotypes relevant to these complex diseases. This review addresses strategies used to map the genetic determinants of physiological and molecular phenotypes relevant to type 2 diabetes pathogenesis and to characterize their biological function *in vivo* through examples derived from genetic and genomic research in the Goto-Kakizaki (GK) rat strain.

2. Origin and phenotypic features of the GK rat model of type 2 diabetes

A strategy of selective breeding of outbred rats exhibiting extreme values of a single phenotype criterion, followed by successive brother x sister matings required for inbreeding, has been successfully used to produce rat models of polygenic inheritance of spontaneous risk factors for cardiometabolic diseases (CMD) (hypertension, glucose intolerance, obesity, dyslipidemia). It was originally used to generate the spontaneously hypertensive rat (SHR) and the Dahl Salt Sensitive (SS/Jr) rat strains using spontaneous (SHR) or salt-induced (SS/Jr) high blood pressure as selection criteria [6]. The GK strain was later produced following selective breeding of spontaneously glucose intolerant rats (Fig. 1A) [7]. This procedure implies that naturally occurring genetic variants contributing to glucose intolerance (GK) or high blood pressure (SHR, SS/Jr) were isolated from either Wistar (GK, SHR) or Sprague-Dawley (SS/Jr) outbred stocks and fixed homozygous to produce genetically and phenotypically stable disease models (Fig. 1A) [8]. In parallel, Wistar Kyoto (WKY) and salt resistant (SR/Jr) control strains were produced from Wistar and Sprague-Dawley stocks, respectively, using normal blood pressure or resistance to salt induced high blood pressure as selection criteria [6].

Extensive physiological studies showed that these disease strains exhibit a very broad pattern of altered phenotypes beyond the main selection criterion, suggesting paralleled isolation of alleles causing increased phenotype severity through for example insulin resistance and hyperlipidemia, as well as disease resistant alleles allowing preserved lifespan and survival of the animals. The GK rat spontaneously exhibits primarily glucose intolerance (Fig. 1B) associated with insulin resistance [9], physiological and molecular evidence of altered insulin secretion and perturbed islet morphology characterized by structural collapse (Fig. 1C) and presence of fibrosis (Fig. 1D) [10–12]. Biochemical and histological evidence of diabetes complications and co-morbidities, including anomalies resembling diabetic nephropathy [13], retinopathy [14] and neuropathy [15], cardiac hypertrophy [16] associated with insulin resistance in the heart [17], and neuronal decline in the cerebral cortex and cognitive impairment [18,19], are also documented in the GK. These anomalies may be secondary to sustained hyperglycemia consecutive to the expression of diabetes susceptibility alleles or have their own genetic determinism.

3. Contribution of molecular phenotyping to the identification of mechanisms involved in diabetes in the GK strain

Altered molecular mechanisms have been documented in the GK strain using gene expression profiling technologies. Transcriptomes generated in several GK tissues, including pancreas islets [20], skeletal muscle [21], liver [22–24], adipose tissue [25], kidney [26], heart [27] and hypothalamus [28], provided comprehensive landscapes of genome-wide gene expression in organs contributing to insulin resistance, impaired insulin secretion and diabetes complications and associated co-morbidities in the GK, when compared to inbred or outbred normoglycemic controls. Renal transcriptome analyses in GK, Brown-Norway (BN), Wistar Kyoto (WKY) and streptozotocin (STZ)-induced diabetic WKY rats identified common and strain-specific gene expression changes that are implicated in diabetes phenotypes or underlie molecular adaptation to spontaneous (GK) or experimentally-induced (WKY-STZ) chronic hyperglycemia in the kidney [24,26,29].

Multi-tissue gene transcription profiling in the GK was paralleled by analyses of microRNA expression in several GK tissues. MicroRNAs are key elements in the regulation of genome expression through mechanisms generally leading to downregulated expression of many mRNAs that share a seed sequence allowing binding to a specific microRNA. Their biological functions in liver, muscle, adipose tissue and pancreas are tissue-specific as they are dependent on simultaneous cellular expression of microRNAs sand their mRNA targets (reviewed in Ref. [30]). Paralleled genome-wide expression profiling of microRNA and mRNA in pancreatic islets and insulin sensitive tissues of GK and normoglycemic strains provided evidence of conserved and tissue-specific differential expression of microRNAs in diabetes [20,31,32]. For example miR-322 was overexpressed in GK only in adipose tissue, whereas miR-30e was overexpressed only in liver. In contrast, miR-125a was strongly overexpressed in the GK rat in both tissues, and further pathway analysis based on expression patterns of its predicted mRNA targets identified significant enrichment of differentially expressed genes involved in mitogen-activated protein kinase (MAPK) signaling in adipose tissue, which may mediate the cellular effects of miR-125a in diabetes in the GK [31].

Analysis of genome expression in the GK was also addressed through metabolome profiling. Metabolomics is a powerful molecular phenotyping technology designed to detect and quantify small metabolic compounds in biofluids and organ extracts, including microbial metabolites, that represent the most distal endpoint of combined expression of the host genome and the microbiome and the most proximal genomic readout in the disease