Chapter XXII
Approaching Type 2 Diabetes Mellitus by Systems Biology

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ABSTRACT

We acquired new computational and experimental prospects to seek insight and cure for millions of afflicted persons with an ancient malady. Type 2 diabetes mellitus (T2DM) is a complex disease with a network of interactions among several tissues and a multifactorial pathogenesis. Research conducted in human and multiple animal models has strongly focused on genetics so far. High-throughput experimentation technics like microarrays provide new tools at hand to amend current knowledge. By integrating those results the aim is to develop a systems biology model assisting the diagnosis and treatment. Beside experimentation techniques and platforms or rather general concepts for a new term in biology and medicine this chapter joins the conceptions with a rather actual medical challenge. It outlines current results and envisions a possible alley to the comprehension of T2DM.

INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is the most common metabolic disease with more than 170 million patients worldwide. It rapidly increases in the developed and developing countries and is a huge, growing burden for health care systems. In the USA T2DM already accounts for over 130 billion Dollar of the health care costs (Stumvoll, Goldstein, & Haeften, 2005).

In the past, T2DM was rarely seen in young people and thus called age-onset diabetes. But its prevalence increases due to changes in the lifestyle. For babies born in 2000 an estimated chance of 33%-50% to develop T2DM leads to 11 to 18 years reduced life expectancy. Several risk factors account for this prevalence including genetics, nutrition, low physical activity and low birthweight. The genetical prevalence is identified by looking at the offspring of diabetic patients, a positive family history confers for a 2.4 fold increased risk for T2DM. For first-degree relatives to an afflicted person the risk is

increased by 15% to 25%. In twin studies the difference of the concordance rate between monozygotic and dizygotic twins returns an estimate of the genetic contribution, as dizygotic twins only share 50% of the genetic code. The concordance rate is 35% to 38% for monozygotic twins and 17% - 20 % for dizygotic twins. Prevalence merges with the environment. Increased availability of food combined with reduced physical activity lead to obesity which itself becomes the major influencing factor. In the USA 1991 12% of the population have been classified to be obese, increasing to 20.9% in 2001 and even 30% today resulting in an anticipated epidemic increase of T2DM in the next decades. Physical inactivity is a controllable factor, so 20 minutes exercise per day is enough for a noticeable improvement in treating T2DM. Unhealthy diet with a surplus of fatty acids completes the problem.

Several molecular mechanisms are proposed to link obesity to T2DM. But the connection to the pathophysiology still remains unknown. Less than 10% of the T2DM variants are monogenic disease forms, on the other hand a high number of susceptibility genes is accounted for T2DM. Alterations in an entire network of genes is thought to be responsible for the disease. Most of the costs do not derive directly from diabetes but from its associated complications like macrovascular and microvascular diseases or accelerated atherogenesis. In an unclear pathogenesis, T2DM is preceded by impaired glucose tolerance, where glucose needed for cell energy cannot penetrate the cell wall anymore. Followed by an impairment in insulin action, increased adiposity drives a progression into insulin resistance.

Since available T2DM therapies are of limited effectiveness, new insight into the disease by biomedical research must be sought. The classic genetic approaches have been more successful in monogenic diabetes like maturity-onset diabetes in the young or mitochondrial diabetes. The unknown hereditary mode poses a challenge, so far resulting in a number of candidate genes. Transgenic and knock-out mice are helpful in dissecting the transcriptional regulatory network. With the dawn of high-throughput methods a novel way to tackle these challenges arises. Microarrays allow us:

1. To dissect the diversity of the disease primarily on the transcriptomic level.
2. To identify transcription factor target sets using ChIP-on-Chip.
3. To search for single nucleotide polymorphisms (SNP) using genotyping arrays.

The complex pathophysiological interactions between the tissues fat, muscle, liver, pancreas and brain are captured in distinct expression profiles for different mouse strains and different diets. On the

Figure 1. Different influences on the metabolism cause T2DM with its subsequent complications