CHAPTER 22

THE PANCREATIC β CELLS IN HUMAN TYPE 2 DIABETES

Piero Marchetti,* Marco Bugliani, Ugo Boggi, Matilde Masini and Lorella Marselli

Department of Endocrinology and Metabolism, University of Pisa, Pisa, Italy

*Corresponding Author: Piero Marchetti—Email: piero.marchetti@med.unipi.it

Abstract: β-cell (beta-cell) impairment is central to the development and progression of human diabetes, as a result of the combined effects of genetic and acquired factors. Reduced islet number and/or reduced β cells amount in the pancreas of individuals with Type 2 diabetes have been consistently reported. This is mainly due to increased β cell death, not adequately compensated for by regeneration. In addition, several quantitative and/or qualitative defects of insulin secretion have been observed in Type 2 diabetes, both in vivo and ex vivo with isolated islets. All this is associated with modifications of islet cell gene and protein expression. With the identification of several susceptible Type 2 diabetes loci, the role of genotype in affecting β-cell function and survival has been addressed in a few studies and the relationships between genotype and β-cell phenotype investigated. Among acquired factors, the importance of metabolic insults (in particular glucotoxicity and lipotoxicity) in the natural history of β-cell damage has been widely underlined. Continuous improvements in our knowledge of the β cells in human Type 2 diabetes will lead to more targeted and effective strategies for the prevention and treatment of the disease.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases almost all over the world, and continues to increase in number and significance.1 Its augmenting incidence appears to be mainly due to changes in life-style leading to increased dietary caloric intake, reduced physical activity and obesity.1,2 The disease has been widely recognized to be a fundamental cause of major health issues, including all types of
cardiovascular disease, and reduction in life expectancy.\(^1\) Type 2 diabetes mellitus (T2DM) accounts for around 90% of all cases of diabetes and results from a combination of genetic and acquired factors that impair β-cell function on one hand and tissue insulin sensitivity on the other.\(^1,2\) However, there is growing evidence that β-cell impairment is the crucial defect for the development and progression of this form of diabetes, as shown by several cross-sectional and, more stringently so, prospective studies. This applies to subjects with high risk of developing diabetes as well as patients after the diagnosis of hyperglycemia. When more than five hundred first degree relatives of diabetic patients with no known history of diabetes were studied,\(^3\) it was found that in every ethnic group (Caucasian, African-American, Asian-American, and Hispanic-American) impaired β-cell function was more important than insulin resistance in determining progressive alterations of glucose metabolism. Similarly, in a small group of non-diabetic first degree relatives of Type 2 diabetic individuals, followed for 7 years, the decline in glucose tolerance over the time was strongly associated with loss of β-cell function.\(^4\) In addition, when insulin action and insulin secretion were measured in a group of Pima Indians, whose glucose tolerance deteriorated from normal to impaired, it was observed that the transition was associated with a modest decline in insulin-stimulated glucose disposal and a marked decrease of acute insulin secretory response to intravenous glucose.\(^5\) Further progression of these subjects to diabetes was accompanied by additional reductions in insulin sensitivity and acute insulin response. However, in a group of Pima Indians who maintained normal glucose tolerance during the follow-up, a reduction of insulin-stimulated glucose disposal also occurred, but their acute insulin response increased sufficiently to guarantee normoglycemia.\(^6\) Similar findings were obtained in Caucasian and African-American subjects with normal glucose tolerance, impaired glucose tolerance or T2DM, followed for more than five years.\(^7\) Over the time, insulin sensitivity declined in each glucose tolerance category. However, subjects who maintained normal glucose tolerance exhibited compensatory increase in insulin secretion, whereas failure to augment insulin release caused the progression to impaired glucose tolerance or overt diabetes.\(^8\)

As mentioned above, the role of β-cell function is crucial also after the onset of diabetes. For instance, in a study conducted with newly-diagnosed Type 2 diabetic patients followed up to ten years, secondary failure of plasma glucose control after initial successful response to diet therapy occurred progressively in those with greater β-cell dysfunction, and the ongoing decline in β-cell function closely mirrored the steady rise in fasting plasma glucose.\(^7\) All this is in agreement with the data from the United Kingdom Prospective Diabetes Study (UKPDS) showing that at the time of diagnosis of diabetes there is already a ~50% loss of β-cell functional mass, which is followed by a further progressive decline over time.\(^8\)

These fundamental observations have been obtained in vivo, and therefore they do not allow to shed light on whether β-cell dysfunction is mainly due to reduced β-cell amount, altered insulin secretion or varying combinations of these two defects. In addition, studying patients does not permit to have insight on the ultrastructural and molecular phenotype of the β cells, with clear limitations in terms of mechanistic and direct intervention studies. To gain information on these issues, work has been conducted with pancreatic samples obtained at autopsy, or by using tissue specimens and/or isolated islets from the pancreas of cadaveric organ donors. The available evidence obtained by these approaches regarding several features of the β cells in human T2DM will be illustrated in this chapter.