Diabetologia (2015) 58:1688–1692
DOI 10.1007/s00125-015-3601-0

COMMENTARY

50 years forward: beta cells

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Received: 5 March 2015 / Accepted: 31 March 2015 / Published online: 10 May 2015

Abstract Our understanding of beta cell development and function has increased substantially these past 50 years but much remains to be learned before this knowledge can be put to clinical use. A comprehensive business plan will be necessary to develop a detailed molecular and functional blueprint of the beta cell in health and disease based on an integrated approach involving all necessary research disciplines. This blueprint will provide a platform for the development of novel therapeutic strategies for the treatment of both major forms of diabetes, foremost among them beta cell replacement therapy. This is one of a series of commentaries under the banner '50 years forward', giving personal opinions on future perspectives in diabetes, to celebrate the 50th anniversary of *Diabetologia* (1965–2015).

Keywords Beta cells · Cell replacement therapy · Islets · Science policy · Type 1 diabetes · Type 2 diabetes

Introduction

What have previous studies taught us about the beta cell, and where might the field be heading from here? What follows is a highly subjective and concise review of major accomplishments to date, with my personal vision and expectations for the future.

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Background

What has driven beta cell studies and what have we learned?

According to PubMed, there were just three papers on the beta cell in 1965 but over 1,500 in 2014, and more than 20,000 for the entire intervening period. What drove this interest? The 1960s saw the first methods for obtaining islets for in vitro studies, culminating with Lacy and Kostianovsky's landmark method for collagenase digestion of the rat pancreas [1]. This method opened the way for detailed functional and molecular studies on the beta cell and islet transplantation, and the underlying principle is used to this day. Investigators rapidly launched a series of important studies that continue to guide current understanding of insulin secretion. Their findings provided extraordinary insight into the cellular pathways leading to insulin storage and exocytosis, powered by transformative use of morphology [2] and biochemical identification of proinsulin as the biosynthetic precursor of insulin [3]. Dissection of metabolic pathways and electrophysiological studies led to the first description of stimulus secretion coupling through modulation of cytosolic Ca^{2+} concentrations [4]. Remarkably, contemporary understanding of these events is the result of fine-tuning these historical findings rather than paradigm shifts.

Type 1 diabetes has long been recognised as an autoimmune disease, but a detailed understanding of the pathological process leading to beta cell destruction remains elusive. Despite this, and thanks to rapid exploitation of islet isolation technology and use of novel immunosuppressive regimens [5], it became possible to treat type 1 diabetes by islet transplantation. This remains very useful to this day for treatment of a small number of individuals with particularly hard to manage (brittle) forms of type 1 diabetes, even if most patients

do not remain insulin-independent for more than a few years and require immunosuppression.

More recently, clinical studies have convinced the community that type 2 diabetes is a disease of relative insulin insufficiency consequent to decreased beta cell function and mass [6]. Historical studies indicating decreased beta cell mass in cadaveric pancreas from type 2 diabetic patients have been confirmed. But maybe beta cells do not die, perhaps they dedifferentiate, so losing their insulin stores by which they are normally identified [7] (even if this concept, based on rodent studies, requires clinical validation). More recent efforts to understand whether beta cell mass is truly decreased in type 2 diabetes, and if so how it might be prevented or reversed, have dominated the field, masking the cardinal clinical feature of type 2 diabetes: beta cell dysfunction, with loss of glucose sensitivity and the opportunity for its reversal [6, 8].

At first, the adult beta cell was considered to be post-mitotic with little capacity for regeneration. Much has changed, even if the debate remains lively [9]. In rodents, adult beta cells have the capacity to self-replicate, while in humans they appear to be quiescent with regeneration, should it occur, possibly arising through neogenesis from precursor cells. Based on rodent studies, an alternative route for beta cell regeneration might be transdifferentiation, or cell type interconversion of non-beta islet cells [10], but here again clinical relevance remains to be established.

Much has been learned about beta cell development and the transcription factors involved. In vitro recapitulation of these events has allowed for derivation of beta-like cells from embryonic and induced pluripotent stem cells [11, 12]. However, much remains to be accomplished before this can be exploited to provide a safe and effective therapy.

There has been extraordinary progress in understanding the genetics of both common and monogenic forms of diabetes. The ever decreasing cost and increasing sophistication of analytical methods will soon provide fresh insight into the pathophysiology of diabetes, with the beta cell likely remaining centre stage.

Looking towards the future

A blueprint of the human beta cell and regulation of function and mass

A detailed molecular and functional blueprint of the beta cell will be essential for curing or preventing diabetes (Fig. 1). We must aim to understand everything about the beta cell in health and disease. What makes this cell so special? Which components are integral to its function? What is its molecular and cellular identity? How is it created, and how and why does it malfunction or die? Why is it so vulnerable, and can we make it more resilient without compromising its function? Answering these questions will depend on collaboration between a variety of disciplines, some more obvious than others.

Rodent and human beta cells differ in many respects: simpler molecular findings in animal cells will need to be confirmed using human cells, while more complex pathways will ideally be validated in non-human primates or, failing that, in large animal models, before progressing to clinical studies.

The combined power of contemporary ‘omics’ at the single cell level will allow us to determine precise levels in individual human beta cells of all RNA species, proteins and metabolites, as well as epigenetic modifications. We shall require greater access to islets from individuals at different stages of diabetes in order to understand how these variables change. It is most likely that cadaveric pancreas will continue to be our only source of islets for research, unless a novel and completely safe approach towards pancreas biopsy can be developed. Artificial organs developed for in vitro study may offer an interesting alternative: while constructing islet cells with the appropriate genetic background and assembling them into vascularised micro-organs within an authentic ‘diabetic’ environment in vitro will be challenging, this should surely be within our grasp in these next 50 years.

All this information should be interpreted using powerful new modelling approaches to understand better the pathophysiological process. Once we have the blueprint we shall have a better understanding of what goes wrong with beta cells in type 2 diabetes and what damages and kills them in type 1 diabetes. This will be the evidence-based platform for the development of novel therapies.

While this article is focused on beta cells, the unique and specialised environment of the islet is known to be essential for normal beta cell function and we should not forget the primordial importance of other islet cell types for normal glucose control. Our blueprint will also need to take these integrative aspects of islet physiology into account.

Curing or preventing diabetes by restoring or preserving beta cell function and mass

Unless our basic understanding of the pathophysiology of both major forms of diabetes evolves in unexpected ways, the beta cell will continue to be a major therapeutic target in diabetes.

Our grasp of the process that selectively damages and kills beta cells in type 1 diabetes remains inadequate. Beta cell replacement therapy will inevitably be a futile exercise if new cells are not protected from destruction. Today, immunosuppression is the only effective way of preventing rejection of islet grafts—this is clearly unacceptable. Hopefully, novel strategies will emerge based on manipulation of the (auto)immune system and/or modification of newly regenerated or implanted beta cells to render them invisible to the

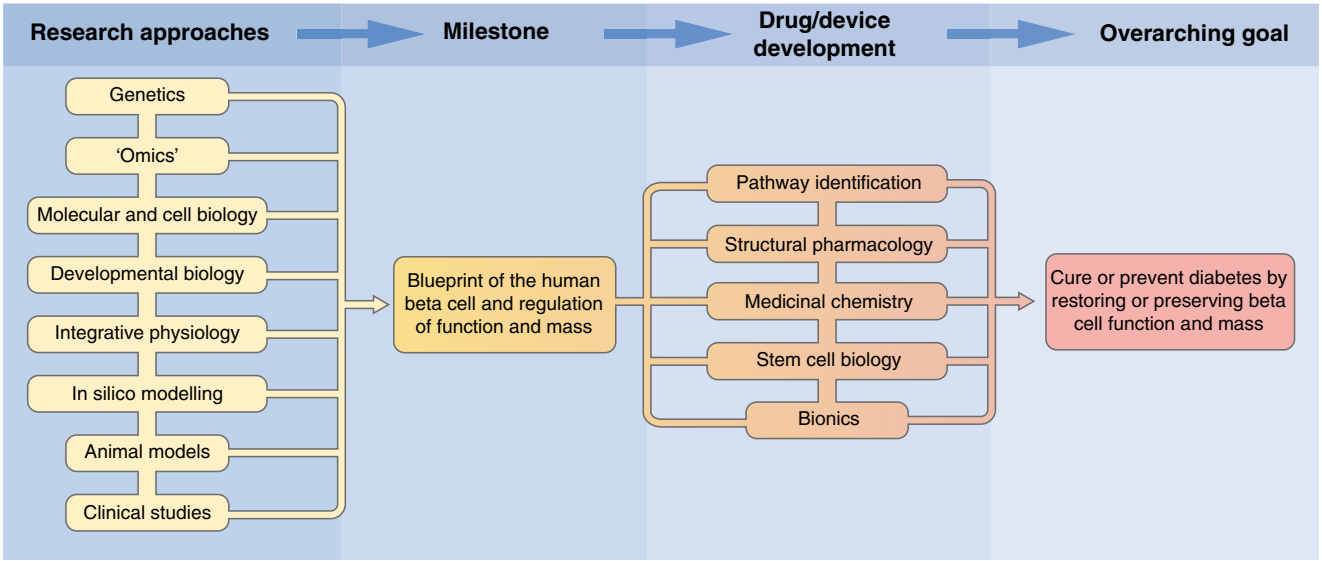

Fig. 1 Flowchart for future beta cell studies. Reaching the ultimate goal of curing or preventing diabetes by restoring or preserving beta cell function and mass will require a multidisciplinary, milestone-driven approach. Adapted from [13] with permission from EURADIA

destructive environment in type 1 diabetes. An alternative strategy that is still in its infancy from a clinical standpoint involves enveloping cells (microencapsulation or implantable device), allowing hormones out and vital metabolites and oxygen in, but preventing immune destruction. While vaccination or tolerance induction are being explored, a better understanding of the underlying biology and pathology will be needed to make this specific enough to allow for aggressive yet safe intervention. Combination therapy will surely be necessary, but increased risk of compromising normal and essential immune circuits will have to be addressed.

We must collaborate with experts in innate immunity and cytokines to combat the inflammation in islets and major insulin target tissues that seems to be central to cellular dysfunction in type 2 diabetes. Integrative physiologists will improve the understanding of inter-organ communication, with the identification of novel tissue 'kines' secreted by one organ to impact on another, positively and negatively in health and disease, respectively. Such factors may emerge as therapeutic targets but again, combination therapy rather than monotherapy will probably be necessary.

Our blueprint will drive development of beta cell-based therapy, through cell replacement or regeneration. Viewed in its broadest sense, this therapy could follow different tracks, converging on the ultimate goal of restoring normal beta cell mass and function [14].

1. Replacement

In this scenario, exogenous beta cells would be generated in vitro for implantation. There is a desperate need for a limitless or, at the very least, a plentiful supply of beta cells (or islets) for cell-based therapy; leaving aside issues of rejection or autoimmune destruction, human islet transplantation is today severely restricted because of a lack of organ donors for islet isolation. While xenotransplantation (perhaps combined with some sort of barrier device) offers a possible interim solution, surely these next 50 years of research will offer effective and universally accessible human cell-based therapy for diabetes!

It is unlikely that in vitro proliferation of adult human beta cells will be achievable, but several alternative approaches might be envisaged. The first depends on mass expansion of stem or precursor cells, followed by in vitro (and/or in vivo, post-implantation) differentiation into beta cells. Ideally, these newly created beta cells would be fully compatible with the patient so as to avoid immunosuppression, by using the patient's own cells in the first place (i.e. induced pluripotent stem cells, perhaps modified epigenetically to make it easier to drive them down the beta cell lineage) or by modifying the new cells to protect them from rejection. Alternatively, one might start with a beta cell or closely related cell type, followed by dedifferentiation, proliferation and redifferentiation into beta cells (epithelial–mesenchymal–epithelial transition). Whether or not it will be necessary to generate islets rather than beta cells, or perhaps reconstitute islets from their elemental cell types, remains to be seen, but I consider this likely.

A more futuristic scenario would involve the development of technology-based bioartificial or fully artificial (mechanical) beta cells/islets using rapidly emerging 'bionics' approaches. While challenging, this should be achievable and is quite seductive, avoiding many of the problems raised

above regarding failure or destruction of implanted surrogate beta cells in individuals with type 1 (and even type 2) diabetes.

2. Regeneration

This is an exciting but also more challenging and potentially dangerous approach. Here, therapeutic intervention would trigger the regeneration of beta cells (or islets) in the patient. This might be achieved in several ways. In the pancreas, new beta cells could be created through (i) recapitulation of the normal developmental process, (ii) regeneration of remaining beta cells, or (iii) differentiation of precursor cells, whether naturally occurring in the pancreas or subsequent to recruitment from remote sites. Today, transdifferentiation of islet non-beta cells into beta-like cells further to massive beta cell loss in mice is the focus of considerable attention; perhaps one day this could be exploited therapeutically. It is also possible to transdifferentiate other cell types into beta cells outside islets (i.e. exocrine pancreas or liver). Right now, it is necessary to transduce cells to express specific genes to drive such transdifferentiation, an approach that is likely to be unsuitable for clinical application. Further refinement or development of small molecules to induce expression of the necessary genes in a targeted and controllable fashion will be essential for future therapeutic purposes.

There are major safety issues surrounding attempts to replace or regenerate beta cells (or islets). Any approach will have to be highly specific so as to avoid tumours or regeneration of unwanted cell types, and limited in extent so as to restore the natural level of beta cell function and mass without the risk of hyperinsulinism. Furthermore, the differentiated function of regenerated cells will have to be very close to that of a bona fide beta cell to ensure tight glucose control.

Meanwhile, closed-loop artificial devices are approaching clinical approval, with continuous glucose monitoring coupled to pumps for controlled infusion of insulin and most likely glucagon, too. This is seen as a useful interim therapeutic approach while waiting for cell-based therapy to become available. This purely mechanical approach towards diabetes treatment is thus not expected to offer the same level of benefit as beta cell/islet replacement therapy but should be superior to existing exogenous insulin therapy. Costs will also prevent its use in all but the richest societies. While cell-based therapy may also be expensive in the first years of clinical application, surely this will become routine practice in the longer term, offering an effective, cheap and durable treatment for diabetes that could ultimately deliver the long-awaited cure, providing patients with an insulin- (and other drug-) free life with perfect metabolic control, with issues of patient compliance becoming an historical anecdote.

Science policy

Beta cell studies should ultimately improve the health and wellbeing of people with diabetes and help to prevent the disease and its complications. Without diminishing the intrinsic scientific importance of the remarkable achievements of the past 50 years, aside from the development of glucagon-like peptide-1 (GLP-1)-based therapy and improved therapy for a handful of patients with particular monogenic forms of diabetes, patients have not yet benefited directly from beta cell studies. Whilst still supporting investigator-initiated science, we must be more responsive to the needs of society and adopt a more business-like approach to research. Having a plan, with milestones and goals can actually be inspirational rather than a constraint on research, particularly if devised by expert members of the research community. We do have a plan devised by just such a panel of experts: DIAMAP, with a chapter devoted to islet research (www.diamap.eu). The major goals of the beta cell tracks are still highly relevant and have served as the basis for Fig. 1. The power of public–private partnerships will also need to be harnessed, with improved collaboration between academia and industry.

Duality of interest The author declares that there is no duality of interest associated with this article.

Contribution statement The author was the sole contributor to this article.

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