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COMMENTARY

M. A. Atkinson · C. J. Rhodes

Pancreatic regeneration in type 1 diabetes: dreams on a deserted islet?

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It is easy to see that Meier and colleagues have set out to gain our collective attention with their report in this issue of *Diabetologia* [1]. Many notions concerning the pathogenesis of type 1 diabetes have been repeated so often that they have hardened into dogma [2]. This list of unquestioned yet unconfirmed concepts might include the assumed autoimmune basis for the disorder, the notion that symptomatic onset is preceded by 85–90% loss of beta cells, and the belief that beta cell destruction is orchestrated by T lymphocytes. Yet another popular postulate maintains that beta cell mass is irrevocably lost in the months or years that follow initiation of insulin therapy, leaving the pancreas devoid of cells capable of insulin production. The proposal that this exocrine desert contains an oasis of insulin-producing cells would therefore be considered, at least by most, to represent a mirage.

The dogma of islet cell extinction is supported on many fronts: C-peptide eventually becomes undetectable in virtually everyone with type 1 diabetes, and vanishingly few cases of true 'spontaneous and permanent' disease remission have been documented. Autopsy specimens from people with long-term type 1 diabetes rarely describe appreciable, let alone healthy, islet cell mass. This picture of islet desolation has, however, been opposed by the concept of 'pancreatic regeneration' [3]. Although 'islet cell regeneration' might be a more appropriate term, the concept has revived hope that endogenous pancreatic insulin secretion might one day be restored to those with type 1 diabetes. This rapidly growing field of investigation, liberally invested with both hype and hope, draws upon observations from stem cell biology, gene therapy, incretin pharmacology, pancreatic transgenic animals and more. The 'more' includes the interpretations set forward by Peter Butler and colleagues from UCLA [1].

Their study focuses on the immunocytochemical detection of insulin-producing cells in the pancreas of subjects with a duration of type 1 diabetes ranging from 4 to 67 years. In addition to ascertaining the presence of insulin-positive cells, the pancreases were also evaluated for beta cell apoptosis, replication, inflammation and periductal fibrosis, and the results compared with those for pancreases from non-diabetic individuals. The investigators observed, somewhat surprisingly—and certainly in contrast to established dogma—that 88% of the type 1 diabetes patients had insulin-producing cells, and that this was unrelated to duration of disease or age at death. They also observed that beta cell apoptosis was more frequent in cases of type 1 diabetes than in controls, and was often accompanied by macrophages, T lymphocytes and periductal fibrosis. The authors put forward the interesting, but highly speculative, proposal that beta cells are subject to continuous rebirth in type 1 diabetes, but that the net effect of this 'regenerative process' is counteracted by low-grade inflammatory autoimmunity.

Some may say that there is nothing new in this, and the work does, by and large, confirm earlier findings by Gepts & De Mey [4], Foulis & Stewart [5] and Lohr & Kloppel [6], among others. However, these new studies represent an important extension of those seminal works, and demonstrate, with some fervour, the potential for islet beta cell regeneration. At least three distinct mechanisms have been proposed for this: replication of existing beta cells; emergence of new beta cells from the pancreatic ductal epithelium (often referred to as neogenesis, and considered by some to indicate the existence of adult pancreatic stem cells); and apparent 'transdifferentiation' of exocrine into endocrine beta cells (Fig. 1). Meier et al. observed negligible replication of beta cells, comparable to that in control subjects, and concluded from this that the residual beta

M. A. Atkinson (✉)
Department of Pathology,
College of Medicine,
University of Florida,
Gainesville, FL 32610, USA
e-mail: atkinson@ufl.edu
Tel.: +1-352-3920048
Fax: +1-352-3928464

C. J. Rhodes
Pacific Northwest Research Institute,
University of Washington,
Seattle, WA, USA

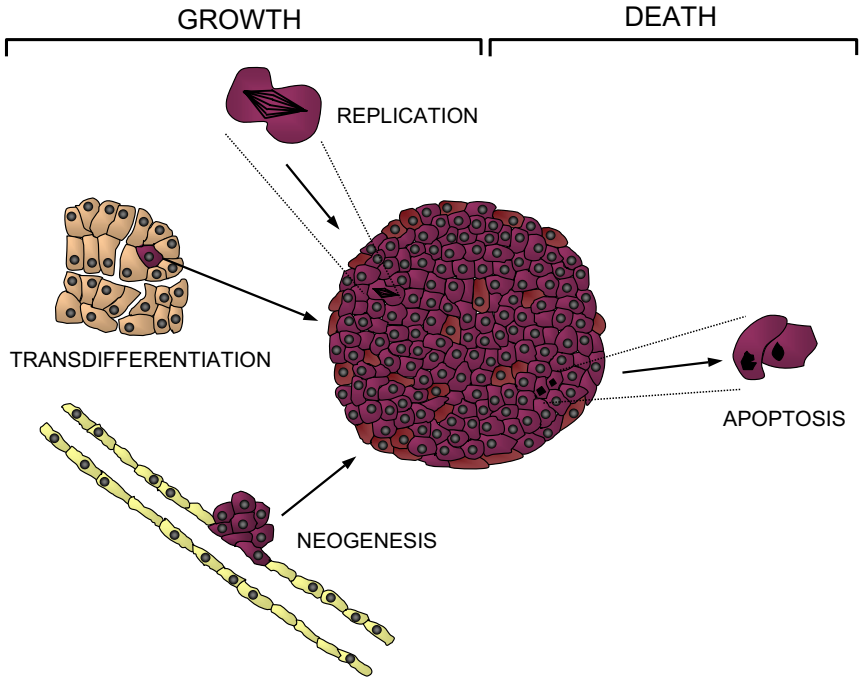

Fig. 1 Contributors to the maintenance of pancreatic islet beta cell mass: a balance between growth and death. Net pancreatic beta cell growth can be influenced by several parameters (*left-hand side*), including replication of existing islet beta cells, neogenesis and transdifferentiation, and is balanced by the incidence of islet beta cell death, usually by apoptosis (*right-hand side*)

cells they observed in pancreases from type 1 diabetic patients were more likely to be derived from either neogenesis and/or transdifferentiation [1].

While this scenario may be accurate, one has to temper it with a few cautions. In the first place, beta cell replication is notoriously difficult to measure in adult human pancreatic specimens, a shortcoming exacerbated by dependence on histological markers, such as Ki67 (which still remains our best marker for indicating cell replication in sections), that only indicate a portion of the cell cycle and therefore lead to underestimation of the degree of replication [7]. Second, no concrete indicators of adult pancreatic stem cells or beta cell progenitor cells currently exist. The concept of beta cell neogenesis, as based on the appearance of insulin-positive cells within pancreatic ducts, therefore rests upon a certain degree of faith. This issue can be addressed experimentally by lineage tracing studies in animal models, but such studies are obviously impossible to perform in humans [7]. Doubts relating to transdifferentiation are based on similar shortcomings. There is also an element of speculation in the belief that a single beta cell identified in the neighbourhood of exocrine cells has transdifferentiated from them. A degree of caution is therefore necessary when (as in this case) multiple serial sections of pancreas are not analysed to reconstruct a 3-D image. Indeed, recent studies with fluorescent beta cells have indicated that what might be perceived as a single beta cell could represent the tip of an iceberg, and might be found to represent the outer limit of an intact islet on delving deeper into the section [8].

Meier et al. [1] acknowledge that current concepts of new beta cells as derived from neogenesis and transdifferentiation are controversial [7]. Some have argued that the phenotype of 'insulin-expressing cells' generated in vitro may result from uptake of insulin from the milieu and not from active expression, so that it would be incorrect to describe them as new beta cells [9]. Others have proposed, on the basis of mouse studies, that beta cell growth is entirely mediated by replication of existing beta cells [10]. While this might be true for an animal with a relatively short life-span, it is hard to believe that humans rely solely on the beta cells they were born with, which would have to last for up to 70 years or more, as the source from which to replicate. Thus, from a physiological perspective, the concept of beta cell neogenesis for humans to supplement the pool of beta cells by an alternative means to replication seems quite valid. However, beta cell growth, whether derived from beta cell replication, neogenesis and/or transdifferentiation, must also be balanced by beta cell death. Meier et al. [1] found that the incidence of apoptosis outweighed that of beta cell growth, and suggest the intriguing possibility that the population of beta cells in type 1 diabetes might be increased by inhibiting apoptosis, assuming that unfettered beta cell regeneration can flourish [1].

It is disappointing that, aside from mean glucose values, a standard for an earlier era, this study lacks additional data relating to metabolic control (e.g. HbA_1c)or C-peptide production to the presence of insulin-positive cells in the pancreas, but this is an historical series, and these informational shortcomings are beyond repair. Furthermore, the mechanisms underlying beta cell death are unknown, let alone whether apoptosis resulted from glucose toxicity or recurrent autoimmunity. Beta cell populations fare better at lower mean glucose concentrations, an observation interpreted as showing the benefits of avoiding glucose toxicity. Alternatively, those with a greater number of residual beta cells might be better at maintaining glucose homeostasis. If true, this raises the hope that even a modest increase in the endogenous beta cell population in type 1 diabetes could be of value in delaying the onset of diabetic complications. These cells would, however, need to resist autoimmune

attack. In this study there was no clear evidence that the macrophages and T lymphocytes detected were directed against beta cells, since these were not limited to islet areas but scattered throughout the entire pancreatic tissue.

Despite these concerns, our prediction is that the work of Meier and colleagues [1] will come to be seen as key evidence supporting the fledgling field of pancreatic regeneration in type 1 diabetes. It flies in the face of existing dogma and will certainly attract much investigational attention. Time will tell whether this bold attempt to re-examine the potential for regeneration of the pancreatic islets in type 1 diabetes will be considered a dream on a deserted islet, or the start of a new reality.

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