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LETTER

Expanding human beta cells

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To the Editor: An understanding of how beta cell number is regulated during normal life and regeneration is crucial not only from a cognitive point of view, but also forms a basis for the development of new strategies to treat or cure diabetic patients. Beta cell homeostasis is the balance between beta cell formation and death. Beta cells can be formed by neogenesis from non-beta cells (differentiation from progenitors, transdifferentiation from exocrine cells) or by the proliferation of beta cells already present in the pancreas. For a long time, it was thought that the rate of beta cell proliferation was extremely low and played a minor role in beta cell expansion occurring during adult life. This hypothesis was convincingly challenged by lineage-based approaches demonstrating that, during physiological adult life, newly formed beta cells are derived from pre-existing beta cells [1]. This important finding led to a large number of teams entering the field of beta cell proliferation, which produced major new information and a better understanding of this important topic [2]. It is thus now proposed that strategies that would enhance beta cell proliferation can be used to develop human endocrine cells in large quantities to be used for diabetes therapy in humans. However, it should be kept in mind that the vast majority of the recent data on beta cell proliferation are derived from rodent models. Thus, in my view, a major question is: is the recent information demonstrating the major role of beta cell proliferation in the rodent true for human beta cells?

Although human and rodent beta cells share a large number of similarities, they are different in several respects. For example, it has long been known that beta cell function and sensitivity to destruction are not perfectly identical in rodents and humans [3, 4]. Moreover, islet cytoarchitecture—thought to have important functional implications—is also different [5]. Finally, there is debate over the proliferative potential of human beta cells. Some groups claim that human beta cells proliferate efficiently [6], while others argue that the proliferation of human adult beta cells is either extremely low or null [7]. In an article published in *Diabetologia*, Halban and colleagues compared beta cell proliferation in rodents and humans [8]. For this purpose, the authors sorted beta cells from adult rats and from 16 human donors, cultured the cells under different conditions, and analysed the effect of different exogenous growth factors on beta cell proliferation. For quantification of beta cell proliferation the cells were incubated with BrdU and then immunostained for BrdU and insulin or pancreatic and duodenal homeobox protein 1 (PDX1). Samples of cells were also stained with Ki-67, another marker used to label proliferating cells. A major finding was that rat beta cells proliferated under some of the different conditions tested, whereas human beta cells did not. This suggests that rat and human beta cells have different rates of proliferation.

At this point, the question is: what is the exact rate of beta cell proliferation in humans, if above zero? One possible explanation for the findings of Halban and colleagues [8] is that human beta cells proliferate, but at a lower rate than rodent beta cells. However, given that not a

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single proliferating human beta cell was counted, while more than 50% of rat beta cells incorporated BrdU under the best culture conditions tested in combination with a long BrdU pulse does not favour this possibility. It could be that all the in vitro conditions tested were poorly permissive for human beta cell proliferation. Alternatively, based on the fact that beta cells proliferate more during the perinatal period and the first weeks of life than later on [9, 10], greater human beta cell proliferation could have been detected if beta cells derived from younger donors had been used. In the present study, some beta cells were derived from young donors (16 years old), but it would be extremely interesting to have access to even younger donors.

The results of this recent publication [8] bring into question whether human beta cells proliferate, and the role of proliferation in the in vivo regulation of beta cell homeostasis in humans remains unresolved at present. We have learned a lot about beta cell proliferation in rodents using in vivo lineage analysis [1], a type of experiment not feasible in humans. However, it is extremely important to define the exact proliferative potential of human beta cells before generalising data generated in rodent models to humans.

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

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