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How do B Cells Regenerate?

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Despite some success with islet transplantation for the treatment of diabetes, the short supply of donor pancreases constitutes a formidable obstacle to the further development and clinical application of this therapy [1-3]. This shortage heightens the need for alternative sources of insulin-producing cells. Since mature beta cells have a very slow proliferation ratio [4], great efforts have been made to identify adult beta cell progenitors [5]. However, whether facultative beta cell progenitors exist in the adult pancreas is still a major unsolved question.

In a milestone study published in 2004, Dor and Melton reported that proliferation of pre-existing β cells is the major mechanism regulating β cell expansion in the adult pancreas [6], which were confirmed independently by several other groups [7-9]. In 2007, another milestone study by Teta and Kushner used a novel double thymidine analogue-labeling strategy to confirm that postnatal β cell growth does not involve progenitor cells [7]. This study did not include a popular tamoxifen inducible lineage tracing technique, which appeared to be the cause of the discrepancy in the experimental outcome on β cell lineage tracing in the past years. Indeed, poor labeling, pre-labeling and acquired pre-labeling that had not been adequately examined were all responsible for the controversy. We recently used another tamoxifen-free technique to examine nearly all models of adult β cell growth/regeneration [10]. Since we used an objective quantification method, and essentially examined the complete pancreas by flow cytometry, our conclusion, which is consistent with Dor and Melton, and with Teta and Kushner, should substantially increase the belief that β cell neogenesis does not occur naturally in the adult pancreas, unless gene manipulations were applied [11]. Moreover, we used another novel technique to prove that neurogenin3 activation is not sufficient to trigger duct-to-β cell transdifferentiation [12].

A major concern is that some of these strong studies are based on the assumption that a putative β cell progenitor should be characterized by de novo expression of insulin. People may argue that progenitors might already express insulin. Evidence has been provided by the identification of a rare pancreatic multipotent precursor (PMP) cell population expressing insulin and low levels of the glucose transporter Glut2 in mouse and in human islets [13,14]. However, conception of insulin-positive β cell progenitor cells does not fit the knowledge from the studies on embryonic pancreas development [15-21]. Moreover, there are more and more reports showing that β cells can dedifferentiate to a certain degree under various conditions, either before replication, or in responsive to stress [22,23]. Thus, caution needs to be taken to distinguish those PMP cells with dedifferentiated β cells. Taken together, so far no solid data have been convincingly shown to support a naturally occurrence of β cell neogenesis in the adult pancreas. Gene manipulation is required to form neogenic β cells from other cell types [11].

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