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When the Skeleton Is Controlling Pancreatic β-Cell Mass During Development and After

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COMMENTARY

The understanding of the phenomenon leading to pancreatic β-cell mass regulation represents a critical step in the development of regenerative therapy for diabetic patients. Type 1 (T1D) and type 2 (T2D) diabetes are characterized by a near-absolute or a relative deficiency of β-cells numbers, respectively. In T1D, at the time of clinical diagnosis, approximately 60–80% of the insulin-producing cells have been destroyed (1). With the currently available treatments, patients with T1D and T2D develop severe long-term complications that clearly reduce their life expectancy (2–4). While insulin replacement continues to be the primary treatment, the need to establish a precise and physiological glucoregulation in order to avoid complications has led to multiple avenues of alternative interventions. Some studies fulfilled this requirement with allogenic transplantation of human islets or insulin-producing cells (5,6). Still under extensive study, the use of pig islets as an alternative source of insulin-producing cells for xenotransplantation seems to be promising and could represent the future of cell therapy for diabetes (7). Other studies have aimed at abrogating the cause of the disease (i.e., the autoimmunity leading to the destruction of β-cells in T1D) (8). Finally, others worked on the reestablishment of an adequate β-cell mass able to restore euglycemia through methods that promote β-cell preservation and/or regeneration in diabetic individuals (9–11).

Pancreatic β-cell mass and function exhibit significant plasticity so that in times of increased insulin demand, such as obesity (12), insulin resistance, and pregnancy (13,14), β-cell numbers and insulin secretory capacity can increase significantly to meet this metabolic demand. During a life span, maintenance of pancreatic β-cell mass is regulated by a complex equilibrium among neogenesis, increase and decrease of cell volume (hypertrophy or atrophy), cell differentiation, and cell proliferation (hyperplasia) and death (apoptosis). Now, there is considerable interest in finding efficient and safe methods to increase β-cell mass by inducing the proliferation of remaining β-cells or favoring the differentiation of resident precursors or progenitors. The proliferation of preexisting β-cells has been shown to be an important source of newly derived adult pancreatic β-cells (15). Under physiological conditions, the rate of primary β-cell replication is very low (in the range of 0–1.2% of the β-cells in adults). Although extensively studied, physiological mechanisms of human β-cell proliferation still remain unknown. Different molecules have been shown to favor β-cell proliferation, mainly prolactin (increasing during pregnancy), serotonin (16), glucagon-like peptide 1 (GLP-1), and betatrophin (17).

In this issue, Wei et al. (18) show that pancreatic β-cell mass is controlled during development and adulthood by osteocalcin via its receptor Gprc6a. Recently, several observations have highlighted that bone, more than supporting tissue, is a real endocrine organ regulating various functions including glucose metabolism and energy expenditure. Osteocalcin, also known as bone γ-carboxyglutamic acid-containing protein, a specific osteoblast-derived hormone, is responsible for these functions (Fig. 1). Osteocalcin can be found in two different forms. In its uncarboxylated form, osteocalcin favors pancreatic β-cell insulin expression and secretion (19) and β-cell proliferation. Several well-documented clinical investigations demonstrated a clear association between

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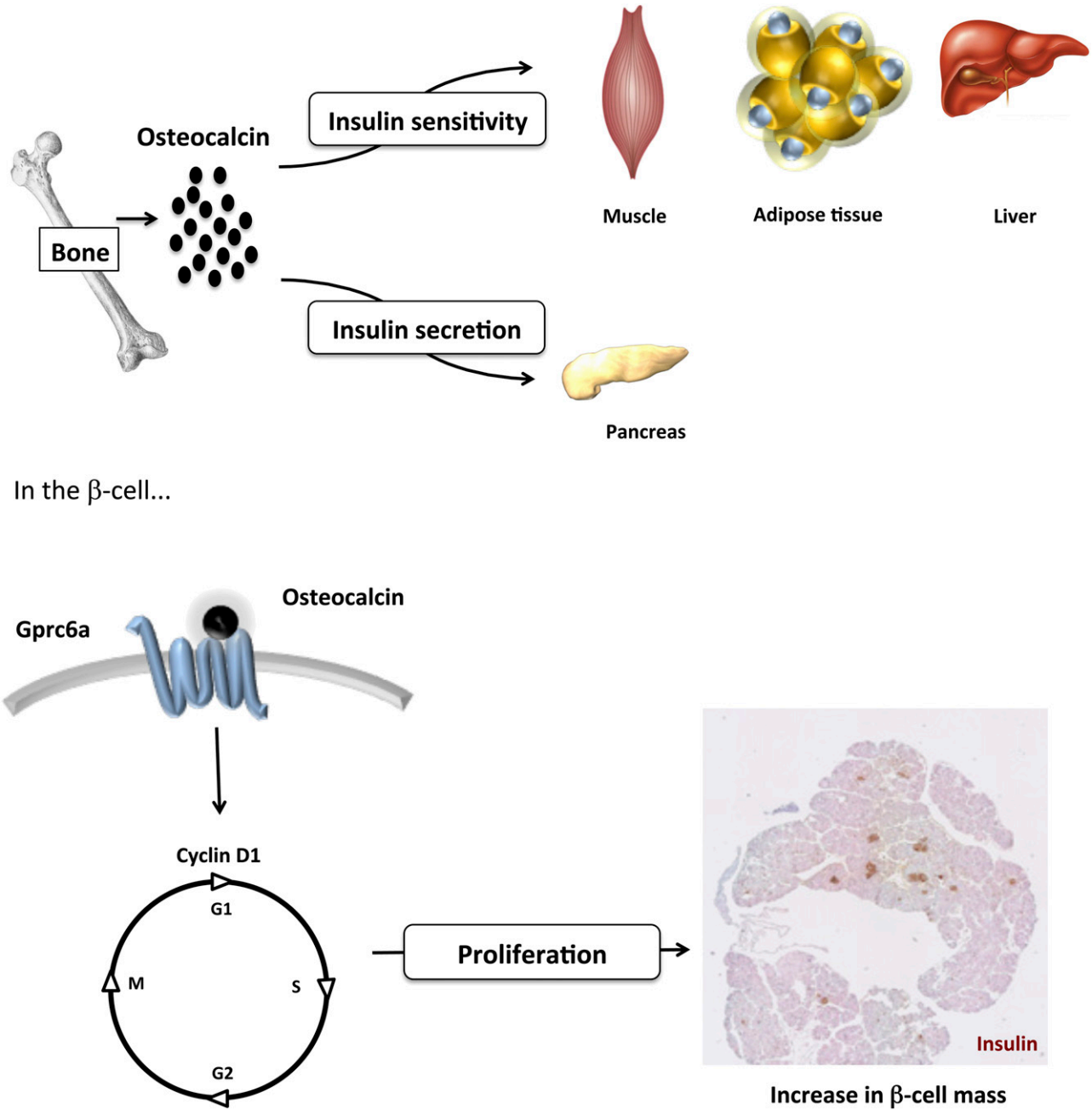

Figure 1—Osteoblast-secreted osteocalcin in its active (undercarboxylated) form favors insulin sensitivity in muscle, adipose tissue, and liver, having a positive action on glycemia. In the pancreas, active osteocalcin stimulates insulin release and β-cell proliferation. In β-cells, osteocalcin binds to its receptor Gprc6a, inducing the activation of cyclin D1 and cell-cycle progression leading to β-cell proliferation and increase in β-cell mass.

glucose metabolism and osteocalcin in humans. Gprc6a is a G-protein–coupled receptor, binding basic and small aliphatic L-α-amino acids and cations, showing a wide tissular expression. More recently, testosterone and osteocalcin have been identified as endogenous Gprc6a agonists. Wei et al. first demonstrated that Gprc6a-specific inactivation in pancreatic β-cells ($Gprc6a_{Pdx1-/-}$) induced glucose intolerance, producing a lower quantity of insulin in response to glucose stimulation but with a normal insulin sensitivity. Compared with their control littermates (*Gprc6a* fl/fl), no significant differences were observed for body and pancreas weight and glucagon expression.

β-Cell proliferation is the main actor of the increasing β-cell mass. In the proliferation process, cyclin and cyclin-dependent kinases play an important role. Previous studies on gene expression analyses of islets or β-cell lines demonstrated that osteocalcin enhances the

expression of the insulin genes as well as those encoding proteins implicated in G1/S cell-cycle transition, such as cyclin D1, cyclin D2, and Cdk4. Wei et al. demonstrate that the inactivation of Gprc6a induced a reduction of β-cell proliferation concomitant with a decrease of cyclin D1 gene expression during development and adulthood. Cyclin D2 and Cdk4 expression were not modified. As a consequence, β-cell mass and area were reduced in $Gprc6a_{Pdx1-/-}$ mice.

With in vitro and in vivo experiments, Wei et al. showed that in the absence of Gprc6a expression in β-cells osteocalcin has no effects on insulin expression and secretion and β-cell proliferation, clearly showing that Gprc6a is the main, if not the only, osteocalcin receptor acting in β-cells. Moreover, they demonstrate that the reduction of the β-cell mass was only due to a reduction of β-cell proliferation and not to an impaired differentiation. Study of β-cell differentiation markers (Pdx1, Nkx6.1, Nkx2.2, or Isl1) and other endocrine hormones in $Gprc6a_{Pdx1-/-}$ mice and their control littermates did not demonstrate any differences.

Interestingly, plasmatic active osteocalcin (undercarboxylated) is detectable early during development and its quantity is constantly increasing to reach a maximum in the postnatal period. During the perinatal period, β-cells undergo a transient peak of proliferation significantly increasing the β-cell mass. This perinatal peak of β-cell proliferation coincides with the enhanced expression of osteocalcin in developing embryos. A recent publication by Mizokami et al. (20) highlighted the effect of osteocalcin via Gprc6a on GLP-1 secretion by the L-cells of the intestine. GLP-1 is known to favor β-cell proliferation and could contribute, to some extent by an indirect way, to the β-cell proliferation observed in the study of Wei et al.

Despite some remaining questions about the complete deciphering of the direct and indirect actions of osteocalcin on β-cell mass, the study by Wei et al. (18) contributes elegantly to bring new important knowledge on the complex and intriguing relation existing between the bones and pancreas. This connection between these two tissues opens new roads for the treatment of diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Hirsch IB. Insulin analogues. N Engl J Med 2005;352:174–183
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
3. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes 2006;55:1463–1469
4. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329:304–309
5. Ludwig B, Reichel A, Steffen A, et al. Transplantation of human islets without immunosuppression. Proc Natl Acad Sci U S A 2013;110:19054–19058
6. Dave SD, Trivedi HL, Chooramani SG, Chandra T. Management of type 1 diabetes mellitus using in vitro autologous adipose tissue transdifferentiated insulin-making cells. BMJ Case Rep 2013;DOI: 10.1136/bcr-2013-200226
7. van der Windt DJ, Bottino R, Kumar G, et al. Clinical islet xenotransplantation: how close are we? Diabetes 2012;61:3046–3055
8. Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. N Engl J Med 2005;352:2598–2608
9. Ding L, Gysemans C, Mathieu C. β-Cell differentiation and regeneration in type 1 diabetes. Diabetes Obes Metab 2013;15(Suppl. 3):98–104
10. Domínguez-Bendala J, Inverardi L, Ricordi C. Regeneration of pancreatic beta-cell mass for the treatment of diabetes. Expert Opin Biol Ther 2012;12:731–741
11. Bouckenooghe T, Vandewalle B, Moerman E, et al. Expression of progenitor cell markers during expansion of sorted human pancreatic beta cells. Gene Expr 2005;12:83–98
12. Saisho Y, Butler AE, Manesso E, Elashoff D, Rizza RA, Butler PC. β-cell mass and turnover in humans: effects of obesity and aging. Diabetes Care 2013;36:111–117
13. Sorenson RL, Brelje TC. Adaptation of islets of Langerhans to pregnancy: beta-cell growth, enhanced insulin secretion and the role of lactogenic hormones. Horm Metab Res 1997;29:301–307
14. Rieck S, Kaestner KH. Expansion of beta-cell mass in response to pregnancy. Trends Endocrinol Metab 2010;21:151–158
15. Dor Y, Brown J, Martinez OI, Melton DA. Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. Nature 2004;429:41–46
16. Kim H, Toyofuku Y, Lynn FC, et al. Serotonin regulates pancreatic beta cell mass during pregnancy. Nat Med 2010;16:804–808
17. Yi P, Park JS, Melton DA. Betatrophin: a hormone that controls pancreatic β cell proliferation. Cell 2013;153:747–758
18. Wei J, Hanna T, Suda N, Karsenty G, Ducy P. Osteocalcin promotes β-cell proliferation during development and adulthood through Gprc6a. Diabetes 2014;63:1021–1031
19. Ferron M, Hinoi E, Karsenty G, Ducy P. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. Proc Natl Acad Sci U S A 2008;105:5266–5270
20. Mizokami A, Yasutake Y, Gao J, et al. Osteocalcin induces release of glucagon-like peptide-1 and thereby stimulates insulin secretion in mice. PLoS One 2013;8:e57375