Age-related impairment of pancreatic beta-cell function: pathophysiological and cellular mechanisms

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TYPE 2 DIABETES: AN AGE-RELATED DISEASE

Diabetes mellitus, a disease characterized by high blood glucose levels resulting from a combination of genetic and acquired factors, represents the most prevalent metabolic disorders. Indeed, the prevalence of the most common form, type 2 diabetes or non-insulin-dependent diabetes mellitus (NIDDM), exploded over the last several decades. Data from the World Health Organization (WHO) and the International Diabetes Federation (IDF) show that the prevalence of type 2 diabetes increased from 100–135 million affected adults worldwide in 1994–1995 to approximately 336 million in 2011, and it is expected to rise to 439 million by 2030 (1–3). These data are even more dramatic considered in the light of the concomitant global aging of the population. Elderly people (by definition, person of over 65 years of age) represented 12–15% of the population in 2008, whereas it has been estimated that the same age group would account for 26% of the population in 2026 and will reach 2 billion people in 2050 (4, 5). Population aging is rapidly becoming a global issue with a major impact on health policies and programs. Such a remarkable improvement in life expectancy considerably contributed to a shift in the leading causes of diseases and death from infectious and parasitic diseases to non-communicable diseases (such as heart disease, cancer, and diabetes) that more commonly affect adults and older adults (6, 7). In particular, aging is an important risk factor for metabolic disorders, including obesity, impaired glucose tolerance, and type-2 diabetes (8, 9). The prevalence of type 2 diabetes increases with age (in older adults it is more than twice that of middle-aged adults) and peaks at 60–74 years of age (10–12). In consideration of the already mentioned nearly doubling of the numbers of elderly persons by the year 2030, it is easy to see why diabetes in older adults is considered as a growing public health concern.

Normal aging is usually associated with a progressive deterioration in most endocrine functions that may be responsible for serious disturbances of metabolic homeostasis (13–16). Actually, the incidence of type 2 diabetes significantly increases with age. The relevance of this association is dramatically magnified by the concomitant global aging of the population, but the underlying mechanisms remain to be fully elucidated. Here, some recent advances in this field are reviewed at the level of both the pathophysiology of glucose homeostasis and the cellular senescence of pancreatic islets. Overall, recent results highlight the crucial role of beta-cell dysfunction in the age-related impairment of pancreatic endocrine function and delineate the possibility of new original therapeutic interventions.

AGING AND INSULIN RESISTANCE

Type 2 diabetes mellitus is a metabolic disorder characterized by high blood glucose levels as a result of the complex interplay of multiple genetic and environmental factors that cause both impaired insulin action on target tissues and defective pancreatic beta-cell insulin secretion in response to glucose (17).

It is well documented that aging is associated with a decline of insulin action. Studies utilizing the euglycemic hyperinsulinemic clamp technique to assess insulin effectiveness in regulating glucose transport usually stress the relevance of the diminished insulin sensitivity on target tissues in the development of age-related glucose intolerance (17, 20, 23, 24). Insulin resistance could increase with age in relation to several well-known age-related changes, such as: (i) increased adiposity (with particular...
AGING AND INSULIN SECRETION

On the other hand, several observations clearly show that insulin resistance alone is not sufficient to lead to type 2 diabetes in the absence of a beta-cell defect associated with abnormal insulin secretion. Consequently, beta-cell dysfunction is increasingly recognized to play a fundamental role in type 2 diabetes pathophysiology (48, 49) and could represent another significant contributing factor to abnormal glucose metabolism with age (9, 50). Indeed, it has been repeatedly reported that the ability of pancreatic beta cells to maintain an insulin secretory function adequate for metabolic demand is impaired with increasing age in both experimental animals (51–55) and humans (11, 56–65), although some of these studies (especially in humans) were characterized by a significant degree of variability (66).

This age-related impairment of beta-cell secretory capabilities has been variously attributed to several factors, including: (i) mitochondrial dysfunction (34, 67–69); (ii) reduced GLUT2 levels (54, 70); (iii) accumulation of advanced glycation end products (AGEs) (71, 72); (iv) telomerase deficiency and reduced telomere length (73, 74); (v) reduced expression of β2-adrenergic receptors (75); (vi) impaired Ca\(^{2+}\) handling (76, 77); (vii) reduced response to GLP-1 stimulation (62, 65, 78–83); (viii) increased autophagy (84); (viii) reduced expression of beta-cell-specific genes and transcription factors such as PDX-1 (54).

Among the above mentioned factors, mitochondrial dysfunction may deserve a particular discussion because mitochondria play a crucial role in the physiological stimulus-secretion coupling in beta cells. In these cells, mitochondria serve as nutrient sensors and signal generators for insulin secretion. In particular, the mitochondrial metabolism of pyruvate, glycolitically derived from glucose, generates ATP, which in turn promotes the closure of ATP-sensitive K\(^{+}\) channels and the consequent cell depolarization, inducing Ca\(^{2+}\) influx through voltage-gated Ca\(^{2+}\) channels, increased cytosolic [Ca\(^{2+}\)], and finally triggering insulin exocytosis (85). On the other hand, due to the central role played in the generation of reactive oxygen species (ROS) at the level of the electron transport chain and ATP production, it has been proposed that mitochondria could represent a primary target of ROS damage (mitochondrial free radical theory of aging) (86). Indeed, increasing evidence suggests that abnormal mitochondrial ROS production and detoxification contribute to mitochondrial dysfunction in old age (87). Thus, age-related impairment of mitochondrial function could easily result in decreased beta-cell function and insulin secretion (88).

We can tentatively conclude this brief survey of the pathophysiology of glucose homeostasis by observing that several risk factors for diabetes associated with aging likely contribute to the development of age-related glucose intolerance and insulin resistance. Adaptation to insulin resistance normally requires compensatory hyperinsulinemia to maintain normal glucose metabolism. On the average, many studies show that, when considered in light of the degree of insulin resistance, all the indexes of insulin secretion appear to be decreased with age, indicating decreased beta-cell secretory reserve. Thus, the main homeostatic defect could be ascribed to age-dependent failure of the endocrine pancreas to provide enough insulin to overcome the state of increased peripheral insulin resistance.

BETA-CELL SENECEENCE

Studies on the age-related glucose intolerance at the pathophysiological level may be difficult to interpret because the development of this condition could depend on a combination of many different factors whose independent influence is not easily controlled, thus making their relative importance a matter of debate. Therefore, more recently several researchers shifted the focus of their interest on the effect of aging on islet biology, with particular reference to the proliferative and regenerative capacity of beta cells. This paradigmatic change arises mainly from the consideration that aging represents a major risk factor for many generally chronic diseases (including cancer, neurodegeneration, and diabetes) and from the related possibility that these pathologies could be linked by a common biology. In the last few decades, a growing consensus has been reached and now it is considered likely that one or more basic aging processes underlie most, if not all, age-related pathologies (89).

One basic process that may contribute to age-related dysfunction, including decreased secretory function (90), is cellular senescence. Cellular senescence was firstly described more than 50 years ago by Hayflick and Moorhead (91) as a process limiting the proliferation of normal human fibroblasts in culture, and this term is now generally used to indicate the essentially irreversible growth arrest that occurs when cells that can divide are challenged by a potentially oncogenic stress (92, 93). Senescent cells have clearly been shown to disrupt normal tissue structures and differentiated functions in complex cell culture models (89).

The growing interest in the cellular mechanisms responsible for the age-related decline in beta-cell proliferation originated from two distinct considerations with either fundamental or clinical implications. (A) Since insulin secretion by pancreatic beta cells represents the key point of the endocrine axis regulating glucose homeostasis, it is obvious that maintenance of beta-cell number and islet mass must be considered crucial in order to sustain normoglycemia. (B) Beta-cell replication represents a major goal of the cellular therapy of diabetes. Indeed, the promising attempt to develop a therapy based on pancreatic islets transplantation is still seriously hampered by the scarcity of cadaver-derived islets. The possibility to enhance replication of islet cells in vitro has been proposed as a solution to overcome the limited supply. Similarly, the expansion of potentially reduced functional beta-cell mass in vivo might represent another therapeutic strategy in type 1 and type 2 diabetes.

In normal healthy conditions, beta cells have a long lifespan with a low proliferation rate (94). However, it has been shown that in particular conditions, such as in response to increased metabolic demand or after injury, the adult pancreas could be able to...
produce new cells, particularly beta cells. Recent experimental evidences indicate that beta-cell mass, like many other tissues, could be dynamically regulated with ongoing beta-cell regeneration throughout life to replace lost or damaged beta cells (95).

**MOLECULAR MECHANISM OF AGE-RELATED BETA-CELL GROWTH ARREST**

Beta-cell cycling is driven by cyclin D1/D2-Cdk activity and is repressed by the Cdk-inhibitor p16INK4a (Figure 1) (96). In mice, it has been shown that beta-cell proliferation is an age-related process and that the expansion of beta-cell mass after pancreatic injury is more robust in young than in old animals (97). However, several pieces of experimental evidence indicate that aging mouse beta cells maintain a partially preserved ability to proliferate when specifically stimulated, both after pancreas injury (such as partial pancreatectomy or beta-cell-specific cell ablation) (98–102) and after islet transplantation in hyperglycemic recipients (103, 104). On the other hand, in recent years it became increasingly apparent that many of the mechanisms identified in these rodent models cannot be transferred easily to human islet cells. Human studies generally consist of observations made from pancreases obtained at autopsy, pancreas donation, and surgical resection, and are mainly based on immunohistochemical markers of proliferation (such as the nuclear Ki-67). As a consequence, data obtained in humans are often less conclusive than those obtained in rodent experimental models (105). It has been shown that human beta-cell mass can increase in obesity, although to a lesser degree than in rodents (30–40% estimated increase in humans with respect to a 30-fold increase observed in mice) (106–108). On the contrary, recent studies failed to detect an increased rate of beta-cell proliferation in pregnant individuals and in type 2 diabetes patients (109).

A major difference between mice and humans is telomere shortening that limits proliferation and leads to cellular senescence in humans (110, 111), whereas in mice that have long telomeres no impairment of replication has been detected for several generations after ablation of telomerase (112, 113). This difference may account for the differential response observed between mice and humans (proliferation vs. differentiation from non-beta-cell progenitors) in beta-cell compensation (114). Human beta cells in adults appear to be largely postmitotic with very low rates of cell proliferation after the age of 20–30 years, as determined by Ki-67 content (115–117), thymidine analog incorporation (118), and increased in vivo lipofuscin accumulation (119, 120). Growth arrest of adult human beta cells cannot be reversed by procedures inducing proliferation in vitro (121, 122). This decline in the proliferative capacity of aging beta cells is directly associated with a decreased expression of the pancreatic and duodenal homeobox 1 (Pdx1) (121, 123), a transcription factor that plays a crucial role in beta-cell replication (124). Several experimental pieces of evidence demonstrated a decreased expression of cell cycle activators (such as, e.g., the transcription factor FoxM1) in aging beta cells with a simultaneous decrease in the expression of cell cycle inhibitors [for a review see Ref. (10)]. p16INK4a tumor suppressor protein has emerged from these studies as a key control point for cell cycle entry of beta cells. p16INK4a is a cyclin-dependent kinase inhibitor (CDKI) encoded by the Cdkn2a locus, which sequesters cdk4 and cdk6, thus preventing their interaction with the D cyclins. It has been shown that p16INK4a expression increases with age in several mouse tissues, including islets (125), and that proliferation of beta cells in young mice was reduced to levels observed in older mice when the transgenic overexpression of p16INK4a was induced (125, 126). On the other hand, in p16INK4a knockout mice, beta-cell proliferation was significantly increased (126). In this context, it could be very intriguing to mention that genome-wide association studies revealed an association between SNPs near Cdk2a (the locus encoding p16INK4a) and increased risk of type 2 diabetes (113, 127, 128). It has also been shown that free fatty acids, whose levels were typically increased in type 2 diabetes patients (109). On the contrary, recent studies failed to detect an increased rate of beta-cell proliferation in pregnant individuals and in type 2 diabetes patients (109).

**FIGURE 1 |** Schematic representation of the molecular pathways involved in the regulation of beta-cell proliferation is shown. P16INK4a is a key regulator of cell cycle entry in aged beta cells through D-type cyclins and cyclin-dependent kinases (CDK). P16INK4a is negatively regulated by the polycomb proteins EZH2 (enhancer of zeste homolog 2) and BMI1 (IB lymphoma Mo-MLV insertion region 1 homolog). BMI1 is stimulated by p38 MAPK.
indicating the crucial role that epigenetic regulation could play in the control of cell cycle progression of beta cells in both aging and type 2 diabetes (134). Indeed, mice with conditional gene inactivation of EZH2 in beta cells exhibited a premature increase in p16\textsuperscript{INK4a} and p19\textsuperscript{arf} expression and a reduced beta-cell proliferation, whereas no changes were observed in the levels of other CDK inhibitors, suggesting a specific effect of EZH2 on the INK4a/arf locus in beta cells (133). However, the transgenic expression of EZH2 was unable to repress INK4a in mice older than 8 months, unless EZH2 was expressed in conjunction with knockdown of trithorax group (TrxG) protein complex components (135).

Overall, these results indicate that cellular senescence could be responsible for the observed decline in the proliferative capacity of pancreatic beta cells. It has been reported that Akita mice with short telomeres are characterized by slower proliferation of beta cells and accumulation of p16\textsuperscript{INK4a} (74). More recently, Zeng et al. (136) showed that in mice the beta-cell-specific genetic deletion of Pten (phosphatase and tensin homolog), encoding a tumor suppressor protein involved in the regulation of the cell cycle (137), prevents the age-related decline in beta-cell proliferation and restores the ability of beta cells to respond to injury-mediated regeneration. Interestingly, the ability of Pten deletion to remove the block in cell cycle re-entry seems to be mediated by a decrease in p16\textsuperscript{INK4a} expression.

The decline in beta-cell proliferation with age may also be the result of an age-related impairment of mitotic signal transduction pathways. It has been shown that p38 MAPK signals are able to influence CDK1 expression in aged islets: the destruction of p38 MAPK signals in aged mutant mice has as a consequence a reduced expression of p16\textsuperscript{INK4a}, p19\textsuperscript{arf}, and other CDK1 with a related increase of beta-cell proliferation (138). This effect seems to be counterbalanced by the p53-induced phosphatase 1 (WIP1), whose overexpression in middle-aged transgenic mice causes a reduced p16\textsuperscript{INK4a} expression as well as an improved capacity of beta-cell regeneration after selective beta-cell destruction by streptozotocin (138). A further important component linking growth signals to beta-cell expansion could likely be represented by Akt activation and its downstream mTORC1 signaling (137). It is well known that alterations in the nutrient-sensing pathways (such as the insulin/IGF-1 and the TOR pathways) have been proposed to underlie the aging process and modulate longevity (139). mTOR is an evolutionarily conserved nutrient-sensing cytoplasmic protein kinase that regulates cell growth and metabolism in response to mitogens, nutrients, and hormones in all eukaryotic cells (140). However, later in life, when growth has been completed, mTOR can drive cellular and organismal aging (141) and can be involved in age-related diseases (138). Indeed, the most well-known TOR inhibitor, rapamycin, is able to extend lifespan in yeast, flies, worms, and rodents (142). Glucose, amino acids, and fatty acids activate mTOR in beta cells, and the consequent increase in beta-cell mass and function may help to compensate the age-related development of insulin resistance (143). However, it has been proposed that, during aging, the chronic hyperstimulation of mTOR could contribute to the development of beta-cell failure (143). Interestingly, metformin, the most widely used antidiabetic drug, has been shown to be an inhibitor of mTORC1 and to decrease the phosphorylation of its substrates S6K1 and 4E-BP1 (144). Metformin was also shown to increase longevity in species ranging from yeast to mice (145). The underlying mechanism of this action of metformin is not fully understood. However,
it is known that metformin inhibits the activity of mitochondrial complex I and increases the activity of AMPK, which in turn inhibits mTORC1 complex activity, thus suggesting a possible link between rapamycin and metformin actions on longevity.

Little is known about the upstream signals that could be responsible for the regulation of beta-cell proliferation and its decline with age. It has been reported that PDGF treatment increased beta-cell proliferation in cultured human islets from young donors but not in islets from adults. Interestingly, PDGF receptor signals seem not to act in part via EZH2 (146). Treatment with the glucagon-like peptide 1 (GLP-1) analog, exendin-4 is able to increase beta-cell mass and markedly decrease p16INK4a expression in young but not in middle-aged mice (147). Recently, it has been shown with parabiosis experiments that a systemic factor (whose exact nature is still unknown) found in the circulation of young mice seems to be able to increase the proliferation rate of old pancreatic beta cells (148).

CONCLUSION

Alterations of glucose homeostasis increase with age and represent leading causes of morbidity and mortality, mainly linked to both the complications associated with type 2 diabetes and the increased risk for several other age-related diseases (149). The classical pathophysiological factors responsible for this age-related failure of glucose homeostasis (insulin resistance and decreased secretory capability of beta cells) are quite well characterized, but new mechanisms have recently been revealed (Figure 2). Central to this new development is the key concept that loss or dysfunction of pancreatic beta cells plays a crucial role in the pathogenesis of type 2 diabetes. Since the predominant mechanism of beta-cell generation seems to be self-renewal, the senescence-associated cell cycle dysregulation and the consequent proliferative arrest assume a particular relevance. In recent years, some of the cellular and molecular mechanisms associated with the decreased proliferation capability of senescent beta cells have been explored, but some others remain to be fully elucidated, and a further effort will be requested in order to efficiently translate this new insight into successful new therapeutic strategies.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care (2004) 27:1047–53. doi:10.2337/diacare.27.10.2569-a
2. Kolb H, Mandrup-Poulsen T. The global diabetes epidemics as a consequence of lifestyle-induced low-grade inflammation. Diabetologica (2010) 53:10–20. doi:10.1007/s00125-009-1573-7
3. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract (2010) 87:4–14. doi:10.1016/j.diabres.2009.10.007
4. Kowal P, Chatterji S, Naidoo N, Brittwum R, Fan W, Lopez Irauira R, et al. Data resource profile: the World Health Organization Study on global AGeing and adult health (SAGE). Int J Epidemiol (2012) 41:1639–49. doi:10.1093/ije/dys210
5. Michalakis K, Goulis DG, Varaiou A, Miniarzi G, Polymenis A, Abrahamian-Michalakis A. Obesity in the ageing man. Metabolism (2013) 62:1341–9. doi:10.1016/j.metabol.2013.05.019
6. Christensen K, Dohhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet (2009) 374:196–208. doi:10.1016/S0140-6736(09)61460-4
7. National Institutes of Health (NIH). Global Health and Aging. NIH Publication no. 11-7737. Washington, DC: Department of Health and Human Services (2011).
8. Kalyani RR, Egan JM. Diabetes and altered glucose metabolism with aging. Endocr Metab Clin North Am (2013) 42:333–47. doi:10.1016/j.ecl.2013.02.010
9. Gong Z, Muramndh RA. Pancreatic function, type 2 diabetes, and metabolism in aging. Int J Endocrinol (2012) 2012:204824. doi:10.1155/2012/204824
10. Gunasekaran U, Gannon M. Type 2 diabetes and the aging pancreatic beta cell. Aging (Albany NY) (2011) 3:856–75.
11. Izzo P, Beck-Nielsen H, Laakso M, Smith U, Yki-Jarvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in nondiabetic humans. European Group for the Study of Insulin Resistance. J Clin Endocrinol Metab (1999) 84:663–8. doi:10.1210/jcem.84.3.5542
12. Cowie CC, Rust KE, Byrd-Holt DD, Eberhard MS, Flegal KM, Engelgau MM, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. Diabetes Care (2006) 29:1263–8. doi:10.2337/dc06-0062
13. Yeap BB. Hormones and health outcomes in aging men. Exp Gerontol (2013) 48:677–81. doi:10.1016/j.exger.2012.07.012
14. Batrinos M. Aging of the endocrine hypothalamus and its dependent endocrine glands. Hormones (Athens) (2012) 11:241–53. doi:10.4131/horm.2002.1354
15. Clegg A, Young J, Ilipe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet (2013) 381:752–62. doi:10.1016/S0140-6736(12)62167-9
16. Vitale G, Salvadore S, Franceschi C. Oxidative stress and the ageing endocrine system. Nat Rev Endocrinol (2013) 9:228–40. doi:10.1038/nrendo.2013.29
17. DeFronzo RA. Glucose intolerance and aging. Diabetes Care (1981) 4:493–501. doi:10.2337/diabetes.34.4.493
18. Jackson RA. Mechanisms of age-related glucose intolerance. Diabetes Care (1990) 13(Suppl 2):9–19.
19. Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. Lancet (2011) 378:169–81. doi:10.1016/S0140-6736(11)60614-4
20. Fink RJ, Koltermann OG, Griffin J, Olsfey JM. Mechanisms of insulin resistance in aging. J Clin Invest (1983) 71:1523–35. doi:10.1172/JCI10908
21. Choi K, Kim YB. Molecular mechanism of insulin resistance in obesity and type 2 diabetes. Korean J Intern Med (2010) 25:119–29. doi:10.3904/kjim.2010.25.2.119
22. Saini V. Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. World J Diabetes (2010) 1:68–75. doi:10.4239/wjd.v1.i3.68
23. DeFronzo RA. Glucose intolerance and aging: evidence for tissue insensitivity to insulin. Diabetes (1979) 28:1095–101. doi:10.2337/diab.28.12.1095
24. Rowe JW, Minaker KL, Pallotta JA, Flier JS. Characterization of the insulin resistance of aging. J Clin Invest (1983) 71:581–7. doi:10.1172/JCI110914
25. Kim JE, Lee YH, Hub JH, Kang DR, Rhee Y, Lim SK. Early-stage chronic kidney disease, insulin resistance, and osteoporosis as risk factors of sarcopenia in aged population: the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV), 2008-2009. Osteoporos Int (2014) 25:2189–98. doi:10.1007/s00198-014-2745-y
26. Outler JE, Maurya SK, Dula J, Roof SR, Devor ST, Ziolto MT, et al. Effects of insulin resistance on skeletal muscle growth and exercise capacity in type 2 diabetic mouse models. Am J Physiol Endocrinol Metab (2014) 306:E592–605. doi:10.1152/ajpendo.00277.2013
27. Atkin JL, Whinicup PH, Morris RW, Wanamethee SG. Low muscle mass in older men: the role of lifestyle, diet and cardiovascular risk factors. J Nutr Health Aging (2014) 18:26–33. doi:10.1016/s12013-013-0336-9
28. Petersen KE, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, et al. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science (2003) 300:1140–2. doi:10.1126/science.1082889
29. Toledo FG, Goodpaster BH. The role of weight loss and exercise in correcting skeletal muscle mitochondrial abnormalities in obesity, diabetes and aging. Mol Cell Endocrinol (2013) 379:30–4. doi:10.1016/j.mce.2013.06.018
30. Phelix E, Sredniodi J, Roden M. Mitochondrial function and insulin resistance during aging: a mini-review. Gerontology (2011) 57:387–96. doi:10.1159/000317691
31. Dela E, Helge JW. Insulin resistance and mitochondrial function in skeletal muscle. J Biol Chem (2013) 45:11–5. doi:10.1016/j.jcbiochem.2012.09.019
triposphosphate synthesis. Endocrinology (2009) 150:2569–76. doi:10.1210/en.2008-1342

38. Kubosh D, Florian S, von Figura G, Weimer S, Schulz N, Petzke KJ, et al. Telomere- 
deficiency impairs glucose metabolism and insulin secretion. Aging (Albany NY) (2010) 2:650–8.

39. Guo N, Parry EM, Li LS, Kembou F, Lauder N, Hussain MA, et al. Short telomeres 
embrace β-cell signaling and survival. PLoS One (2011) 6:e17585. doi:10.1371/journal.pone.0017585

40. Santulli G, Lombardi A, Sorrentino D, Anastasio A, Del Giudice C, Formisano P, et al. Age-related impairment in insulin release: the essential role of β2-adrenergic receptor. Diabetes (2012) 61:692–701. doi:10.2337/db11-1027

41. Ribeiro RA, Battista TM, Coelho FM, Boscheri AC, Lopes GS, Carneiro EM. Decreased 
β-cell insulin secretory function in aged rats due to impaired Ca2+ handling. Exp Physiol (2012) 97:1065–73. doi:10.1113/expphysiol.2012.064790

42. Lin Y, Sun Z. Antiaging gene Klotho enhances glucose-induced insulin secretion 
by up-regulating plasma membrane levels of TRPV2 in MIN6 β-cells. Endocrinology (2012) 153:3029–39. doi:10.1210/en.2012-1091

43. Elahi D, Andersen DK, Muller DC, Tobin JD, Brown JC, Andres R. The 
enteric enhancement of glucose-stimulated insulin release. The role of GIP in aging, obesity, and non-insulin-dependent diabetes mellitus. Diabetes (1984) 33:950–7. doi:10.2337/diab.33.10.950

44. Menellés GS, Ryan AS, Minaker KL, Elahi D. The effect of age and glycemic level on 
the response of the β-cell to glucose-dependent insulinotropic polypeptide 
and peripheral tissue sensitivity to endogenously released insulin. J Clin Endocrinol Metab (1998) 83:2925–30. doi:10.1210/jcem.83.8.2925

45. Wang Y, Perretti R, Greig NH, Holloway HW, Deore KA, Montonse-Rafizadeh C, et al. Glucagon-like peptide-1 can reverse the age-related decline in glucose tolerance in rats. J Clin Invest (1997) 99:2883–9. doi:10.1172/JCI91482

46. Fan R, Kang Z, He L, Chan J, Xu G. Exendin-4 improves blood glucose 
control in both young and aging normal non-diabetic mice, possible contribution of β cell independent effects. PLoS One (2011) 6:e20443. doi:10.1371/journal.pone.0020442

47. Irwin N, McClean PL, Harriott P, Flatt PR. Beneficial effects of sub-chronic activation 
of glucagon-like peptide-1 (GLP-1) receptors on deterioration of glucose homeostasis and insulin secretion in aging mice. Exp Gerontol (2007) 42:296–300. doi:10.1016/j.exger.2006.10.017

48. Menellés GS, Veldhuis JD, Elahi D. Deconvolution analysis of rapid insulin 
pulses before and after six weeks of continuous subcutaneous administration 
of GLP-1 in very old mice retain capacity for compensatory proliferation. J Biol Chem (2012) 287:27407–14. doi:10.1074/jbc.M112.350376

49. Chen X, Zhang X, Chen F, Larson CS, Wang LJ, Kaufman DB. Comparative 
study of regenerative potential of beta cells from young and aged donor mice 
using a novel islet transplantation model. Transplantation (2009) 88:496–503. doi:10.1097/TP.0b013e3181b0ee2e

50. Tian L, Gao J, Weng G, Yi H, Tian B, O’Brien TD, et al. Comparison of exendin-
4 on β-cell replication in mouse and human islet grafts. Transpl Int (2011) 24:856–64. doi:10.1111/j.1432-2277.2011.01275.x

51. Gianani R. β Cell regeneration in human pancreas. Semin Immunopathol (2011) 33:23–57. doi:10.1007/609281-010-0325-7

52. Bruijning JC, Winnay J, Bonner-Weir S, Taylor SJ, Accili D, Kahn CR. Development 
of a novel polygenic model of NIDDM in mice heterozygous for IR and IRS-1 null alleles. Cell (1997) 87:561–72. doi:10.1016/S0092-8674(00)80196-9

53. Klöppel G, Lühr M, Habich K, Oberholzer M, Heitz PU. Iṣlet pathology and the 
pathogenesis of type 1 and 2 diabetes mellitus revisited. Surv. Synth Pathol Res (1985) 4:110–25.

54. Rahier J, Guiot Y, Sempoux C, Henquin JC. Pancreatic β-cell 
mass in European subjects with type 2 diabetes. Diabetes Obes Metab (2008) 10(Suppl 4):32–42. doi:10.1111/j.1463-1326.2008.00699.x

55. Rieck S, Kaestner KH. Expansion of β-cell mass in response to pregnancy. 
Trends Endocrinol Metab (2010) 21:151–8. doi:10.1016/j.tem.2009.11.001

56. Lin AW, Barradas M, Stone JC, van Aelst L, Serrano M, Lowe SW. Pre-
mature senescence involving p53 and p16 is activated in response to con-
stitutive MEK/ERK mitogenic signaling. Genes Dev (1998) 12:3008–19. doi:10.1101/gad.12.19.3008

57. Zhu J, Woods D, McMahon M, Bishop JM. Senescence of human fibroblasts 
induced by oncogenic Raf. Genesis (1998) 12:997–3007. doi:10.1111/gad.12.19.2997

58. Butler AE, Hansen J, Bonner-Weir S, Rizell R, Rizza RA, Butler PC. β-cell 
deficit and increased beta-cell apoptosis in humans with type 2 diabetes. 
Diabetes (2003) 52:102–10. doi:10.23737/diabetes.52.1.102

59. Reers C, Erbel S, Elispoét I, Schmied B, Büchler MW, Nawroth PP, et al. 
Impaired islet turnover in human donor pancreas with aging. Eur J Endocrinol (2009) 160:851–91. doi:10.1530/EJE-08-0596

60. Forsyth NR, Wright WE, Shov JW. Telomerase and differentiation in multicell-
ular organisms: turn it off, turn it on, and turn it off again. Differentiation (2002) 69:188–97. doi:10.1046/j.1432-0432.2002.00411.x

61. Meier JT, Butler AE, Saisyo Y, Monchamp T, Galasso R, Bhusan A, et al. β-
cell replication is the primary mechanism subserving the postnatal expansion 
of β-cell mass in humans. Diabetes (2008) 57:1384–94. doi:10.2337/db07-1369

62. Saisyo 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) 36:111–7. doi:10.2337/dc12-0421

63. Gregg BE, Moore PC, Demozy D, Hall BA, Li M, Hussein A, et al. Formation 
of a human β-cell population within pancreatic islets is set early in life. J Clin 
Endocrinol Metab (2012) 97:3197–206. doi:10.1210/jc.2012-1296
118. Perl S, Kushner JA, Buchholz BA, Meeker AK, Stein GM, Haieh M, et al. Significant human beta-cell turnover is limited to the first three decades of life as determined by in vivo thymidine analog incorporation and radiocarbon dating. J Clin Endocrinol Metab (2010) 95:2343–9. doi:10.1210/jc.2010-0932

119. Cnop M, Hughes SJ, Igilollo-Esteve M, Hoppa MB, Sayred F, van de Laar L, et al. The long lifespan and low turnover of human islet beta cells estimated by mathematical modelling of lipofuscin accumulation. Diabetologia (2010) 53:321–30. doi:10.1007/s00125-009-1562-x

120. Cnop M, Igilollo-Esteve M, Hughes SJ, Walker JN, Cnop I, Clark A. Longevity of human islet a- and β-cells. Diabetes Obes Metab (2011) 13(Suppl 1):39–46. doi:10.1111/j.1463-1643.2011.01443.x

121. Maedler K, Schumann DM, Schultheiss F, Oberholzer J, Bosco D, Berney T, et al. Aging correlates with decreased beta-cell proliferative capacity and enhanced sensitivity to apoptosis: a potential role for Fas and pancreatic duodenal homeobox-1. Diabetes (2006) 55:2455–62. doi:10.2337/db05-1586

122. Scharffmann R. Expanding human beta cells. Diabetologia (2008) 51:692–3. doi:10.1007/s00125-007-0909-4

123. Gannon M, Ables ET, Crawford L, Lowe D, Offield MF, Magnuson MA, et al. Pdx-1 function is specifically required in embryonic beta cells to generate appropriate numbers of endocrine cell types and maintain glucose homeostasis. Dev Biol (2008) 314:606–17. doi:10.1016/j.ydbio.2007.10.038

124. Krishnamurthy J, Ramsey MR, Ligon KL, Torrice C, Koh A, Bonner-Weir S, et al. mTORC1 signaling and regulation of pancreatic β-cell mass. Cell Cycle (2012) 11:1892–902. doi:10.4161/cc.20036

125. Gahlwitz I, Kepp O, Kroemer G. TP53 and M TOR crosstalk to regulate cellular senescence. Aging (Albany NY) (2010) 2:535–7.

126. Blagosklonny MV. TOR-centric view on insulin resistance and diabetic complications: perspective for endocrinologists and gerontologists. Cell Death Dis (2013) 4:e964. doi:10.1038/cddis.2013.506

127. Dhawan S, Tschen SI, Bhushan A. Bmi-1 regulates the Ink4a/Arf locus as a potential conflict of interest. Frontiers in Endocrinology | Aging and pancreatic endocrine function September 2014 | Volume 5 | Article 138 | 8