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COMMENTARY

β-Cell senescence in the pathogenesis of type 2 diabetes

The prevalence of type 2 diabetes increases with aging. Type 2 diabetes developing in the elderly is often accompanied by a gradual impairment of β-cell function and reduced β-cell mass along with aging. However, the contribution of β-cell senescence to the pathogenesis of type 2 diabetes remains uncertain.

In a recent *Cell Metabolism* article, Aguayo-Mazzucato *et al.*[1] described their efforts to identify the signatures of senescent β-cells, and explored role(s) of senescent β-cells in type 2 diabetes.

First, the authors sorted primary β-cells isolated from 7- to 8-month-old mice based on β-galactosidase (β-gal) activity, and compared gene expressions between β-gal-positive and -negative β-cells using ribonucleic acid (RNA) sequencing analyses. The β-gal-positive cells accounted for 8–10% of the β-cell populations in these mice. Using RNA sequencing analysis, the authors observed downregulation of key hallmark β-cell identity genes, such as *Ins1*, *Mafa*, *Nkx6.1* and *Pdx1*, and upregulation of aging and senescence-related genes in β-gal-positive β-cells, as compared with β-gal-negative β-cells. Using these data, the authors generated indices for assessment of β-cell identity, aging and senescence.

The authors then examined the expressions of senescence-associated secretory phenotype (SASP) genes in β-gal-positive β-cells. They found that SASP genes, such as *TNF* and *CXCL1*, were increased in β-gal-positive β-cells, as compared with β-gal-negative β-cells. In addition, conditioned media from cultured β-gal-positive β-cells upregulated expressions of *p16Ink4a* in isolated islets, showing that senescent β-cells secrete functional SASP factors (Figure 1).

Next, the authors explored whether insulin resistance promotes β-cell senescence *in vivo*. They generated two mouse models of insulin resistance by chronically administering S961, an insulin receptor antagonist, using a mini-pump and by high-fat diet loading. In both models, β-gal-positive β-cells, as well as aging and SASP indices of β-cells, were significantly increased, indicating promotion of β-cell senescence. Therefore, these results suggest that insulin resistance is a driver of β-cell aging (Figure 1), which supports this group's previous findings that β-cell aging marker appearance is accelerated by insulin resistance[2]. Interestingly, 2 weeks after the discontinuation of S961 administration, increased aging and SASP indices of β-cells returned to normal, along with the normalization of hyperglycemia. Accordingly, β-cell senescence is reversible at least under these experimental conditions.

Based on these findings, the authors administered senolytic therapy by eliminating senescent β-cells in insulin resistance-induced and in aged INK-apoptosis through targeted activation of caspase (INK-ATTAC) mice in which administration of B/B homodimerizer leads to deletion of cells expressing p16Ink4a. In aged female INK-ATTAC mice of 15–18 months old, treatments with B/B homodimerizer improved β-cell aging and SASP indices. Glucose tolerance was unaffected by B/B homodimerizer administration in aged INK-ATTAC mice. However, glucose-stimulated insulin secretion was augmented on glucose tolerance testing. Interestingly, basal insulin levels were reduced after an overnight fast, suggesting hepatic insulin resistance to be improved by B/B homodimerizer administration. With the second model, insulin resistance was induced by chronic administration of S961 for 2 weeks in 9- to 14-month-old INK-ATTAC mice, and the effects of B/B homodimerizer were analyzed in these mice. In the second model, B/B homodimerizer administration improved not only aging and SASP indices in β-cells, but also blood glucose levels. With the third model, insulin resistance was induced by high-fat diet feeding for 12 weeks to 9-month-old INK-ATTAC mice. In this model, improvements of glucose tolerance, as well as aging and identity indices in β-cells, were observed after B/B homodimerizer administration. These results suggest the significance of β-cell senescence in glucose homeostasis (Figure 1).

Anti-apoptotic pathways are known to be upregulated in senescent cells. The authors found that the B-cell lymphoma gene 2 (BCL2) pathway, one of the anti-apoptotic pathways, is upregulated in β-gal-positive β-cells. Therefore, the authors administered β-cell senolytic therapies with ABT263, which targets the BCL2 pathway. ABT263 effectively killed β-gal-positive islet cells *in vitro*. Then, the authors administered ABT263 to 6- to 9-month-old INK-ATTAC mice in which insulin resistance had been induced by chronically administering S961. Blood glucose levels of INK-ATTAC mice treated with both S961 and ABT263 were reduced as compared with those in INK-ATTAC mice given only S961. The β-gal-positive islet cells were significantly decreased, by 25%, in INK-ATTAC mice treated with both S961 and ABT263. as compared with control INK-ATTAC mice. This decrease was accompanied by a significant decrement in the SASP index. Furthermore, the effects of ABT263 were also examined in INK-ATTAC mice in which insulin resistance had been induced by high-fat diet loading. This model yielded a significant decrease in β-gal-positive islet cells, as

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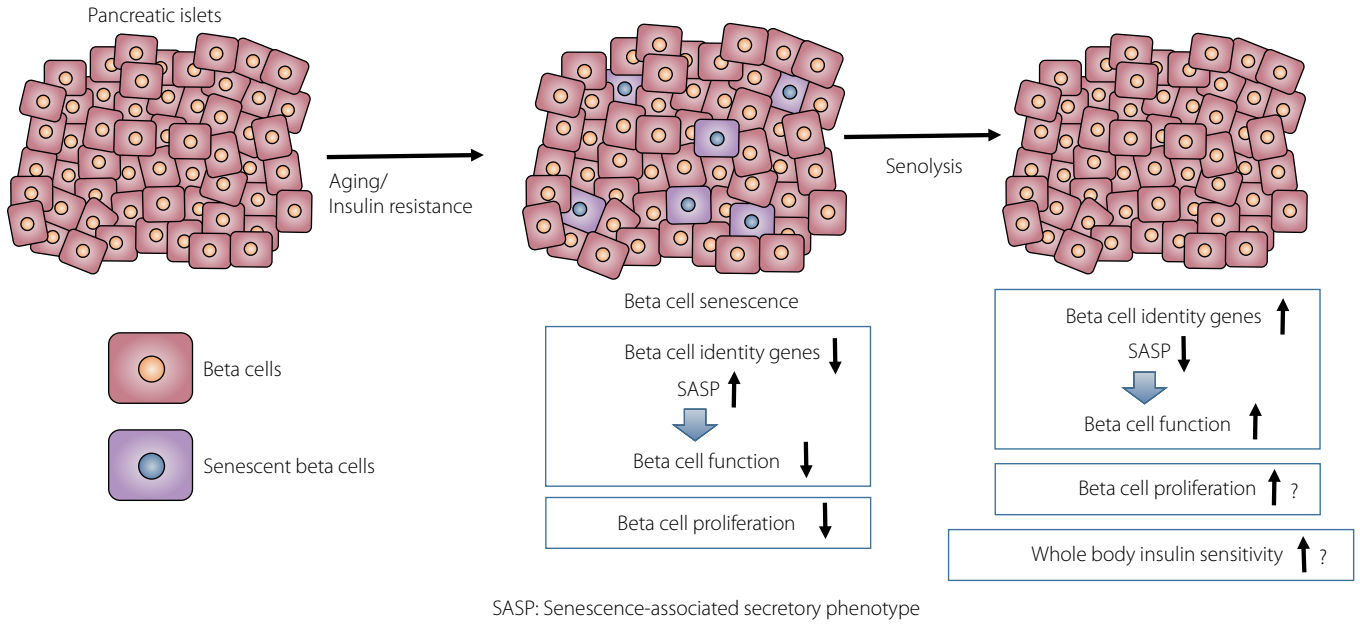

Figure 1 | Proposed mechanisms by which β-cell aging contributes to the development of type 2 diabetes. Aging and/or insulin resistance accelerated β-cell senescence, downregulating β-cell identity genes and increasing senescence-associated secretory phenotype (SASP), thereby impairing β-cell function. Adaptive β-cell proliferation also decreases, by an unknown mechanism, along with aging. β-Cell senolytic therapies improved β-cell function, likely through upregulation of β-cell identity genes and by reducing SASP. Whether β-cell senolytic therapies can restore adaptive β-cell proliferation remains to be determined.

well as aging and SASP indices, although effects on blood glucose levels were minimal. These results showed the senolytic drug to partially reverse the adverse metabolic effects induced by insulin resistance (Figure 1).

Finally, the authors explored the clinical significance of β-cell senescence in patients with type 2 diabetes. Islets isolated from donors of different ages with and without type 2 diabetes were analyzed, and the population of β-gal-positive islet cells was found to be increased in older donor-derived isolated islets. Furthermore, the population of β-gal-positive islet cells appeared to be further increased in islets from donors with type 2 diabetes. In addition, expressions of *p16Ink4a*,as well as SASP factors, such as *CCL4* and *IL6*, were significantly increased in β-gal-positive human islet cells. The authors previously identified insulin-like growth factor 1 receptor (IGF1R) as a novel senescent marker of β-cells[2]. Therefore, pancreatic sections from different aged human donors with or without type 2 diabetes were stained for IGF1R. The authors found that, in donors aged <40 years, the intensity of IGF1R was higher in specimens from donors with type 2 diabetes, suggesting early β-cell senescence in type 2 diabetes. Furthermore, staining for tumor protein p53 binding protein 1 (p53BP1), a well-known cell senescence marker, showed the intensity of p53BP1 to be increased in pancreatic islets from donors with type 2 diabetes whose body mass index values were <33. Collectively, these results raise the possibility of human β-cells being a potential target of senolytic therapies for type 2 diabetes.

Senolytic therapies improved glucose metabolism in aged mice, as well as in insulin-resistant model mice, suggesting that accelerated β-cell senescence contributes to the progression of glucose metabolism impairments induced by insulin resistance. The authors speculate that impairment of glucose metabolism might be due mainly to a decline in β-cell function. Downregulation of β-cell identity genes in senescent cells is one possible explanation for the decline in β-cell function. However, as just 8–10% of β-cells were β-gal-positive in aged mice, it is conceivable that SASP secreted from β-gal-positive cells might affect surrounding β-gal-negative β-cells in a paracrine fashion, thereby impairing insulin secretion. Another intriguing finding was that B/B treatment appeared to improve hepatic insulin resistance in aged INK-ATTAC mice. As the authors noted that B/B treatment had no significant effects on the expression of *p16Ink4a* in peripheral tissues important for glucose homeostasis, such as the liver, adipose tissues and muscles, a direct hepatic effect of B/B is unlikely. It would be interesting to explore how the reduction of senescent β-cells improves insulin resistance in the liver.

It is important to clarify the involvement of β-cell senescence in restricting β-cell proliferation in aged animals. Terminally differentiated β-cells retain proliferative potential. Self-replication of pre-existing β-cells is a primary mechanism of islet expansion during the neonatal stage or β-cell mass maintenance in adult animals. In addition, in insulin-resistant states, β-cells adaptively proliferate and secrete more insulin to meet the increased systemic demand for this

hormone, thereby maintaining glucose homeostasis at the whole-body level. Therefore, these responses appear to be an endogenous mechanism acting to prevent diabetes development. Several recent studies have shown that signals from the liver mediated through neuronal pathways[3,4] or by humoral factors[5] regulate adaptive β-cell proliferation. Proliferation of cells in aged animals is recognized as being severely impaired. Regarding β-cells as well, the proliferative capacity declines with aging in animal models. Considering the high prevalence of diabetes in the elderly, impairment of adaptive β-cell proliferation is likely to be involved in the pathogenesis of type 2 diabetes in the elderly. This assumption is based on aging often being accompanied by insulin resistance. In this regard, elucidating the mechanism of decline in adaptive β-cell proliferation in aged animals is critical for overcoming type 2 diabetes affecting the elderly. However, the importance of either intrinsic factors involving senescent β-cells or extrinsic factors in the aged systemic environment, such as the signals from other organs, for impaired adaptive β-cell proliferation has yet to be clarified. Exploring the effects of senolytic therapies on adaptive β-cell proliferation in aged mice is an attractive avenue of future research.

This novel study appears to provide evidence that β-cell senescence contributes to the pathogenesis of type 2 diabetes. The findings of this study might open a new window for developing innovative therapeutic strategies for a broad range of type 2 diabetes with insulin resistance, including that in the elderly.

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DISCLOSURE

The author declares no conflict of interest.

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