COMMENTARY

The Yin and Yang of Modulating β-Cell DNA Damage Response and Functional Mass

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Pancreatic β-cells secrete the hormone insulin, which is essential to maintain systemic glucose homeostasis. β-Cell insufficiency due to impaired function, loss of identity, and increased cell death is central to the pathogenesis of diabetes. β-Cells in adult life are postmitotic, with a limited capacity to replicate and expand, and this ability further declines with age (1–3). Cells like the adult β-cell must deploy robust strategies, such as efficient repair of DNA damage, to ensure their genomic integrity and survival throughout their lifespans. DNA damage can alter the genomic output (e.g., transcription) and trigger genomic instability, which can lead to cellular dysfunction and ultimately death. Cells possess a battery of mechanisms, collectively called the DNA damage response (DDR), that sense and repair DNA damage (4). The DDR is also intimately linked with cell cycle control, with the cell cycle checkpoints also serving as checkpoints for DNA structure (5). Although emerging evidence suggests that prolonged DDR can trigger β-cell dysfunction and death, very little is known about the molecular control of DDR in β-cells and its impact on β-cell proliferation and function.

In this issue of *Diabetes*, Peçanha et al. (6) provide insights in this area and uncover a novel mechanistic link between β-cell replication and DDR that is defective in diabetes. The authors observed that β-cells of the insulin-resistant young *db/db* mice display profound alterations in genes associated with cell cycle and DDR pathways and identified the polycomb protein Yin Yang 1 (YY1) as a shared regulator of the two aspects. Notably, they found that YY1 levels were reduced in β-cells from diabetic *db/db* mice, mice fed a high-fat diet, and human donors with type 2 diabetes (T2D). They also leveraged multiple models of β-cell–specific *Yy1* deletion to define its mechanistic role in β-cell homeostasis. The observed cell cycle arrest in the β-cells lacking YY1, along with the chromatin immunoprecipitation data presented here, firmly points to a role for YY1 in cell cycle progression and DDR to support β-cell survival (Fig. 1).

Peçanha et al. (6) also provide novel insights into the islet growth and maturation process. Along with increased DNA damage, YY1 deletion from developing as well as adult β-cells leads to loss of β-cell identity and markers of maturity. However, the extent of cell death appears to be different in the two scenarios, with YY1 ablation in developing β-cells having a more severe effect. This is consistent with the higher vulnerability of rapidly dividing β-cells (7–9). Here, the authors did not observe any change in β-cell proliferation in the neonatal (2- to 3-week-old) *Yy1* knockout (KO) mice, in contrast to a prior study that reported reduced replication in 6-week-old *Yy1* KO mice (10). This suggests temporal differences in YY1-dependent control of β-cell proliferation during the neonatal growth phase versus the adult postmitotic phase. Considering the higher cell death in the rapidly expanding neonatal β-cells, it is likely that the changes in β-cell replication are accompanied by concurrent changes in survival and DDR pathways. Chromatin immunoprecipitation for YY1 along with a comparative transcriptomic analysis of islets from stage-specific *Yy1* KO models is required to identify YY1 gene targets during β-cell maturation. This will help define the precise temporal contribution of YY1 in regulating β-cell replication, function, and survival. This is especially relevant given that several other polycomb protein genes (e.g., *Bmi1* and *Ezh2*) are downregulated in β-cells post-weaning to facilitate the transition from a highly proliferative to functionally mature state (11,12).

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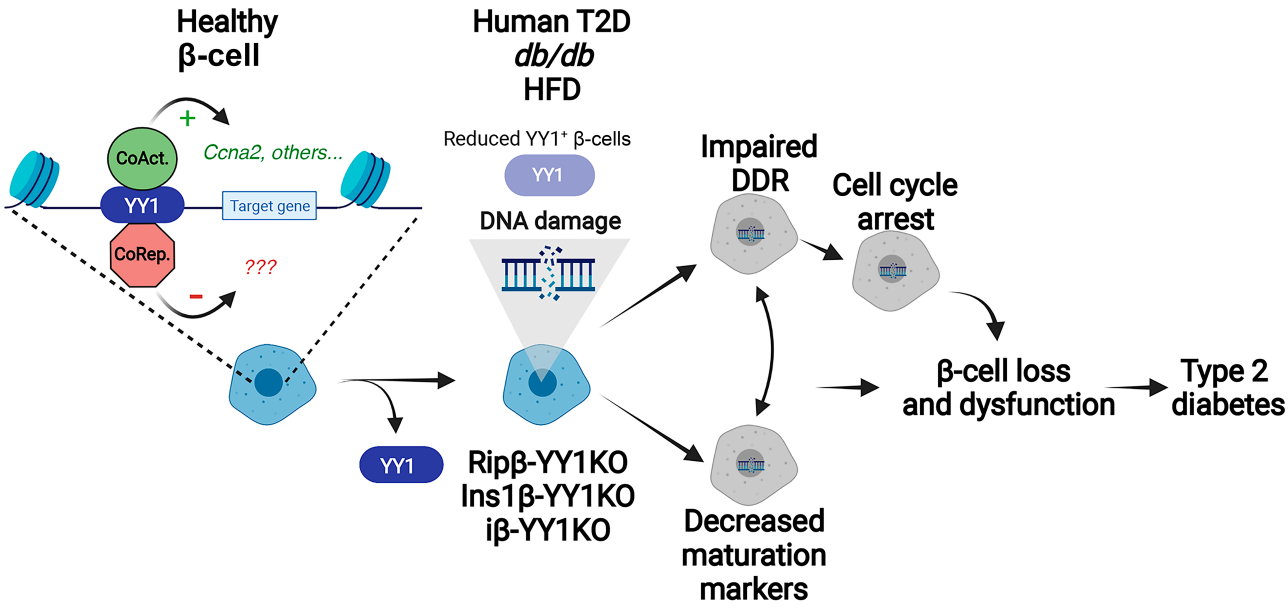

Figure 1—Regulation of β-cell maintenance by YY1. Polycomb protein YY1 binds to both hypomethylated DNA and sequence-specific elements present in enhancers and promoters of target genes to regulate transcription. Islet stress induced by overconsumption (*db/db*), high-fat diet (HFD), and T2D leads to reduced expression of numerous genes essential for islet β-cell function, including *Yy1* and its target, *Ccna2*. Targeted deletion of *Yy1* from developing or mature β-cells leads to accumulated DNA damage, cell cycle arrest, and loss of maturity markers. As a result, β-cell mass and function are diminished, and systemic glucose homeostasis is compromised. CoAct, coactivator; CoRep, corepressor. Figure created with BioRender.com.

A key finding of this study is the downregulation of YY1 under conditions of β-cell stress, such as those for the *db/db* mice and T2D donors. β-Cells undergo a transition from successful to failed functional compensation during the pathogenesis of T2D (13), accompanied by changes in transcriptional programs (14,15). Intriguingly, Peçanha et al. (6) observed reduced expression of cell cycle genes in the young *db/db* mice, which appears to be at odds with the massive β-cell expansion that occurs in these mice during the compensation phase. They propose that as β-cells accumulate DNA damage with age, DNA repair defects do not impact replication during the compensation phase but can drive cell cycle arrest and cell death in the later stages. It would be important to define the temporal changes in YY1 control during β-cell compensation and decompensation, determine whether these effects occur independently of hyperglycemia, and identify the human triggers underlying YY1 dysregulation. YY1 is an epigenetic regulator and one of the few molecules to target hypomethylated DNA (16). It is therefore likely that changes in YY1 recruitment modulate the overall chromatin state of target genes, like other polycomb proteins. For instance, the polycomb protein Eed is similarly downregulated in T2D and contributes to the epigenetic and transcriptional dysregulation in β-cell failure (17). It remains to be seen if these two proteins target similar pathways and whether polycomb dysregulation is a general hallmark of β-cell failure.

Recent work has shown that DDR is a key component of p21/p53-dependent pathologic senescence associated with β-cell failure in T2D, type 1 diabetes, and maturity-onset diabetes of the young (18–20). YY1 was previously implicated in the negative regulation of p53 in response to DNA damage and genotoxic stress (21). Future work is required to determine whether loss of YY1 induces p21/p53-dependent senescence and the concomitant senescence-associated secretory phenotype, which involves secretion of inflammatory cytokines and promotes β-cell failure (18).

In summary, Peçanha et al. (6) provide new insights into the importance of YY1 in controlling β-cell DDR to promote growth, survival, and maturation. On a larger scale, this study provides supporting evidence that early events during the development of T2D, such as impaired β-cell identity and survival, are linked to DNA damage. Efforts like these that identify the molecular mechanisms underlying DDR impairment in diabetes are essential for designing targeted approaches to combat senescence and protect β-cell mass.

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