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 insulin sufficiency 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 β-cell replication process. Using 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. In addition, 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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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, Pec¸anha 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 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, Pec¸anha 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.

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).

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