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Senescence: a double-edged sword in beta-cell health and failure?

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Cellular senescence is a complex process marked by permanent cell-cycle arrest in response to a variety of stressors, and acts as a safeguard against the proliferation of damaged cells. Senescence is not only a key process underlying aging and development of many diseases, but has also been shown to play a vital role in embryogenesis as well as tissue regeneration and repair. In context of the pancreatic beta-cells, that are essential for maintaining glucose homeostasis, replicative senescence is responsible for the age-related decline in regenerative capacity. Stress induced premature senescence is also a key early event underlying beta-cell failure in both type 1 and type 2 diabetes. Targeting senescence has therefore emerged as a promising therapeutic avenue for diabetes. However, the molecular mechanisms that mediate the induction of beta-cell senescence in response to various stressors remain unclear. Nor do we know if senescence plays any role during beta-cell growth and development. In this perspective, we discuss the significance of senescence in beta-cell homeostasis and pathology and highlight emerging directions in this area that warrant our attention.

KEYWORDS

beta cells, differentiation, maturation, proliferation, epigenetics, aging, senescence, diabetes

1 Introduction

Cellular senescence is the phenomenon of permanent cell cycle arrest (1) that occurs in response to a variety of stressors, and can serve as a protective mechanism by preventing the proliferation of stressed or damaged cells (2). Senescence plays an important role in embryonic development, tissue regeneration, and repair (3). Senescence is also a fundamental process underlying aging and the pathogenesis of many diseases, including diabetes (4). Accordingly, targeting senescence has emerged as a major therapeutic opportunity in many contexts (5). While the importance of senescence in beta-cell regenerative decline with aging and beta-cell failure in diabetes is firmly established (6–11), we know little about senescence in the context of beta-cell growth and development. As well, the molecular mechanisms that trigger and perpetuate beta-cell

senescence remain far from clear. Here, we discuss the role of senescence in beta-cell homeostasis and pathology and highlight key emerging questions.

2 The senescence phenotype – a spectrum, not a singularity

Senescence is a highly dynamic and heterogenous process, with the phenotype and function of senescent cells unique to the specific inducer and physiologic context (12) (Figure 1). Several types of senescence responses have been identified based on the inducing stimulus; these include the classical replicative senescence in response to telomere shortening, oncogene-induced senescence, mitogen-induced senescence, mitochondrial dysfunction associated senescence, and the stress and DNA damage induced premature senescence (5, 12). These stimuli trigger cell-cycle arrest via the activation of two key "tumor-suppressor" modules, namely the p53/p21 and the p16/Rb pathways. Activation of these two pathways propels a variety of the phenotypic changes associated with senescence (2–5, 12–14).

2.1 Hallmarks of senescence

Besides replicative arrest and mitogen refractoriness, senescent cells display a variety of phenotypic and molecular hallmarks (12). They often exhibit a flattened and hypertrophic morphology with enlarged nuclei, as well as altered metabolic and mitochondrial activity. Another frequent feature of senescence is lysosomal dysfunction marked by increased senescence-associated β-galactosidase activity (SA-β-gal) (13). Senescent cells also present a hypersecretory phenotype and a characteristic secretory profile consisting of pro-inflammatory cytokines, chemokines, growth factors and proteases, termed the Senescence-Associated Secretory Phenotype (SASP). SASP can attract immune cells such as macrophages, natural killer cells, and T-cells, facilitating immune surveillance and senescent cell elimination (15). Several nuclear changes, such as nuclear LaminB1 depletion and heterochromatic foci, also mark the senescent phenotype (16). Finally, senescent cells exhibit a persistent DNA damage response (DDR) and upregulation of anti-apoptotic programs (2).

2.2 Nuclear mechanisms – transcriptional and epigenetic changes

Cell-cycle arrest during senescence primarily involves the activation of either p53/p21 or p16/pRB pathways, or both. p53 and RB serve as transcriptional regulators while p21 and p16 are Cyclin-dependent kinase inhibitors (CDKIs) which mediate cell-cycle arrest (2, 17). The p53/p21 pathway is activated in response to DNA damage caused by telomere attrition, oxidative stress, or oncogenic stimuli (17, 18). A key event in p53 response is the activation of p21, which inhibits CyclinE-Cdk2 complex to mediate cell-cycle arrest. The p53 dependent phosphorylation cascade also stimulates DNA repair and is called the DNA damage response (DDR) (18). Collectively, this response delays cell-cycle until damage is repaired. The RB/p16 pathway, on the other hand, is appropriated not only for oncogene induced senescence, but also during the age-dependent replicative senescence. p16 and p14, both encoded by the *Ink4a/Arf* locus, constitute the cell-cycle inhibitor

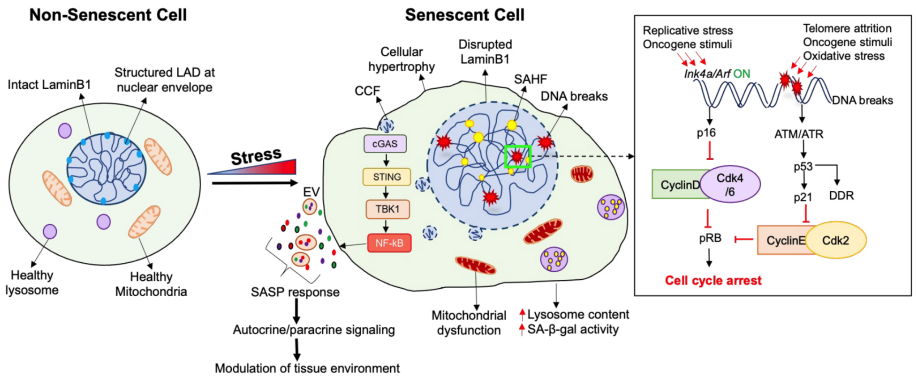

FIGURE 1
Characteristics of a senescent cell. Senescence, which is a state of irreversible cell cycle arrest, is induced by a variety of stress conditions, resulting in several cellular and morphological changes. Cell cycle arrest in senescence is achieved through the activation of the p16/pRb and/or the p21/p53 pathways, depending upon the type of stress. Apart from cell cycle arrest, the senescent phenotype is heterogenous and may display a combination of morphological features. Overall, a senescent cell (right) exhibits a flattened and hypertrophic morphology compared to a non-senescent cell (left). The structure and function of several organelles is also altered during senescence, such as dysfunctional mitochondria with increased production of Reactive Oxygen Species (ROS), and increased lysosomal number and size along with the induction of a lysosomal senescence associated β-galactosidase (SA-β-gal). In contrast to the intact LaminB1 and structured Lamin Associated-Domains (LADs) in the nucleus of a non-senescent cell, a senescent cell displays an enlarged nucleus with disrupted LaminB1, formation of senescence-associated heterochromatin foci (SAHF), increased DNA breaks, and an elevated DNA damage response (DDR). Senescence can also involve the formation of cytoplasmic chromatin fragments (CCFs) that translocate from the nucleus to the cytosol, and activate the cytosolic DNA sensor cGAS-STING-TBK pathway which further activates the pro-inflammatory senescence associated secretory phenotype (SASP). The SASP response involves direct or extracellular-vesicle (EV) mediated secretion of extracellular matrix modulators, growth factors, cytokines, chemokines, to modulate the tissue micro-environment through autocrine/paracrine signaling.

components of the RB/p16 pathway (17, 19). p16 blocks the formation of the cyclinD-CDK4/6 complexes to prevent RB phosphorylation and promote cell-cycle arrest, while p14 establishes a cross-talk between the p53 and pRB pathways by stabilizing p53 (17).

The transcriptional reprogramming in senescence is assisted by a variety of underlying epigenetic changes. The initial epigenetic changes mediate cell-cycle arrest and establish a pro-survival response to cope with irreparable damage, while the subsequent epigenetic alterations facilitate the pro-inflammatory SASP to modify inter-cellular communication (2). Chromatin changes in senescence involve reduced expression of certain histones and the incorporation of non-canonical histones such as macroH2A. Senescent cells often display a loss of the DNA-nuclear lamina interactions (20). Specifically, the loss of LaminB1 at the Lamina Associated Domains (LADs) leads to heterochromatin redistribution and the formation of senescence-associated heterochromatin foci (SAHF) to facilitate the silencing of proliferation related genes (16).

2.3 Cytoplasmic and extracellular responses

DNA damage and genomic instability not only induce changes in gene expression and cell fate, but also trigger an inflammatory response by releasing cytoplasmic chromatin fragments (CCFs) (21). The CCFs are recognized by the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS), which generates cytosolic GMP-AMP (22). This, in turn, activates the stimulator of interferon genes (STING) and TANK-binding kinase 1 kinase (TBK1), leading to NF-kB activation and the production of inflammatory cytokines and type 1 interferons (23). The CCF-cGAS-STING pathway couples DNA damage sensing to the innate immune response to promote the SASP response (24). SASP modulates the tissue microenvironment and enforces senescence through autocrine and paracrine signaling. The contents of SASP vary based on the cellular context and stress signal (25). This can involve the release of extracellular-vesicles (EVs) which contain nucleic acids such as CCFs along with the pro-inflammatory proteins, to produce long-range effects which can impact distant tissues (26).

2.4 Senescence *versus* cell-death – a cell-fate choice

Cells can respond to high levels of stress by triggering senescence or cell-death depending on the specific stressor and cell type, often by repurposing the same pathways (27). Both p53/p21 and Rb/p16 pathways serve pleiotropic roles in this context, and the level and duration of their induction can determine the cell fate choice between apoptosis and senescence. Low levels of p16 induce transient cell-cycle arrest, while high levels trigger senescence (28, 29). Similarly, low levels of p53 promote cell-cycle arrest and senescence, while chronically high p53 levels block pro-senescence signals and promote a pro-apoptotic transcriptional response (30, 31). In contrast to apoptosis, senescence offers cellular viability and paracrine communication to neighboring cells through SASP and thus facilitates adaptation to stress (28).

3 Senescence in pancreatic beta-cells – in health and disease

Senescence has traditionally been defined as a permanent loss of replicative capacity and therefore studied predominantly in replication-competent cells. However, senescence is also a multifaceted stress and damage response that initiates as an adaptive process and can turn maladaptive upon prolonged stress (3, 32). Activation of many facets of senescence has been reported in a variety of postmitotic cells including beta-cells (6, 9–11, 33–36), suggesting that senescence in such cells begins as a stress-response (36, 37), temporally separated from permanent replicative arrest. Terminally differentiated cells can enter a senescence-like state from the quiescent G_0 phase in response to DNA damage or telomere attrition, a phenomenon termed postmitotic cellular senescence (PoMiCS) or 'amitosenescence' (34, 38). In some instances, unscheduled re-entry of postmitotic cells into cell-cycle in the context of stress may cause abnormal DNA content and DDR, triggering a senescence like-response labeled as "pseudo-mitosenescence" (38).

3.1 Beta-cell senescence – distinct from quiescence

Pancreatic beta-cells transition from a wave of replication dependent expansion in the neonatal growth phase to a functionally mature, postmitotic state in postnatal life marked by a form of cell-cycle exit termed "quiescence". Quiescence is different from senescence; while quiescence occurs in the G0 phase of cell-cycle, senescence primarily occurs in the G1 and sometimes the G2 phases (12, 39, 40). Furthermore, quiescent cells retain the capacity to re-enter cell-cycle in response to mitogens, unlike senescent cells. The quiescent, postmitotic nature of beta-cells presents a unique scenario in response to stress; it demands robust stress- and pro survival-responses to protect existing cells, while the ability to re-enter cell-cycle offers a way to regenerate beta-cell mass through replication. These two potential responses can create a conflicting choice for beta-cells; to either attempt replication under conditions of stress or activate pro-survival stress-responses. Depending on the severity and duration of the stressor, this may foster successful adaptation, trigger senescence, or induce apoptosis in the most extreme case (3, 32). Table 1 provides a summary of the unique markers of beta-cell senescence in various contexts.

3.2 Replicative senescence in beta-cells – implications for function and regeneration

Adult beta-cells can expand by replication to adapt to increased insulin demand due to injury or insulin resistance. However, their expansion capacity declines with age due to replicative senescence

accompanied by the epigenetically controlled, gradual accumulation of p16 (6–8, 42, 43). In young beta-cells, Polycomb proteins Ezh2 and Bmi1 repress the *p16* locus. The levels of Ezh2 gradually decline with aging, resulting in reduced binding of both polycomb proteins and concomitant reduction of repressive chromatin modifications (7, 8). This is accompanied by an age-related increase in binding of the Trithorax complex containing Mll1 and JmjD3 which mark the chromatin with activating histone modifications, leading to p16 accumulation (44). The epigenetic control of p16 is driven by age-related changes in growth-factor signaling pathways (45). Platelet-derived Growth Factor (PDGF) signaling, which is essential for Ezh2 expression, declines with aging (46). On the other hand, age-related increase in Transforming Growth Factor-beta (TGFb) signaling promote Trithorax complex recruitment to the *Ink4a/Arf* locus, thus contributing to the onset of replicative senescence (47) (Figure 2A).

The induction of p16 in adult beta-cells is first observed around 2.5 months of age in mice (8), and appears to occur as a part of their normal functional maturation (48). In agreement, ectopic expression of p16 in beta-cells of juvenile mice not only induces replicative senescence but also enhances GSIS (48). This agrees with data in murine islets showing the epigenetic activation of transcriptional programs underlying insulin secretion with age, while the genes related to beta-cell replication are epigenetically repressed (49). In contrast, plenty of evidence suggests that basal insulin secretion increases with aging, accompanied by either unaltered or increased stimulated insulin secretion (50). It is possible that p16 represents only a part of the replicative senescence program, and other mechanisms are maybe involved in the age-related changes in glucose responsiveness and insulin secretion. The presence of p16 in beta-cells of young mice points to that (8, 48), and suggests that p16 expression alone may not indicate replicative senescence. Alternatively, the levels and duration of p16 expression may account for these age-related differences in beta-cell phenotype. In agreement, many key hallmarks of senescence, such as SA-β-gal only appear in islets of really old mice (51). Furthermore, a transcriptomic comparison of SA-β-gal+ and SA-β-gal- beta-cells showed impaired glucose-sensing machinery in the senescent cells (11). Replicative senescence prevents the replication of cells that have accumulated damage with age, while the concomitant hypersecretory phenotype could allow beta-cells to compensate for an acute and modest increased insulin demand. However, this may not suffice for chronically high insulin requirement and can cause impaired glucose homeostasis, as has been observed in old mice in many contexts that warrant beta-cell expansion (42, 43, 52).

3.3 Stress-induced senescence in beta-cells – relevance for diabetes

Beta-cell fragility is a shared underlying feature of both type 1- and type 2- diabetes (T1D and T2D), with the activation of unfolded protein response (UPR) and DDR preceding beta-cell failure (53–57). In addition, the immune-mediated islet inflammation is a well-established stress trigger in T1D and is now also recognized to contribute to beta-cell failure in T2D (58, 59). One of the key sequalae of beta-cell stress in both T1D and T2D is the activation of premature senescence involving both p16 and p21, DDR, and SASP, along with the induction of Bcl-2 as a pro-survival mechanism (9, 11). The beta-cell SASP secretome in diabetes not only harbors inflammatory cytokines and chemokines, but also includes extracellular matrix modulators such as Mmp2, Serpine1, Igfbp3, and FilaminB (9). The SASP response displays non-cell-autonomous activities, such as paracrine senescence and promoting the chemotaxis of immune cells (60, 61).

Besides the immune and metabolic factors as triggers for beta-cell stress (57, 62, 63), the contribution of beta-cell intrinsic changes is becoming increasingly evident (64). For instance, genetic vulnerability due to mutations in DNA repair genes can trigger beta-cell failure independent of immune defects (53). Beta-cells can accumulate oxidative-stress induced DNA damage and somatic mutations, which could predispose to senescence (65). More recently, a missense mutation in the beta-cell transcription factor MafA associated with a form of maturity onset diabetes of the young (MODY) was shown to induce premature senescence and SASP (10). These data reiterate the involvement of beta-cell intrinsic triggers for SASP in diabetes. Given the role of MafA in mature beta-cell identity, this also suggests a link between impaired beta-cell identity and senescence. In agreement, beta-cells harboring SASP signatures in T1D display reduced levels of the maturity marker Ucn3 (9). Similarly, senescent beta-cells in the context of insulin resistance display a loss of the mature beta-cell identity (11). Thus, beta-cell intrinsic factors such as loss of mature identity and impaired stress-response may be critical in initiating senescence.

Whether a beta-cell adapts or fails in response to stress depends on the severity and duration of the stressor, as well as its intrinsic capacity to handle stress (Figure 2B). Different beta-cell subtypes display differential stress-responsiveness and predisposition to senescence (11, 51, 66–68). Stress-induced changes in beta-cell identity and heterogeneity (69–73) can therefore impair the collective stress responsiveness of the beta-cell pool and induce senescence. Indeed, increased UPR and DDR precede senescence and have an additive effect towards inducing senescence (74–76). UPR initiates as an adaptive response and allows cells to cope with a high demand for protein synthesis and processing, while DDR protects against genomic instability due to replication stress and oxidative stress (77, 78). The link between UPR, DDR, and senescence is especially relevant for beta-cells that produce and process a large amount of protein load, rely on replication for adaptive expansion, and are highly susceptible to oxidative damage (79–81) (Figure 2C). While the initial induction of these stress-sensing adaptive mechanisms in response to stress facilitates cellular repair and adaptation, persistent activation of these mechanisms leads to tissue maladaptation, senescence, and even death (53–57). Recent data show that p21 is a temporal stress-sensor that shapes the cellular response by placing cells under immunosurveillance, which either disengages or eliminates damaged cells depending on the duration of p21 persistence (82). This suggests that the duration of such responses can dictate whether cells undergo repair, become senescent, or undergo cell death, effectively determining the choice between adaptation vs maladaptation.

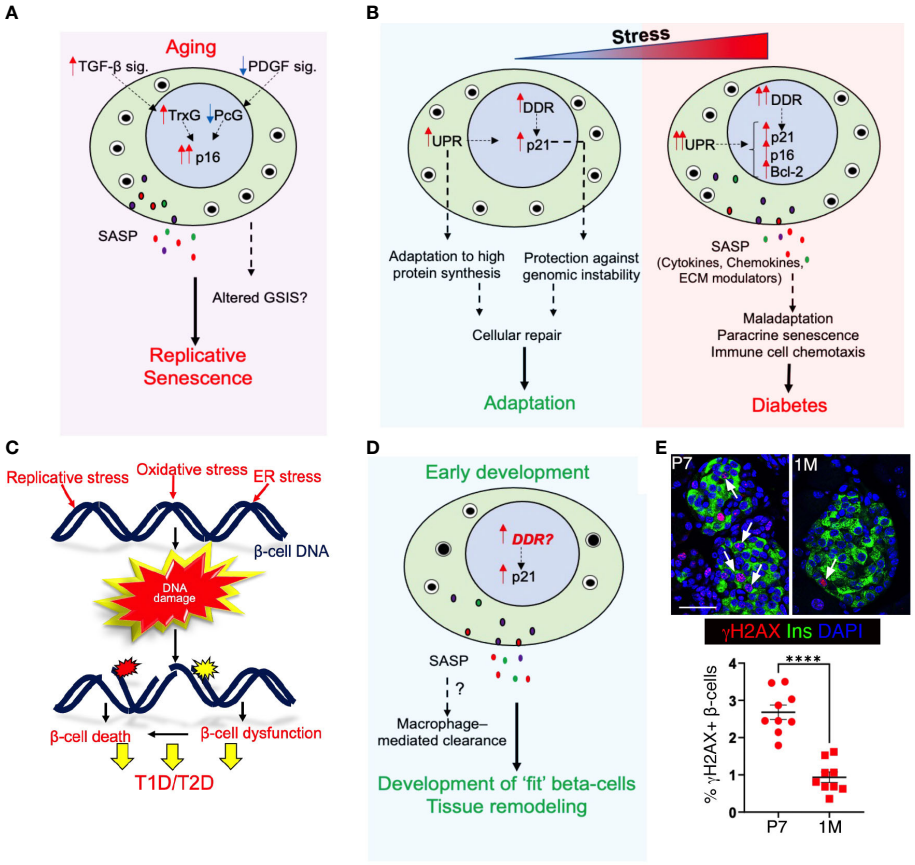

FIGURE 2
Senescence in pancreatic beta-cell health and disease: **(A)** Aging induces p16 accumulation and leads to replicative senescence, which limits beta-cell self-renewal. Age associated transcriptional changes may also alter basal insulin secretion without any accompanying changes in glucose stimulated insulin secretion (GSIS). With aging, reduced Platelet Derived Growth Factor signaling (PDGF sig.) and increased Transforming Growth Factor-beta signaling (TGFb sig.) leads to alleviation of Polycomb (PcG)- mediated repression of p16 locus and drives Trithorax (TrxG)-mediated activation of p16 locus. **(B)** The duration or intensity of exposure to cellular-stress stimuli dictates the beta-cell response; either facilitating adaptation or causing maladaptation. Exposure to transient stress initiates DDR and unfolded protein response (UPR) and facilitates cellular repair and adaptation. However, prolonged stress exposure aggravates both DDR and UPR and induces SASP, leading to premature senescence. This can cause beta-cell dysfunction and maladaptation, and pre-dispose to diabetes. **(C)** Both intrinsic and extrinsic stress stimuli can induce DNA damage in beta-cells through a myriad of triggers such as replicative stress, ROS, and ER-stress, and result in beta-cell dysfunction and/or death. **(D)** We propose that unresolved DNA damage in the developing postnatal pancreas may trigger a p21 response and SASP to mediate the macrophage-mediated clearance of damaged beta-cells during this phase, allowing only health and fit beta-cells to mature. Our data shown in **(E)** imply that indeed the early postnatal beta-cell expansion phase is vulnerable to DNA damage accumulation. Top panel shows representative images of wild-type mouse pancreatic sections at postnatal day 7 (p7) and I month (1m), immuno-stained for the DNA damage marker γH2AX (red) along with Insulin (green) and DAPI (blue), while the lower panel show a quantification of % γH2AX+ beta-cells in the two stages, pointing to high DNA damage vulnerability in early postnatal beta-cells. Error-bars show SEM. ****$P<0.001$, determined by using a two-tailed Student's t-test . Scale bar: 50 mm.

3.4 Senescence in beta-cell development – making "fit" beta-cells

Senescence is also known to occur during embryonic development and is essential for growth and patterning. Such developmentally programmed senescence relies on p21 activation and SASP, which induces macrophage mediated clearance of senescent cells and contributes to tissue remodeling (83–86). Macrophage infiltration is observed in both mice and humans during pancreas development (87–90), and regulates pancreatic progenitor migration, cell cycle progression, and beta-cell expansion (91, 92). Macrophages likely also assist the clearance of damaged cells that may accumulate due to the extensive cell turnover during pancreas development (93–96). While prior work on developmental senescence showed that p21 induction did not involve DNA damage and p53 activation (85, 86), the scenario in the maturing pancreas might be different (Figure 2D). High rates of beta-cell replication during postnatal growth appear to increase vulnerability to DNA damage (Figure 2E). Beta-cells with extensive DNA damage could then initiate a SASP response towards their clearance by macrophages, allowing only "fit" beta-cells to mature and establish a healthy beta-cell pool. Alternatively, as a recent lineage tracing study suggests, some senescent cells may resolve senescence to re-enter cell-cycle during development, and progress to maturation (97, 98). Impaired clearance or aberrant cell-cycle entry of damaged beta-cells during development due to any genetic or epigenetic causes could therefore predispose to impaired beta-cell mass and future disease vulnerability (99). Indeed, peak incidence of the development of islet autoimmunity in T1D occurs during the

TABLE 1 Features of beta-cell senescence in different contexts, highlighting the SASP markers unique to beta-cells in each context. M indicated data from mouse models, while Hu indicates data from human samples.

	T1D	T2D/IR	MODY	Aging
Cell cycle inhibitors	Cdkn1a, Cdkn2a (M) CDKN1A, CDKN2A (Hu)	Cdkn1a, Cdkn2a (M) *CDKN2A (Hu)*	Cdkn1a (M)	Cdkn1a, Cdkn2a (M)
Unique SASP markers (mRNA/protein)	IL-6, Igfbp3, Serpine1, Mmp2, Flnb (M) IL-6, SERPINE1 (Hu)	*Gstp1, Gdf15, Hsp90aa1 (M)* *CCL4, IL6 (Hu)*	Serpine 1, Cxcl1, Cxcl2, Il6, Tnf (M)	Il6, Tnf and Cxcl1 (M) *Dusp3, Gdf15, Ing1, and Kpnb1 (M)*
DDR	γ-H2Ax (M)	53BP1 (Hu)	γ-H2Ax, 53BP1(M)	53BP1 (M)
Loss of mature beta cell identity	Yes (M)	Yes (M)	Yes (M)	Yes (M)
SA β-gal positivity	Yes (M)	ND	Yes (M)	Yes (M)
Antiapoptotic phenotype	Yes (M)	Yes (Hu)	Yes (M)	Yes (M)
Other features	N/A	*IGF1R* activation	Sex-linked effect of the MODY MAFA S64F mutation, observed in males, Loss of nuclear LaminB1	Sensitive to Cdkn2a targeting
References	(9)	(11, 41)	(10)	(11, 41)

IR, insulin resistance; T2D, Type 2 Diabetes; T1D, Type 1 Diabetes.

growth phase (100–102). Recent evidence shows that maternal diabetes induces premature senescence in the neuroepithelium, leading to neural tube defects (103). Similar events may occur during beta-cell differentiation and result in impaired beta-cell mass. Investigating senescence during islet morphogenesis is therefore important to identify the triggering events underlying beta-cell pathologies.

3.5 Targeting senescence – beta cell therapies

Administration of senolytic agents has been shown to improve glucose homeostasis in mouse models T2D and T1D (9, 11, 104, 105). Inhibitors of the pro-survival Bcl2, such as ABT-199 or ABT-737, can induce apoptosis of senescent beta-cells in the prediabetic Non-obese diabetic (NOD) mice, and reduce the expression of SASP markers *in vivo* (9). Similarly, Bcl2 targeting using ABT-263 has also been shown to partially restore beta-cell mature phenotype and reverse metabolic defects in both acute and chronic insulin resistance (11). The bromodomain extra-terminal (BET) domain proteins, key inducers of SASP in T1D, are another emerging target whose inhibition using iBET-762 prevents SASP and autoimmune diabetes in the NOD mice (104). Transcriptomic profiling of senescent beta-cells in the context of insulin resistance shows potential of targeting the HIF1a pathway using desatinib and quercetin (D+Q) (11), a senolytic strategy that is in phase-I trials for other diseases (106). While senolytics are highly promising, they may have off-target effects (107). Moreover, the heterogeneous frequency of senescent beta-cells in pre-diabetes precludes the identification of patients who would benefit the most from senolytics (9). Development of beta-cell targeting approaches and serum biomarkers for SASP would facilitate the optimization of senolytics for clinical translation.

4 Summary and emerging directions

Beta-cells undergo profound phenotypic changes in diabetes, recapitulating several features of the functionally immature fetal and neonatal beta-cells. These changes likely initiate as an adaptation to stress, to protect cells from damage and promote repair and regeneration. With chronic stress, attempted regeneration and increased functional workload can aggravate genotoxic and proteotoxic stress, and result in senescence and maladaptation. Moreover, any defects in stress-response during beta-cell growth in early life can set the stage for future beta-cell failure. Therefore, it is essential to identify mechanisms that define the mature beta-cell phenotype, protect beta-cell genomic stability, and are altered in response to genotoxic and metabolic stress as beta-cells adapt or fail. These may include critical growth signals and epigenetic mechanisms that program the mature beta-cell transcriptional landscape. Stress-responsive modulators of chromatin 3D architecture such as the cohesin complex and the CCCTC binding factor (CTCF) that are essential for genomic stability and transcriptional control may be suitable candidates for such studies (108–111). Another critical question is the link between senescence and the islet-immune interaction during development and diabetes. It would also be pertinent to compare the beta-cell SASP in aging, T1D, and T2D to determine its context specificity. Understanding the mechanisms that safeguard beta-cell genomic stability and stress-response and their impact on replicative and stress-induced senescence programs will be key to identifying the molecular triggers of beta-cell failure in diabetes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by Institutional Animal Care and Use Committee (IACUC) at City of Hope.

Author contributions

Both SV and SD contributed to the conception of the article layout, critical review of the literature, preparation and editing of the manuscript contents, and approving the final version for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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