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Early senescence of pancreatic β cells induced by unfolded protein response deficiency prevents type 1 diabetes

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Type 1 diabetes (T1D) is a T lymphocyte-mediated autoimmune disease caused by pancreatic β-cell destruction, which eventually leads to reduced insulin level and increased blood glucose level (Syed, 2022). As a multifactorial disease, T1D is characterized by a genetic predisposition associated with various environmental and cellular elements (Syed, 2022). Pancreatic β cells have long been considered the "innocent victims" in T1D pathogenesis since the pancreas is attacked by the immune cells, resulting in a process known as insulitis, in which the immune cells infiltrate pancreatic islets and secrete pro-inflammatory cytokines. However, growing evidence suggests that various β-cell stresses, dysfunction, and death contribute to T1D pathogenesis, as it has been observed that β-cell dysfunction in autoantibody-positive (Aab^+) individuals exists long before T1D diagnosis (Evans-Molina et al., 2018).

The endoplasmic reticulum (ER) is an important organelle, which is responsible for protein synthesis, folding, and processing, as well as preserving cellular Ca^{2+}. Because of the high demand for insulin secretion, pancreatic β cells undergo physiological ER stress. The imbalance between the high demand for numerous proteins and the capacity to fold these proteins causes ER stress, leading to activation of the unfolded protein response (UPR) through three sensors: inositol-requiring enzyme 1α (IRE1α), activating transcription factor 6 (ATF6), and protein kinase RNA-like ER kinase (PERK) (Makam et al., 2022). Under normal physiological conditions, activation of the UPR alleviates ER stress and preserves β-cell survival and function. However, under pathological conditions, the UPR cannot cope with the persistent or severe ER stress created by T1D, leading to β-cell dysfunction and eventually death. It is well known that environmental factors that damage β cells, including viral infections, oxidative stress, and chemicals exposure, trigger ER stress, and thus they are regarded as key culprits in T1D (Makam et al., 2022). The association between ER stress and the development of T1D was established based on the discovery that markers of ER stress increased in β cells of T1D compared with β cells in healthy controls (Makam et al., 2022). This observation highlights the crucial role of ER stress in the progression of T1D. Morita et al. (2017) demonstrated that both Imatinib (an anti-cancer tyrosine kinase inhibitor) and kinase-inhibitory RNase attenuators (KIRAs) blunted IRE1α activity, reduced β-cell apoptosis, and efficaciously reversed T1D in non-obese diabetic (NOD) mice. Also, Engin et al. (2013) found that T1D incidence was markedly reduced by mitigating β-cell ER stress with tauroursodeoxycholic acid

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(TUDCA), which suggests a direct association between a defective β-cell UPR and T1D.

To explore the role of UPR sensors in T1D, Lee et al. (2020) constructed β-cell-specific IRE1α-knockout mice on an NOD background. Intriguingly, they found that IRE1α deletion induced short-term β-cell dedifferentiation, significantly attenuated immune cell attack and β-cell apoptosis, and therefore prevented diabetes in NOD mice. This is in line with responses to inflammatory stress in NOD mice (Rui et al., 2017) and oxidative stress in human β cells (Leenders et al., 2021), as evidenced by partial loss of β-cell identity. Namely, IRE1α deficiency-induced dedifferentiation could be regarded as an adaptive mechanism for β cells to escape from immune-mediated destruction and minimize damage.

To further investigate the mechanisms of UPR deficiency that affect β-cell survival, Lee et al. (2023) strikingly established an association between β-cell UPR and cellular senescence. They demonstrated that specific deletion of ATF6 in β cells of NOD mice markedly preserved β-cell function and decreased diabetes incidence. Using RNA sequencing (RNA-seq) and single-cell RNA-seq (scRNA-seq) analyses, they observed that several markers of the p53/p21 pathway were significantly upregulated in β cells of both ATF6$^{\beta-/-}$ and IRE1α$^{\beta-/-}$ mice, indicating alterations in the senescence program. To further elucidate the role of early senescence marker p21, they found that p21 inhibition with UC2288 (a p21 chemical inhibitor) markedly upregulated the cleaved caspase-3 level in control and ATF6$^{\beta-/-}$ islets. Genetic inhibition of p21 in adeno-associated virus serotype 8 (AAV8)-mediated *p21*-knockdown mice also resulted in an increased incidence of diabetes in the IRE1α$^{\beta-/-}$ mouse model, supporting the idea that p21 is important for β-cell survival and diabetes prevention (Lee et al., 2023). In addition, compared with control animals, numerous genes involved in antioxidant and anti-inflammatory responses and DNA damage response (DDR) in β cells of both ATF6$^{\beta-/-}$ and IRE1α$^{\beta-/-}$ mice were markedly upregulated (Lee et al., 2023). Sturmlechner et al. (2021) demonstrated that p21 initiated a unique bioactive secretome in early senescent cells, termed p21-activated secretory phenotype (PASP), which promptly attracted macrophages. Lee et al. (2023) consistently detected significantly increased levels of PASP markers, along with an increased p21 level, in compromised UPR cells. Subsequently, immunofluorescence (IF) staining demonstrated an increased number of M2 macrophages in ATF6$^{\beta-/-}$ and IRE1α$^{\beta-/-}$ islets induced by PASP. Furthermore, inhibition of p21 markedly diminished infiltration of M2 macrophage to the islets of knockout mice, supporting the notion that p21 induces islet M2 macrophage recruitment in UPR-deficient models.

Previously, Shan et al. (2017) observed that IRE1α ablation promoted M2 polarization in a cell-autonomous manner to enhance the thermogenic activity of both brown and beige adipose tissues, thus increasing the energy expenditure of floxed IRE1α (*Ern1*$^{f/f}$) lysozyme 2 (*Lyz2*)-Cre mice. Because of their anti-inflammatory effects, immunomodulatory M2 macrophages were reported to be sufficient to promote β-cell survival and stop ongoing autoimmune T1D (Parsa et al., 2012). In line with this, M2 macrophages promote immune surveillance and dramatically remove terminal/late senesced β cells, as evidenced by decreased senescence-associated β-galactosidase (SA-β-gal) activity and reduced cell size, resulting in alleviation of islet inflammation and protection against T1D in NOD mice (Lee et al., 2023) (Fig. 1). Notably, an early senescence signature, including signals of the p53/p21 pathway, as well as PASP and DDR was also present in residual β cells of T1D donors (Lee et al., 2023), indicating that this adaptive response might contribute to human β cells escaping from autoimmune attack.

Growing evidence suggests that serious ER stress and hyperactivated UPR are associated with pancreatic β-cell failure in T1D (Makam et al., 2022). Thus, β-cell-specific deficiency of ATF6 or IRE1α is a cytoprotective mechanism to relieve ER stress and prevent β-cell death in NOD mice. In addition to ER stress, pancreatic β cells are highly fragile and vulnerable to different stress signals, including severe oxidative stress and inflammatory stress, which contributes to β-cell loss during the progression of T1D. In this project, β-cell-specific deletion of ATF6 induced a remarkable increase in expression of antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2). As a key modulator, Nrf2 tightly modulates a series of antioxidant or anti-inflammatory genes, including glutathione peroxidase 3 (*Gpx3*), glutathione *S*-transferase P1 (*Gstp1*), heme-oxygenase 1 (*Hmox1*), thioredoxin reductase 1 (*Txnrd1*), glutathione *S*-transferase Mu 2 (*Gstm2*), and glutamate-cysteine ligase catalytic subunit (*Gclc*), in β cells of ATF6$^{\beta-/-}$

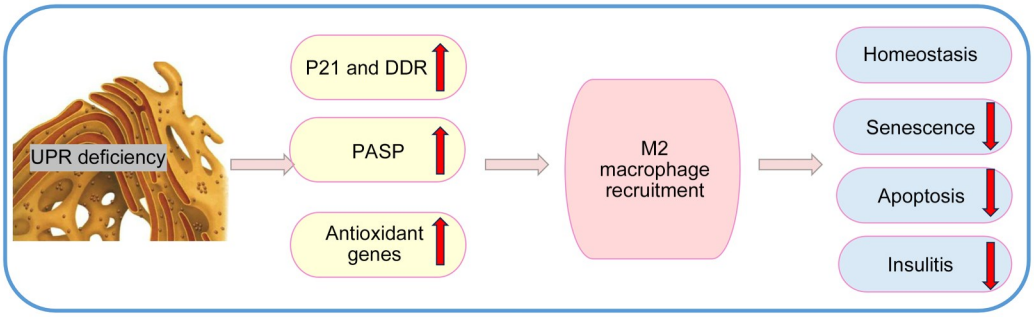

Fig. 1 Preventive role of UPR deficiency-induced β cell early senescence against type 1 diabetes. Pancreatic β-cell-specific deletion of UPR sensors (ATF6 and IRE1α) in NOD mice prior to insulitis triggers early senescence and initiates a unique and transient PASP, which induces M2 macrophage recruitment to the islets. Subsequently, M2 macrophages initiate immune surveillance and the clearance of late senesced β cells, resulting in restoration of tissue homeostasis and reduction of insulitis. UPR: unfolded protein response; ATF6: activating transcription factor 6; IRE1α: inositol-requiring enzyme 1α; NOD: non-obese diabetic; PASP: p21-activated secretory phenotype; DDR: DNA damage response.

mice, which is beneficial for releasing stress and re-establishing tissue homeostasis (Lee et al., 2023).

Cellular senescence is regarded as an intricate cytoprotective response to diverse stressors, and is involved in a wide range of physiological activities (Paramos-de-Carvalho et al., 2021). Senescent cells are much more than what they were initially considered—just undead cells. They acquire numerous phenotypic changes and are often coupled to a complex senescence-associated secretory phenotype (SASP) secretion to modify the surrounding microenvironment (Paramos-de-Carvalho et al., 2021). The SASP plays an important role in tissue repair, inflammation, immune modulation, differentiation, and plasticity, depending on time duration and specific senescence contexts. Normally, a transient SASP response is beneficial and has anti-inflammatory effects that favor immune-mediated clearance of senescent cells, while a persistent SASP is deleterious and has pro-inflammatory effects on the microenvironment. Permanent accumulation of senescent cells results in chronic inflammation, tissue dysfunction, and various diseases (Paramos-de-Carvalho et al., 2021). Thompson et al. (2019) previously demonstrated that clearance of late senescent β cells reduces immune-mediated destruction, preserves β-cell mass, and prevents progression of T1D. Consistent with this result, Lee et al. (2023) found that compromised UPR in the early stage of T1D drives an acute early senescence program and a short-term SASP, which triggers immune-mediated elimination of the terminal senescent cells in order to prevent permanent accumulation of senescence-induced signals. They were the first to establish an association between ER stress and cellular senescence, providing a hot target in terms of therapeutic approaches for T1D. However, further investigation on how M2 macrophages eliminate late senescent cells will be necessary to reveal the mechanisms by which senescent cells escape from immune clearance. From a therapeutic perspective, it is critical to accurately detect and target different types of senescent cells and SASP in vivo, guiding their translation into clinical interventions.

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Author contributions

Yufei WANG and Min ZHANG provided the theme and design, and edited the manuscript. Haipeng CHENG wrote and edited the manuscript. Zhenwang ZHAO and Dan LIU participated in searching and summarizing the relevant literature as well as editing the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Haipeng CHENG, Zhenwang ZHAO, Dan LIU, Yufei WANG, and Min ZHANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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