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Transcription factor ATF4 maintains pancreatic β -cell identity during ER stress

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Activating transcription factor 4 (ATF4) is a regulator of the unfolded protein response and integrated stress response (ISR), which are known as adaptive mechanisms to endoplasmic reticulum (ER) stress. Previous reports demonstrated that dysregulation of the ISR showed development of severe diabetes. However, the roles of ATF4 in pancreatic β -cells remain unclear. First, we investigated the therapeutic effect of ISR enhancer Sephin1 on an animal model of diabetes using Akita mice. Sephin1 improved glucose metabolism and increased ATF4 expression in Akita mice. Next, we established β -cell-specific ATF4 knockout (β *Atf4*-KO) mice, which were then crossed with Akita mice. Akita/ β *Atf4*-KO mice showed hyperglycemia and diabetic death caused by ketoacidosis. Interestingly, numbers of α -, δ -, and PP-cells were increased in the islets of Akita/ β *Atf4*-KO mice, suggesting that ATF4-deleted β -cells are more vulnerable to dedifferentiation under ER stress condition. Finally, we identified ATOH8 as a downstream factor of ATF4, and showed that the downregulation of ATOH8 increased expressions of undifferentiation markers, *Nanog* and *Oct4*. These results indicated that the ATF4 contributes to maintaining β -cell identity and that ISR modulation could be a promising approach in the treatment of diabetes.