Transcription Factor MAFA in Pancreatic β-cells

Subjects: Endocrinology & Metabolism

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MAFA is a basic leucine zipper family transcription factor. In pancreas, MAFA can activate the expression of insulin in β-cells with PDX1 and NEUROD1. MAFA is indeed indispensable for the maintenance of not only insulin expression but also function of adult β-cells. Here, role of MAFA in pancreatic β-cells is mainly described.

Keywords: MAFA ; MAFB ; insulin ; β-cells ; diabetes mellitus ; plasticity

1. Introduction

The total population of patients with diabetes worldwide is predicted to reach 537 million in 2021 and 783 million in 2045 [1]. Pancreatic β-cells secrete insulin to regulate blood glucose. The dysfunction and/or reduced mass of pancreatic β-cells results in impaired glucose-stimulated insulin secretion (GSIS), leading to diabetes. Therefore, it is important to clarify the molecular mechanism of β-cell failure for elucidation of the pathophysiology of diabetes.

Recent studies challenge the concept of cell fate determination, suggesting that cell differentiation is a dynamic state [2][3]. Many studies in various tissues have demonstrated that the manipulation of a few master transcription factors can specifically allow somatic cell fate conversion into a particular cell type in vivo [4][5][6][7]. The plasticity of somatic cells in a pathological state, with loss of these transcription factors, has been intensively investigated in pancreatic endocrine cells. Recent research shows that the molecular mechanism of β-cell failure in type 2 diabetes involves identity loss or dedifferentiation. Lineage tracing studies have demonstrated that several transcription factors critical for β-cell differentiation or maturation [8][9][10][11], including v-Maf musculoaponeurotic fibrosarcoma oncogene family transcription factor A (MAFA) [12], control the maintenance of the mature phenotype of β-cells.

2. Targets of the Transcription Factor MAFA

The insulin 2 promoter in rat pancreatic β-cells is regulated by three major elements, A3, C1-A2 and E1 [13][14][15]. Mutation in any of these elements resulted in reduction in the promoter activity of rat *Ins2*, suggesting the importance of transcription factors that can bind to these elements [16]. MAFA was identified as a binding factor and an activator of the C1-A2 element [17]. An electrophoretic mobility-shift assay using a probe from −139 to −101 bp of the rat *Ins2* promoter successfully detected a 47 kDa protein from the HIT T-15 hamster insulinoma cell line, which was identified as MAFA by mass spectrometry. This finding was later confirmed by three independent studies [18][19][20]. Meanwhile, PDX1, a homeodomain transcription factor, and NEUROD1, a transcription factor that belongs to the basic helix-loop-helix family, can bind A3 and E1, respectively [13][14][16]. These three factors can interact with each other and cooperatively activate the insulin gene in β-cells [21][22].

The glucose-dependent expression of MAFA in β-cells [15] prompted researchers to investigate the function of MAFA in β-cells. Accumulating evidence has revealed that MAFA is critical for the expression of not only *Ins2* but also *Ins1*, *Slc2a2*, *Slc30a8*, *Pcsk1*, *Pdx1*, *Sytl4*, *Maob*, *Vdr*, *Prlr*, *Ccnd2*, *Ucn3* and *ChrnB4* in β-cells [23][24][25][26][27][28][29]. Most of these molecules are involved in GSIS and play a functional role in mature β-cells. The results of another study have also revealed that MLL3/4 function as transcriptional coactivators of MAFA and play a role in inducing the expression of *Ins2*, *Slc2a2*, *G6pc2*, *Slc30a8* and *Ccnd2* in β-cells [30]. Studies revealed that the expression of exocytosis-related genes *Stx1a* and *Stxbp1*, subunits of voltage-gated Ca^{2+} channels *CaVy4*, and *Ppp1r1a* that is involved in GLP1R-mediated amplification of GSIS, is also regulated by MAFA, further demonstrating the importance of MAFA in insulin secretion [31][32][33]. Analysis of islet-specific enhancers by ChIP-seq of mouse islets revealed 3638 MAFA-enriched loci [29].

So far, the analysis of global [12][23][24] and pancreas-specific *Mafa* knockout mice [25] has been reported. These mice have similar phenotype, showing impaired mass and function of β-cells by 3 to 4 weeks of age, reduced proliferation with no accelerated apoptosis of β-cells, downregulation in the expression of *Ins1*, *Ins2*, *Slc2a2*, *Slc30a8* and *Pdx1* in their islets, and glucose intolerance. Transcriptome analyses of islets isolated from *Mafa* knockout mice have further elucidated candidate molecules that are regulated by MAFA. Genes downregulated in both knockout mice include *Trpm5*, *Sytl4*, *Slc14a2*, *BC039632*, *Gad1*, *Maob*, *Ttc28*, *Lifr*, *Rhobtb1*, *Slc2a2*, *Car10*, *Atp7a*, *Papss2*, *Scel*, *Prlr*, *F13a1*, *Nup93*, *Slc30a4*[25]. In addition, it has been recently reported that MAFA plays a role in the inhibition of cytokine production from β-cells, which is involved in islet inflammation [34].

3. The Role of Maf Factors in the Developing Pancreas

PDX1 is expressed in early pancreatic buds at E8.5. *Pdx1* knockout embryos are apancreatic [35]. The expression of NEUROD1 is restricted to the endocrine cells of the pancreas. A striking reduction in the number of endocrine cells is observed in the pancreases of *Neurod1* knockout embryos [36]. These data underscore the importance of insulin gene transcription factors in pancreatic development. The expression of MAFA occurs during pancreatic development starting at E12.5 to E13.5 and can be observed exclusively in insulin-expressing (insulin$^+$) cells [37][38]. Meanwhile, another large Maf factor MAFB is expressed in glucagon$^+$ cells as early as at E10.5 and also in insulin$^+$ cells prior to MAFA during embryonic development of murine pancreas [37][38]. Interestingly, MAFB shares a DNA-binding region with MAFA and thus can bind the C1-A2 element of insulin promoter in vivo, activate it in vitro, and can also bind R3 region of *Mafa* promoter during β-cell development [39][40]. MAFB expression persisted in glucagon$^+$ and insulin$^+$ cells but not in either somatostatin$^+$ or pancreatic polypeptide$^+$ cells during development, which is gradually restricted to glucagon$^+$ cells after birth, and it is selectively expressed in the glucagon-producing α-cells of the adult pancreatic islets [37][39][41]. β-cell-specific and α-cell-specific expression of MAFA and MAFB in adult mice pancreas, respectively, have been confirmed not only by immunohistochemistry but also by promoter activities of *Mafa* and *Mafb* that drive the expression of two fluorescent proteins independently in mice [42]. Numerous studies have demonstrated that immature β-cells express MAFB, while mature β-cells express MAFA in the embryonic or neonatal pancreas [37][39][43][44]. The changes in the expression of Maf factors during development of the pancreas indicate that the terminal differentiation process toward mature β-cells occurs even after the expression of insulin. These observations are further supported by the results of stem cell studies showing that the ability to secrete insulin from ES-derived insulin$^+$ cells accompanied the expression of MAFA [45][46][47]. In adult islets, the expression of MAFA is not homogenous [37], which has been validated by recent single-cell analyses [48] and reveals the heterogeneity of islet cells, indicating that transcriptionally mature and immature β-cells coexist within the adult islet together [49]. Other than MAFA, UCN3 is recognized as a marker for mature β-cells, although the genetic deletion of *Ucn3* does not cause a loss of β-cell maturity or an increase in β-cell dedifferentiation [50], suggesting the importance of MAFA as a marker of mature β-cells.

Mafb-deficient pancreas have a reduced number of insulin+ and glucagon+ cells with reduced expression of PDX1 and MAFA, without affecting endocrine progenitor cells expressing NEUROG3, NKX2-2, NKX6-1 and PAX6 [39][44]. *Pax6*-deficient pancreas have a similar phenotype, but the expression of MAFB is downregulated [44]. In contrast with these mutant embryos that have a reduced number of insulin$^+$ cells, the embryonic development is normal in the *Mafa*$^{-/-}$ pancreas [12][23][51]. Meanwhile, the overexpression of MAFA in *Pdx1*-expressing cells in the early pancreatic bud does not convert these cells into insulin$^+$ cells but inhibits differentiation and proliferation, suggesting that the sequential activation of the expression of transcription factors is critical for endocrine differentiation in the embryonic pancreas [52].

In addition to these data, it is intriguing that the ectopic expression of MAFA, PDX1 and NEUROD1 (or NGN3) converts adult liver or pancreatic acinar cells to β-cells [4][53][54]. These three transcription factors may be master genes of pancreatic β-cells, which can induce the expression of genes necessary for cell fate conversion.

4. The Role of MAFA in the Maintenance of the Mature β-Cell Phenotype

Numerous studies have demonstrated that the expression of MAFA is impaired in β-cells of rodents and humans with diabetes [55][56][57][58]. This reduction in the expression of MAFA in compromised β-cells occurs prior to the downregulation of other transcription factors that are expressed in β-cells, such as PDX1 and NKX6-1 [55]. The loss of MAFA results in the reduced expression of molecules that are critical for the function of β-cells, as discussed above [12][23][24][25][51].

In addition, accumulating evidence suggests that MAFA is not only critical for insulin biosynthesis and GSIS but also indispensable for maintenance of the mature phenotype of β-cells [12][59][60]. Although *Mafa*-deficient mice have a comparable number of β-cells throughout embryonic development and at birth, they become intolerant to glucose with reduced or no expression of insulin in the islets, although they do not show overt diabetes [12][23][51]. The β-cell to α-cell ratio in the islets of the pancreas decreases during the neonatal period. Importantly, genetic lineage tracing analysis revealed that *Mafa*$^{-/-}$ β-cells retain an endocrine cell phenotype with the expression of SYP and CHGA but have reduced or lost the expression of insulin, although a few expressed glucagon. These insulin-negative “empty” endocrine cells in *Mafa*$^{-/-}$ islets have decreased expression of molecules critical for β-cell function, such as *Ins1*, *Glut2*, *Slc30a8*, *Pcsk1*, *Vdr* and *Ucn3*, as well as increased expression of molecules conventionally repressed in β-cells, such as *Gcg*, *Mafb*, *Pax4*, *Neurog3*, *Sox9*, *Sox2*, *Nanog* and *Mct1*, some of which are recently identified as β-cell disallowed genes [61][62]. These phenomena are now recognized as the dedifferentiation of β-cells [9][12], which has been described earlier [3][63] and validated by lineage tracing [64]. Not only in *Mafa*-deficient mice but also diabetic mice with reduced expression of MAFA have a deeper loss of β-cell identity with the changes in gene expression above [12]. These results suggest that MAFA is critical for the formation and maintenance of the mature β-cell phenotype and that dedifferentiation with a loss of MAFA could be the common mechanism of β-cell dysfunction in type 2 diabetes in both mice and humans.

In the rodent study, this ‘loss of β-cell identity’ is characterized by (1) the decreased or completely absent biosynthesis of insulin in β-cells demonstrated by genetic lineage tracing studies, (2) the existence of “empty” endocrine cells in islets

shown by electron microscopy and (3) the impaired expression of genes critical for β-cell function with increased expression of molecules that are normally repressed in β-cells, including the upregulation of transcription factors that are transiently expressed in endocrine precursors such as the 'immature β-cell marker' MAFB. A certain fraction of β-cells with loss of identity are transdifferentiated to glucagon^{+} cells. These observations can also be seen in *Foxo1*, *Pdx1*, *Pax6* and *Nkx2-2* knockout mice (**Table 1**) [8][9][10][11][12][65], most of which are also important for β-cell specification during pancreatic development [62][63][64][65][66]. In dedifferentiated β-cells, the increased expression of genes such as the transcription factors *Mafb* and *Arx*, which are critical for α-cell specification, may be induced by epigenetic modifications such as promoter demethylation [67][68]. Interestingly, the deletion of *Mafb* in diet-induced obese *Mafa*-deficient mice shows impaired islet formation, a decreased number of β-cells and diabetes, which is more advanced than those in diet-induced obese *Mafa*-deficient mice, suggesting that MAFB may have a role in the maintenance of adult β-cells with a reduced expression of MAFA [69], although another study demonstrated that MAFB alone was unable to rescue the β-cell defects in mice lacking *Mafa* [70]. Taken together, MAFA is critical for the fate of β-cells in adult pancreas.

Table 1. Genetic lineage tracing studies of transgenic mice to show adult β-cell dedifferentiation.

References	Genes	Mice	Insulin $^{(-)}$ β-Cells	Upregulated Genes	Trans-Differentiation	β-Cell Death
Talchai et al. Cell 2012	*Foxo1*	*RIPCre;Foxo1$^{fl/fl}$;RosaEGFP* with metabolic stress	Detected	Neurog3, Oct4, Nanog	β- to α, δ, γ--cells	Similar to the controls (TUNEL, cleaved caspase-3)
Gao et al. Cell Metab 2014	*Pdx1*	*RIPCreER;Pdx1$^{fl/fl}$;RosaYFP*	Detected	Mafb, Gcg	β- to α-cells	Not marked (Cleaved caspase-3)
Wang et al. Cell Metab 2014	*Kcnj11* (K_{ATP}-GOF *)	*RIPCre or Pdx1CreER;RosaKir6.2* [K185Q,DN30] IRES-GFP	Detected	Neurog3	β- to α-cells	No significant difference (TUNEL, cleaved caspase-3)
Nishimura et al. Diabetologia 2015	*Mafa*	*Mafa$^{-/-}$;RIPCreER;RosaYFP*	Detected	Neurog3, Mafb, Mct1	β- to α-cells	No significant difference (TUNEL)
Ahmad et al. PLoS ONE 2015	*Pax6*	*RIPCreER;Pax6$^{fl/fl}$;RosaYFP*	Detected	Ghrl	β- to ε-cells	Not affected (TUNEL)
Ediger et al. J Clin Invest 2017	*Ldb1*	*MIPCreER;Lbd$^{fl/fl}$;RosaYFP*	Detected	Neurog3, Rfx6	(-)	No change in islet size and density
Gutiérrez et al. J Clin Invest 2017	*Nkx2-2*	*RIPCre;Nkx2-2$^{fl/fl}$;RosaTomato*	Detected	Ppy, Sst, Acot7	β- to α, δ, γ-cells	Little evidence (Cleaved caspase-3)
Lee et al. Diabetologia 2022	*Xbp1*	*Pdx1CreER;Xbp1$^{fl/fl}$;RosaGFP* with metabolic stress	Detected	Arx, Irx2, Gcg	β- to α-cells	Significantly increases (TUNEL)

* Gain-of-function mutation.

Recent studies have also shown that there is a redifferentiation of β-cells via intensive insulin therapy in a diabetes mice [10]. This phenomenon may also take place in humans and contribute to the recovery of insulin secretion that has been observed in diabetic patients who have undergone intensive insulin therapy [71]. These results raise the possibility that factors that can upregulate MAFA or inhibit MAFA downregulation may induce the redifferentiation of β-cells in individuals with diabetes. Indeed, the expression of MAFA induced by a Cre-loxP-Rosa system in β-cells of diabetes model mice increased plasma insulin, ameliorated elevated blood glucose and HbA1c, and preserved β-cell function [71].

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