MINIREVIEWS

Transcriptional factors, Mafs and their biological roles

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Abstract

The Maf family of transcription factors is characterized by a typical bZip structure; these transcription factors act as important regulators of the development and differentiation of many organs and tissues, including the kidney. The Maf family consists of two subgroups that are characterized according to their structure: large Maf transcription factors and small Maf transcription factors. The large Maf subgroup consists of four proteins, designated as MAFA, MAFB, c-MAF and neural retina-specific leucine zipper. In particular, MAFA is a distinct molecule that has been attracting the attention of researchers because it acts as a strong transactivator of insulin, suggesting that Maf transcription factors are likely to be involved in systemic energy homeostasis. In this review, we focused on the regulation of glucose/energy balance by Maf transcription factors in various organs.

Key words: Cell; Insulin; MAFA; Microarray; siRNA

Core tip: This manuscript demonstrates that Maf transcription factors are likely to be involved in the regulation of hormonal systems related to glucose metabolism, with regulation by Maf transcription factors likely occurring near the start of the cascade or acting directly on the expression of genes in coordination with other factors in multiple organs and tissues. The Maf family plays diverse roles as transcription factors in the establishment of energy balance in peripheral organs, such as the pancreas, liver, and adipose tissue.

INTRODUCTION

Maf is a family of oncogenes that were first discovered in the genome of the avian transforming retrovirus, AS42[1,2]. Maf-related proteins have been identified in many species and exhibit a universally recognized DNA binding site, enabling the proteins to act as transcription

factors. These Maf transcription factors are well known to play active roles in many organs, tissues, and cells for the development, differentiation and establishment of specific functions, including effects in the pancreas[3], lens[4], myeloma cells[5], and cartilage[6,7].

The Maf family has two distinct subgroups that are categorized according to their molecular size: small Maf transcription factors (150-160 amino acids: MAFF, MAFG, and MAFK), and large Maf transcription factors (240-340 amino acids: MAFA, MAFB, c-MAF, and NRL). Small Maf transcription factors lack a transactivation domain, and these protein products form homodimers or heterodimers within the Maf family or with other transcription factors, inducing transactivation factors[2,8]. A complex regulatory network is known to link small Maf transcription factors with other regulatory proteins[9,10]. On the other hand, large Maf proteins consist of a family of transcription factors characterized by a typical bZip structure, which is a motif for protein dimerization and DNA binding[11,12]. Several reports have revealed that Maf proteins are involved in the essential functions of developing, differentiating and establishing the function of cells, tissues and organs. These transcription factors reportedly regulate several distinct developmental processes, cell differentiation, and the establishment of cell functions; for example, the mouse *Mafb* gene is responsible for the segmentation of the hindbrain[13], while *c-Maf* has been identified in the liver, renal tubules[14], adipocytes, and muscle. In this review, we will mainly focus on large Maf transcription factors and their roles in the regulation of various organs, as well as their effects on energy balance.

MAF TRANSCRIPTION FACTORS AND PANCREATIC β CELLS

One of the large Maf transcription factors, transcription factor MAFA, is an interesting molecule among the Maf family members since it promotes the differentiation of pancreatic β cells[15,16]. Several reports have also indicated that *Mafa* activates the insulin gene C1 element, contributing to β cell function and differentiation[17,18]. The formation of β cells has been described in detail in several reports and has been summarized in reviews. Two types of large Maf transcription factors, MAFA and transcription factor MAFB, are known to coordinate with each other and with other transcription factors and related genes to induce the generation and differentiation of β cells[3,19]. MAFB is known to function as a transcription factor in many tissues and organs and has been detected in the pancreas. MAFB was initially identified as a transactivator of β cells, acting on the glucagon gene G1 element. Further studies subsequently revealed that MAFB can be detected in both α and β cells during the early phase of development, followed by a reduction in expression and then a switch to mainly MAFA expression[20-22]. An additional study has demonstrated that the loss of *Mafa* causes a decrease in insulin gene expression in glucotoxic

β cells[23], while MAFA deficient mice could not activate insulin transcription, even though the insulin content of the β cells was not significantly diminished[24]. Recently, Hang *et al*[25] described the collaboration of MAFA and MAFB in the development of pancreatic β cells in greater detail[25,26]. As for the transcription factor c-MAF, which is known to play a role in hematopoietic cell differentiation, its expression has been confirmed in the pancreas and is thought to be involved in α cell differentiation and function[27].

Previously, Maf transcriptional factors could be shown to stained in premature and mature pancreas tissue in our report[28]. Cells that stained positive for Maf transcription factors were diffusely localized in premature pancreas tissue, with some cells exhibiting double staining. The staining pattern for each Maf protein was different: unlike, MAFA-positive cells, which exhibited a diffuse staining pattern, MAFB and c-MAF were stained prominently in the branching ducts and acinar buds. Subsequently, MAFA and MAFB were stained more intensely in the islet areas of adult pancreas tissue, suggesting that Maf transcription factors are involved in the differentiation and acquisition of pancreatic endocrine cells, coordinating with each other in some situations (Figure 1). In contrast, non-endocrine composite cells of the pancreas, such as acinar cells and ductal cells, may also be affected by several Maf transcriptional factors during their maturation and differentiation process. More interesting observation is that cells positive stained for Maf transcription factor continued to be detected not only in the islets but around the ductal and interstitial area after maturation.

ACTIVITIES OF MAF TRANSCRIPTION FACTORS BEYOND β CELLS

Despite the details that have been revealed regarding the activities of Maf transcription factors in β-cell function and differentiation, the precise mechanism and coordination of Mafs and other transcriptional factors regarding the regulation of insulin production and its activity remain unknown. The precursors of pancreatic endocrine cells and the mechanism of β cell replication in the islets have been reported[29-31]. However, several types of Maf transcription factors are likely to be implicated in both the pancreatic endocrine cell lineage and interaction with other transcription factors. Each Maf transcriptional factor were often co-stained in one endocrine cell in immature pancreas.

The network of targeted genes and transcription factors, including several Maf transcription factors, needs to be clarified as part of efforts to accelerate β cell regeneration or preparation for cell therapy. Maf transcriptional factors are reportedly expressed in other tissues and cells, for example, epithelial cells and lymphocytes[32,33], where they accelerate specific cell function and differentiation. Lumelsky *et al*[34] reported the development of embryonic stem cells into insulin-producing cells in the pancreas[34], while Kawai *et al*[1] described the mechanism of β cell replication in islets.
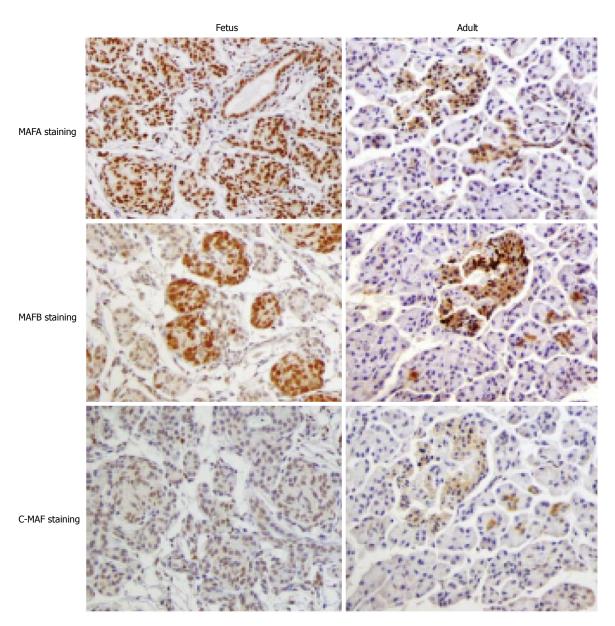
Fetus | Adult

MAFA staining

MAFB staining

C-MAF staining

Figure 1 Immunostaining for MAFA, MAFB, and c-MAF in fetal and adult human pancreas tissues. An immunohistochemical analysis was performed using primary antibodies against MAFA (BL1069; Bethyl Laboratories, Inc.), MAFB (P20; Santa Cruz Biotechnology, Inc.), and c-MAF (M153; Santa Cruz Biotechnology, Inc.). The details are described in reference[28]. Samples of human normal fetal tissue (female, 20 wk, catalog No. T2244188, Lot No. A607380) and adult pancreas tissue (male, 23 years, catalog No. T2234188, Lot No. A604382) were purchased from BioChain. The fetal pancreas tissues were diffusely stained for the Maf transcription factors, and characteristic histological differences were observed between the fetal and adult tissues, with a more intense staining pattern observed in the islet areas of the adult pancreas tissue.

In addition, several reports have described the existence of tissue-specific stem cells in the pancreas[35,36]. Recently, several reports have discussed the more efficient production of β cells (glucose-sensitive and insulin-secreting cells) through the introduction of a combination of transcription factors, including Maf transcription factors, or the use of induced pluripotent stem cells[37,38].

Large Maf transcription factors have been identified during the development of the pancreas, and the expressions of these large Maf transcription factors exhibited different localizations in newborn and adult pancreas tissues, which differ in their endocrine characteristics. Thus, Maf transcription factors may contribute to establish all the cells in pancreatic tissue, including cells involved in endocrine

cell differentiation, such as α and β cells, exocrine cells, and ductal cells.

MAF TRANSCRIPTION FACTORS AND THE KIDNEY

In the kidney, large Maf transcription factors may be implicated in both normal development and pathophysiological processes responsible for kidney disease. We previously reported the expression profiles of large Maf transcription factors in the kidney. We have reported the expression of *c-Maf* mRNA levels in mouse kidney tissue from embryonic day 12 (E12) until 1 or 4 wk after birth.
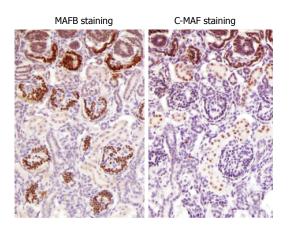
MAFB staining   C-MAF staining

Figure 2 Immunostaining for MAFB and c-MAF in fetal human kidney tissue. An immunohistochemical analysis was performed using primary antibodies against MAFA (BL1069; Bethyl Laboratories, Inc.), MAFB (P20; Santa Cruz Biotechnology, Inc.), and MAF c-Maf (M153; Santa Cruz Biotechnology, Inc.). The details are described in reference[40]. A sample of human normal fetal kidney tissue (male, 25 wk) was purchased from BioChain (catalog No. T8244431, Lot No. A606275). Glomerular podocyte lesions stained positive for MAFB, and while the proximal tubules stained positive for c-MAF.

c-Maf mRNA was firstly expressed at E16 in the proximal tubules and continued to be expressed until 4 wk after birth. Meanwhile, MAFB expression has been identified in the glomeruli (Figure 2)[39,40].

The *Mafb* mouse gene (also known as Kreisler and *Krml*) is known for its role in hindbrain patterning. Sadl *et al*[41] showed that mice homozygous for the kr (enu) mutation develop renal disease, in which the glomerular podocytes are affected, resulting in nephrotic syndrome. The fusion and effacement of the podocyte foot processes were observed histologically, and MAFB was shown to be essential for the cellular differentiation of the podocytes. Since the podocytes of the kr (enu) homozygotes differentiated abnormally, the homozygotes exhibited proteinuria, as is observed in nephrotic syndrome. The authors speculated that MAFB acted during the final stages of glomerular development, *i.e.*, the transition between the capillary loop and the mature stages, and downstream of the Pod1 basic domain helix-loop-helix transcription factor[41]. In *Mafb*-knockout mice, renal dysgenesis with abnormal podocyte differentiation and tubular apoptosis were prominent, accompanied by the suppression of F4/80 expression in mature macrophages[42].

A prominent phenotypic feature of *c-Maf* - knockout mice is a small cell volume of the kidney proximal tubules and hepatocytes[40]. The precise mechanism underlying this dysregulation of cell structure formation has not been clarified, but the *c-Maf* transcriptional factor has been suggested to contribute to the embryonic cell development and differentiation of at least the proximal tubules and hepatocytes. The mRNA expression profile in kidney tissue from *Maf*-knockout mice, as evaluated using a DNA microarray, showed that the plasma level of glutathione peroxidase 3 (GPx-3) was predominantly downregulated. Since GPx-3 is an antioxidant enzyme,

C-MAF may be related to the antioxidant system mediating the modulation of GPx-3 in the kidney[14]. Recently, c-Maf-inducing protein (also known as c-Mip; protein designation, CMIP), a pleckstrin homology (PH) and leucine-rich repeat (LRR)-domain-containing protein, has been identified; CMIP inactivates GSKbeta and interacts with RelA, a key member of the NF-kappaB family. Interestingly, the expression of CMIP (c-Maf-inducing protein) was increased in the podocytes of patients with idiopathic nephrotic syndromes[43]. Membrane nephropathy is characterized by nephrotic-range proteinuria in clinical and subepithelial deposits of immune complex in the basement membrane of the glomerulus. The primary cause of the disease has not been clarified, but antibodies against podocytes located on the outer layer of the basement membrane of the glomeruli form complexes that lead to deposits. A recent report has shown that CMIP was overexpressed in podocytes in an experimental glomerulonephritis rat model exhibiting heavy proteinuria and membranous nephropathy in human. This overexpression was suppressed by immunological treatment resulting in a reduction of proteinuria; thus, while the role and significance of CMIP in podocytes and how it induces massive proteinuria have not yet been elucidated, CMIP or c-MAF-related transcriptional activities may deregulate podocyte function and cause proteinuria[44].

The expression of MAFA in the kidney is uncertain; however, based on the UniGene databank, human MAFA is also expressed in the kidney, lung, and blood. One interesting report described transgenic mice with a disease in which the hybridized gene complex resulted in MAFA deficiency and MAFK overproduction in pancreatic β cells. The phenotype of these transgenic mice was severe diabetes with large amount of proteinuria. A histological examination showed a reduction in β cells in the pancreas and typical histological diabetic nephropathy accompanied by a characteristic nodular lesion in the glomeruli.

The combination of several Maf dysfunctions generate diabetes with diabetic nephropathy, suggesting one possible mechanism for the onset of diabetic nephropathy. Consequently, these mouse models mice may suggest a mechanism for disease onset and could be useful in investigations of treatments for diabetic nephropathy[45].

MAF TRANSCRIPTION FACTORS AND THE CENTRAL NERVOUS SYSTEM

Energy balance in humans is well regulated by multiple organized systems, and the central nervous system (CNS) is likely to be involved and to play important roles in these systems[46]. The CNS contributes to the maintenance of energy balance in part by controlling feeding behavior and also by changing biological conditions and the homeostasis of intra-body conditions. Systemic adjustments of the metabolic state are achieved by the coordination of
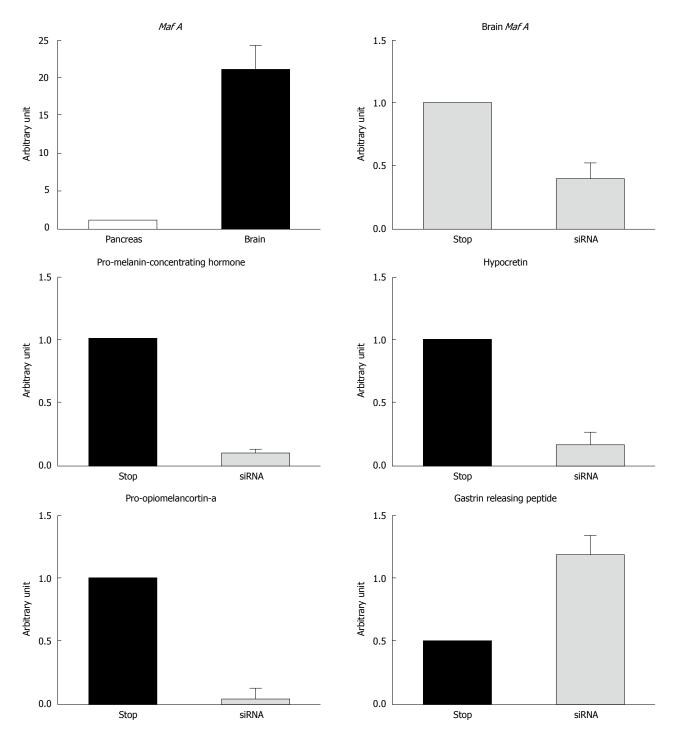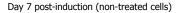
Figure 3 Suppression of *MafA* mRNA by siRNA in the brain and resulting alternation of related genes. A designed small interfering RNA (siRNA) oligomer for mouse *Mafa* was intravenously injected using the hydrodynamic method according to a procedure described by Hamar *et al*[58]. A DNA microarray analysis was then performed using Affymetrix GeneChip technology. The mRNA levels were quantified using real-time PCR. The details of the experiment have been described previously. Expression level of *Mafa* mRNA in the brain. The expression level of *Mafa* mRNA in the brain was 20 times higher than that of *Mafa* mRNA in the pancreas, as assessed using real-time PCR. Suppression of *Mafa* in mice using siRNA in the brain. The mRNA expression level take out in the brain tissue are shown. The *Mafa* mRNA expression level was significantly downregulated by the siRNA. Pro-melanin-concentrating hormone, Hypocretin, and Pro-opiomelanocortin-a were downregulated, and Gastrin-releasing peptide was upregulated, as assessed using real-time PCR with specific primers.

the CNS and peripheral effector organs. In the CNS, transcription factors are involved in the regulation of behavior and intra-body biological conditions[47]. Calorie intake is sensed in the CNS, altering the expression of signal transduction-mediating transcription factors. These responses are then translated into intra-CNS hormones

(resulting in changes in eating behavior) and peripheral hormones take out including insulin and leptin, which function to regulate energy balance by direct effects on peripheral organs in coordination with calorie intake and consumption balance.

In our previous mouse study, the *Mafa* mRNA level

Day 7 post-induction (non-treated cells)   Day 7 post-induction (mafA-siRNA-treated cells)
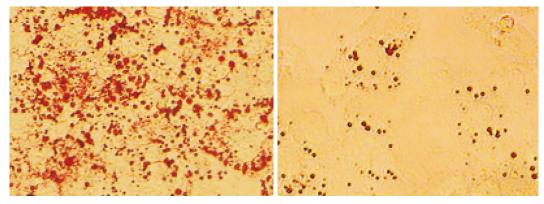

Figure 4 Comparison between histological changes and the Oil-Red-O staining of stop-mafA-siRNA- and mafA-siRNA-treated cells. Mouse 3T3-L1 pre-adipocytes were induced to differentiate, and *Mafa* SiRNA was transfected using a transfection reagent. The morphological appearances of the pre-adipocyte culture before induction and 7 d after induction were then compared. The morphology of the 3T3-L1 cells was directly observed, and lipid droplets were stained using Oil Red O. Oil Red O staining was compared between untreated and *Mafa*-siRNA-treated cells. Intracellular lipid staining was not observed in the *Mafa*-siRNA-treated cells.

was significantly downregulated in brain tissue *in vivo*, as observed using a siRNA technique, and changes in the gene profile in the CNS were screened[48] (Figure 3). The results showed distinct effects on gene expressions in brain tissue, and some of the affected genes were related to eating behavior and energy consumption, such as growth hormone and arginine vasopressin. In addition, several interesting genes and related gene products were identified in this profiling. Pro-melanin-concentrating hormone (Pro-MCH) regulates body weight[49], and changes in its expression can alter the susceptibility to fat metabolism[50,51]. Orexin is a topical neuronal peptide that regulates arousal and sleep[52], and defective orexin producing neuronal cells cause narcolepsy. Orexin may work in the brain-gut network, which regulates appetite during wakefulness[53]. In addition, pro-opiomelanocortin-alpha (an alpha-melanocyte stimulating hormone) and gastrin-releasing peptide, which are important neuropeptides regulating eating behavior and modifying the excretion of several hormones required for food digestion, have also been implicated in the above-mentioned network.

Thus, MAFA is a strong transactivator of insulin in peripheral organs and pancreas, while the modulation of *MAFA* mRNA expression in the CNS induces change in related genes resulting in upregulation and downregulation of neuropeptides that influence appetite, behavior, arousal, and sleep.

MAF TRANSCRIPTION FACTORS AND ADIPOCYTES

Adipocytes develop from mesenchymal stem cells in adipose tissue and various other tissues. Mesenchymal stem cells destined to become adipocytes develop and differentiate into mature adipocytes as a result of transcriptional regulation. PPARγ is known to coordinate with members of the C/EBP family to exert well-documented and important functions at different time points during adipocyte differentiation[54]. Siersbæk *et al*[55]

also reported transcriptional networks for adipogenesis take out in which two waves of transcriptional cascades composed the adipogenetic pathway. Maf transcription factors are likely to be involved in this process, and Serria *et al*[33] reported that the expression of c-MAF is downregulated during 3T3-L1 cell differentiation and proliferation. Furthermore, an age-related decrease in the expression of c-MAF in mesenchymal cells has been reported, and present evidence indicates that c-MAF regulates mesenchymal cell bifurcation into osteoblasts and adipocytes. A role of c-MAF in osteogenesis and adipogenesis was also observed in *c-Maf*-knockout mice[56].

As discussed previously, MAFA may be involved in the differentiation of both adipocytes and pancreatic β cells. To explore the role of MAFA in adipose tissue, alterations in the expressions of MAFA-related genes in a cultured adipocyte cell line, 3T3-L1, were observed after *Mafa* mRNA interference had been induced[57]. *Mafa* mRNA suppression induced morphological changes in 3T3-L1 cells during differentiation. As shown in Figure 4, the cytoplasm of spindle-shape cells expanded after differentiation and lipid droplets formed in mature adipocytes, as revealed by the presence of red droplets of Oil Red O stain in the cytoplasm. This morphological change was not observed during *Mafa* siRNA suppression, and no expansion of the cytoplasm was observed. Since lipid droplet formation is essential for adipocyte differentiation, MAFA may play a critical role in the process of adipocyte differentiation. The expression levels of peroxisome proliferator-activated receptor (PPARγ2) and CCAAT/enhancer-binding protein (C/EBPα) were recognized as being essential for the differentiation and function of 3T3-L1 cells. PPARγ 2 plays a leading role in the synthesis and accumulation of lipid droplets in adipocytes, and C/EBPα is critical for the establishment of insulin sensitivity[54]. At the molecular level, the mRNA expression levels of the *PPARγ* gene or the *C/EBP* gene, which encode master adipogenic transcription factors, were markedly suppressed by *Mafa*-siRNA treatment, *i.e.,* by the suppression of MAFA expression. In conclusion,

adipocyte differentiation and formation is regulated by a network of multiple transcription factors, and Maf transcription factors are likely to be involved, in coordination with other transcription factors.

ACKNOWLEDGMENTS

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