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REVIEW ARTICLE

Multiple functions of Maf in the regulation of cellular development and differentiation

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Summary

Cellular muscular aponeurotic fibrosarcoma (c-Maf) is a member of the large macrophage-activating factor family. C-Maf plays important roles in the morphogenetic processes and cellular differentiation of the lens, kidneys, liver, T cells and nervous system, and it is particularly important in pancreatic islet and erythroblastic island formation. However, the exact role of c-Maf remains to be elucidated. In this review, we summarize the research to clarify the functions of c-Maf in the cellular development and differentiation. The expression of c-Maf is higher in pancreatic duct cells than in pancreatic islet cells. Therefore, we suggest that pancreatic duct cells may be converted to the functional insulin-secreting cells by regulating c-Maf. © 2015 National Natural Science Foundation of China. *Diabetes/Metabolism Research and Reviews* Published by John Wiley & Sons Ltd.

Keywords diabetes mellitus; β cell; c-Maf

Abbreviations c-Maf, cellular muscular aponeurotic fibrosarcoma; Maf, macrophage-activating factor; MAREs, Maf recognition elements; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Introduction

Diabetes mellitus is a disease that can lead to dangerously high blood glucose levels, causing numerous complications, such as heart disease, glaucoma, skin disorders, diabetic retinopathy, kidney disease and nerve damage. In healthy individuals, β cells of the pancreas produce the hormone insulin, which stimulates cells in the liver, muscles and fat to take up glucose from the blood. However, patients who have deficient or malfunctioning of β cells develop impaired glucose regulation and diabetes mellitus, such patients either have too few pancreatic β cells (type 1 diabetes mellitus) or a lack of a progressive insulin secretory defect on the background of insulin deficiency (type 2 diabetes mellitus) [1]. Thus, the replacement or regeneration of functional human β cells is an intensely sought goal. Prior studies have shown that duct cells, which constitute nearly one third of human pancreas [2], can be converted into cells capable of producing, storing and secreting insulin in response to glucose or other depolarizing stimuli [3]. Promoting the survival of transplanted insulin-secreting cells is a general problem for transplant-based islet replacement approaches. Therefore, studies of transcription factors that enhance the survival of Insulin + ductal cell progeny are an important current focus.

Macrophage-activating factor (Maf) is a family of oncogenes that was first identified in the genome of the avian transforming retrovirus, AS42, which induces musculoaponeurotic fibrosarcoma *in vivo* and transforms chicken embryo fibroblast cells *in vitro* [4]. The Maf protein is a family of transcription factor proteins that belongs to the activated protein-1 super family of transcription factors. It has two distinct subgroups categorized according to their molecular size: large Maf transcription factors [240–340 amino acids: cellular muscular aponeurotic fibrosarcoma (c-Maf) [5,6], MafA/L-Maf [7], MafB [8] and neural retina-specific leucine zipper [9]] and small Maf transcription factors (150–160 amino acids: MafK [10], MafF [10], MafG [11] and MafT [12]). c-Maf is a lineage-specific transcription factor that contains an acidic transactivation domain, the histidine/glycine repeats domain, the extended homology region, as well as the basic-leucine-zipper domain [13]. The acidic transactivation domain is rich in acidic residues and is often responsible for protein's transcriptional activator functions [14]. The basic-leucine-zipper domain is an evolutionarily conserved sequence located N-terminally to the basic domain that mediates dimerization and DNA binding to either Maf recognition elements or the 5-AT-rich half Maf recognition element [15]; see Figure 1.

There have been several reports that c-Maf plays important roles in morphogenetic processes and cellular differentiation. For example, c-Maf has been identified in the lens [16], kidneys [23], liver [24], T cells [26], nervous system [35] and, in particular, pancreatic islets [40], as well as in erythroblastic island formation [34]. However, the exact role of c-Maf remains to be elucidated. In this review, we summarize the research to clarify the functions of c-Maf in cellular development and differentiation, particularly that of pancreatic islet cells. We suggest that pancreatic duct cells can convert to the functional insulin-secreting cells with the regulation of c-Maf, with the long-term aim of developing a new type of therapy for diabetes mellitus.

c-Maf in the regulation of cellular development and differentiation

c-Maf in lens

To elucidate the regulatory mechanisms underlying lens development, Kawauchi *et al.*[16] searched for members of the large Maf family, c-Maf, MafB and neural retina-specific leucine zipper, which are expressed in the murine lens. Among these factors, c-Maf is the earliest to be expressed in the lens. The expression of c-Maf is the most prominent for normal lens development, and its function cannot be replaced by other large Maf proteins. C-Maf plays a critical role in regulating lens fibre cell-specific expression of the numerous *crystalline* genes. Studies show that the *Maf* gene participates in transcriptional regulation during the development of the lens in the rat [17]. In the ocular lens, previous studies have shown that c-Maf plays a key role in lens development [18], while other Mafs, such as MafA/LMaf and MafB, are dispensable [19]. In another study, the localization of cyclin D1, a cell cycle-related molecules, was examined immunohistochemically in developing lens cells of *c-Maf* knockout (−/−) mice. In c-Maf−/− mice, a variety of round epithelial cells were located in the anterior and posterior lens. Many cyclin D1-positive nuclei were observed in lens epithelial cells as well as in posterior lens cells. These results are consistent with a role for c-Maf in the regulation of cyclin D1 in developing lens cells [20].

C-Maf is also required for the differentiation of the lens. Kim *et al.* [21] found that a lack of c-Maf caused severe defects in the embryonic mouse lens differentiation. *In vitro* differentiation model, knockdown of p53, significantly inhibited lens differentiation, which is associated with down-regulated expression of c-Maf. Liu *et al.*[22] revealed that p53 regulates lens differentiation through modulation of two important transcription factors, one of which is c-Maf, and through c-Maf and Prox-1, p53 controls the expression of various differentiation-related downstream *crystallin* genes.

c-Maf in the liver, kidneys and T cells

In the liver, the cytoplasmic volume of the cells was smaller in the *c-Maf* knockout mice at 4 weeks. This finding suggests that expression of the *c-Maf* gene may be involved in the embryological development and/or cellular differentiation of liver cells [23]. Recently, studies show that c-Maf is abundantly expressed in foetal liver macrophages and that it regulates the expression of F4/80, which mediates immune tolerance [24].

In the kidneys, the expression of c-Maf mRNA was first detected on embryonic day 16 in the renal proximal

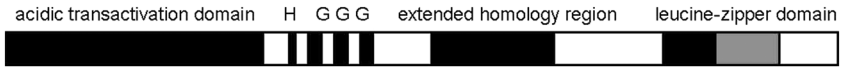

Figure 1. The structure of C-Maf. It contains an acidic transactivation domain, the histidine/glycine repeats domain and the extended homology region, as well as the basic-leucine-zipper domain [13]. The acidic transactivation domain is rich in acidic residues and is often responsible for protein's transcriptional activator functions [14]. The basic-leucine-zipper domain is an evolutionarily conserved sequence located N-terminally to the basic domain that mediates dimerization and DNA binding to either Maf recognition elements or the 5-AT-rich half-MARE [15]

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tubules, and it was expressed until 4 weeks after birth. The cytoplasmic volume of the proximal tubule was smaller in the c-Maf knockout mice at 4 weeks. The *mafB* and *c-Maf* genes are expressed in the kidneys in the late foetal phase, with continued expression after birth in the proximal tubule cells and the podocytes in the glomeruli, suggesting that Mafs may play a much more critical role in functional differentiation in the late phase of development than in the early phase [23]. C-Maf may be a transcriptional regulator of glutathione peroxidase-3 expression and may modulate the antioxidative pathway in the kidneys *in vivo* and *in vitro* [25].

Blonska *et al.*[26] find that c-Maf regulates the mechanism of T-cell activation and differentiation. Both the scaffold protein CARMA1 and the kinase inhibitor of NF-κB kinase β (IKKβ) are two essential regulators of the transcription factor nuclear factor κB. They show that CARMA1-deficient or IKKβ-deficient mice has defects in the generation of Tfh cells, formation of germinal centres and production of antigen-specific antibodies. Thus, the scaffold protein CARMA1 and IKKβ are critical to the activation of c-Maf. The amount of c-Maf increases after stimulation of the T-cell receptor, which results in the production of multiple cytokines. C-Maf is implicated in the differentiation of other Th cell subsets, including Tfh cells [27] and regulatory type 1 cells [28]. Sato *et al.*[29] used a transcriptome analysis combined with factor analysis to show that the expression level of c-Maf increases significantly during the course of Th17 differentiation. Futhermore, the experimental data show that the overexpression of c-Maf leads to the expansion of memory phenotype cells, particularly those with Th1 and Th17 traits. Thus, the authors propose that c-Maf is important for the development and/or maintenance of memory Th17 and Th1 cells.

Clarification of the mechanisms of memory Th-cell development in the context of c-Maf induction would be beneficial to the understanding of the pathophysiology of various autoimmune inflammatory diseases. In macrophages, c-Maf is reported to regulate interleukin-10 (IL-10) expression, which is essential for the differentiation of regulatory T cells [30]. C-Maf is a lineage-specific transcription factor that promotes Th2-cell development through direct transactivation of the IL-4 gene [31]. Previous studies have demonstrated that induction of the Th2 response can prevent non-obese diabetic (NOD) mice from developing diabetes [32,33]. Deficiency of c-Maf leads to a profound defect in IL-4 production and Th2-cell development and differentiation.

c-Maf in the erythroblastic island and the nervous system

A study showed that c-Maf is critical for erythroblastic island formation [34]. The authors performed mixing experiments with c-Maf-deficient erythroblasts and macrophages. First, c-Maf was expressed in macrophages but not in erythroblasts in the foetal liver, which suggests that macrophages are the primary sites of c-Maf activity. Second, adult mice transplanted with c-Maf-deficient foetal liver cells did not develop anaemia. Finally, consistent with the proposed role of the central macrophage, survival of mature c-Maf-deficient erythroblasts was defective *in vivo*. Thus, these findings convincingly show that c-Maf deficiency causes defective macrophage development and impairs erythroid cell survival and development through its effect on the erythroblastic island. In c-Maf-deficient embryos, the number of erythroblasts surrounding the macrophages in erythroblastic islands was significantly reduced and exhibited embryonic anaemia. These results strongly suggest that c-Maf is crucial to definitive erythropoiesis in the foetal liver, which plays an important role in macrophages that constitute erythroblastic islands.

In the nervous system, Wende *et al.*[35] showed that the transcription factor c-Maf is crucial for mechanosensory functioning in mice and humans. Another study showed that c-Maf controlled many parameters of rapidly adapting mechanoreceptor (RAM) development, morphology and function and modulates functional aspects of SAMs. Thus, the authors concluded that the transcription factor c-Maf directs RAM development and formation of RAM mechanoreceptive end organs [36].

c-Maf in the regulation of the development and differentiation of pancreatic endocrine cells

C-Maf is expressed in both α and β cells in pancreatic islets, but not in γ and δ cells [37]. The expression of c-Maf has been confirmed in the pancreas and is thought to be involved in α-cell differentiation and function [38]. Furthermore, c-Maf functionally interacts with the α-cell-specific DNA element G1 to activate basal expression of the *glucagon* gene in mouse islets [39]. *C-Maf* gene regulated by pax6 directly or indirectly is critical for pancreatic α-cell development and differentiation as well as glucagon biosynthesis in *Pax6* knockout mice [37]. It has been suggested that transgenic c-Maf can strongly influence autoimmune diabetes development in some models. Pauza *et al.*[40] used previously established *c-Maf* transgenic mice to examine the influence of c-Maf on diabetes and showed that c-Maf inhibited disease onset of transgene-mediated spontaneous diabetes and virus-induced diabetes in rat insulin promoter lymphocytic choriomeningitis virusnucleoprotein (RIP-LCMV-NP) mice. The onset of disease was significantly delayed, and the overall

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Table 1. Effects of c-Maf in the regulation of pancreatic endocrine cells

Effect/result	Experimental tissue/cell type	References
C-Maf is critical for α-cell development, differentiation and glucagon biosynthesis	Primary rat pancreatic α cells	[38]
Activate glucagon gene expression	Mouse pancreatic cell	[39]
Onset of diabetes delayed and overall incidence decrease	Transgenic mouse islet β cells	[40]
Tyrosine phosphorylation of c-Maf decreases severity of diabetes	NOD mouse Th cells	[43]
Tyrosine phosphorylation of c-Maf positively correlates with IL-4 expression in peripheral Th cells		
C-Maf expressed in both α and β cells	Embryonic and adult mice pancreatic cell	[49]

c-Maf, cellular muscular aponeurotic fibrosarcoma

incidence decreased in mice that carry the *c-Maf* transgene; see Table 1.

Post-translation modification is an important step in the regulation of c-Maf activity. Interestingly, sumoylation of c-Maf represses its binding to the IL-4 promoter, leading to a reduction in IL-4 production, by which it limits the protective Th2 responses [41]. Thus, enhanced c-Maf sumoylation is considered to contribute to immune deviation in type 1 diabetes mellitus by reducing c-Maf access to and transactivation of the *IL-4* gene [42]. Recently, research findings have shown that the level of tyrosine phosphorylation of c-Maf in Th cells decreases the severity of diabetes in NOD mice [43]. These data indicate that post-transcriptional modification of c-Maf by tyrosine phosphorylation is important, and attenuated tyrosine phosphorylation may bring about the pathogenesis of autoimmune diabetes. Therefore, abnormal post-translation modification in c-Maf may contribute to the reduced IL-4 production by cluster of differentiation four (CD4) T cells in NOD mice.

Non-islet-derived cells and pancreatic duct cells may be converted to islet-like cells with the use of certain transcription factors. Recently, it was shown that fully differentiated non-islet-derived cells could be made to transdifferentiate to islet-like cells and that combining epigenetic modulation with transcription factors (Pdx1, MafA, Nkx6.1, NeuroD1 and Pax4) modulation leads to enhanced insulin expression [44]. Interestingly, another study indicated that the expression of Pdx1 prior to Neurog3 and MafA increased the reprogramming efficiency from pancreatic duct cells to insulin-producing cells, while excessive expression of MafA together with Pdx1 and Neurog3 inhibited the reprogramming of pancreatic duct cells into insulin-producing cells. Consequently, the authors found that the expression of Pdx1 prior to that of Neurog3 and MafA enhanced the expression of the *insulin* gene, compared with the simultaneous induction of these three transcription factors [45].

C-Maf is prominent in areas around the branching ducts and acinar buds. Zhang *et al.* [46] have found that the expression of c-Maf is higher in the pancreatic duct than in the pancreatic islets. Although some transcription factors including MafA are used to convert pancreatic duct cells to islet-like cells, it is not known whether c-Maf has a role in the regulation of the development and differentiation of islet cells. Therefore, we suggest that pancreatic duct cells may be converted to the functional insulin-secreting cells with the regulation of c-Maf. Although MafA is likely to be more specific for β-cell differentiation and functional insulin secretion, insulin-positive cells are co-expressed with MafB or c-Maf in addition to mafA, suggesting that c-Maf may take part in the process of insulin-producing β-cell differentiation [47].

The oncogene c-Maf is involved in the translocation found in approximately 5–10% of multiple myelomas. It is proposed that c-Maf transforms plasma cells by stimulating cell cycle progression and by altering bone marrow stromal interactions [48]. Thus, the stimulation of c-Maf could induce unwanted severe side effects like tumour development and growth, such as multiple myeloma. In this regard, it is one of the most important obstacles to conquer when we are trying to use the overexpression of c-Maf to stimulate cell proliferation for therapeutic purpose.

Conclusion

In this review, we summarized the functions and roles of c-Maf in various biological processes and the recent progress in elucidating the mechanisms with which c-Maf regulates cellular development and differentiation. To depict the entire regulatory network involving c-Maf in various tissues and in cellular transformation, it will be necessary to identify target genes and to elucidate crosstalk with other transcription factors, interactions with transcriptional regulation and regulatory mechanisms of post-translational modifications. The role of c-Maf, in particular in pancreatic islets, remains to be elucidated. The expression of c-Maf is higher in pancreatic duct cells than in pancreatic islets cells, and we suggest that pancreatic duct cells can be converted to

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functional insulin-secreting cells with the regulation of c-Maf, with the long-term aim of developing a new type of therapy for diabetes mellitus.

Conflict of interest

None declared.

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