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

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Correction added on 22 September 2015, after first online publication: The order of authors and the corresponding author’s information were previously wrong. These were corrected in this version.

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.

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.

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
Macrophage-activating factor (Maf) is a family of oncoproteins 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 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/L-Maf 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 mouse 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...
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. Furthermore, 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 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 type 1 diabetes and virus-induced diabetes in rat insulin promoter lymphocytic choriomeningitis virus nucleoprotein (RIP-LCMV-NP) mice. The onset of disease was significantly delayed, and the overall
incidence decreased in mice that carry the \textit{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 \textit{insulin} gene, compared with the simultaneous induction of these three transcription factors [45].

\textit{C-Maf} is prominent in areas around the branching ducts and acinar buds. Zhang \textit{et al.} [46] have found that the expression of \textit{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 \textit{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 \textit{c-Maf}. Although MafA is likely to be more specific for \beta-cell differentiation and functional insulin secretion, insulin-positive cells are co-expressed with MafB or \textit{c-Maf} in addition to mafA, suggesting that \textit{c-Maf} may take part in the process of insulin-producing \beta-cell differentiation [47].

The oncogene \textit{c-Maf} is involved in the translocation found in approximately 5–10% of multiple myelomas. It is proposed that \textit{c-Maf} transforms plasma cells by stimulating cell cycle progression and by altering bone marrow stromal interactions [48]. Thus, the stimulation of \textit{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 \textit{c-Maf} to stimulate cell proliferation for therapeutic purpose.

\textbf{Conclusion}

In this review, we summarized the functions and roles of \textit{c-Maf} in various biological processes and the recent progress in elucidating the mechanisms with which \textit{c-Maf} regulates cellular development and differentiation. To depict the entire regulatory network involving \textit{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 \textit{c-Maf}, in particular in pancreatic islets, remains to be elucidated. The expression of \textit{c-Maf} is higher in pancreatic duct cells than in pancreatic islets cells, and we suggest that pancreatic duct cells can be converted to

\begin{table}[h]
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\begin{tabular}{lll}
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Effect/result & Experimental tissue/cell type & References \\
\hline
C-Maf is critical for \alpha-cell development, differentiation and glucagon biosynthesis & Primary rat pancreatic \alpha cells & [38] \\
Activate glucagon gene expression & Mouse pancreatic cell & [39] \\
Onset of diabetes delayed and overall incidence decrease & Transgenic mouse islet \beta 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 & Embryonic and adult mouse pancreatic cell & [49] \\
C-Maf expressed in both \alpha and \beta cells & & \\
\hline
\end{tabular}
\caption{Effects of \textit{c-Maf} in the regulation of pancreatic endocrine cells}
\end{table}
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.

**References**

1. American Diabetes Association. Standards of medical care in diabetes 2014. Diabetes Care 2014; 37(Suppl 1): S14–S80.
2. Bouwens I, Pipeleers DG. Extra-insular beta cells associated with ductules are frequent in adult human pancreas. Diabetologia 1998; 41(6): 629–633.
3. Lee J, Sugiyama T, Liu Y, et al. Expansion and conversion of human pancreatic ductal cells into insulin-secreting endocrine cells. Elife 2013; 2(e00991): 1–22.
4. Kawai S, Goto N, Katoaka K, et al. Isolation of the avian transforming retrovirus, AS42, carrying the v-maf oncogene and initial characterization of its gene product. Virology 1992; 188: 777–784.
5. Chesi M, Bergsagel PL, ShoukoukOU, et al. Frequent dysregulation of the c-maf proto-oncogene at 16q23 by translocation to an Ig locus in multiple myeloma. Blood 1998; 91: 4457–4463.
6. Katoaka K, Nishizawa M, Kawai S. Structure-function analysis of the maf oncogene product, a member of the b-Zip protein family. J Virol 1993; 67(4): 2133–2141.
7. Ogino H, Yasuda K. Induction of lens differentiation by activation of a b-Zip transcription factor, L-Maf. Science 1998; 280: 115–118.
8. Katoaka K, Fujiwara KT, Noda M, et al. Maβ, a new Maβ family transcription activator that can associate with Maf and Fos but not with Jun. Mol Cell Biol 1994; 14(11): 7581–7591.
9. Swaroop A, Xu JZ, Pawar H, et al. A conserved retina-specific gene encodes a basic motif/lucine zipper domain. Proc Natl Acad Sci U S A 1992; 89(1): 266–270.
10. Fujiwara KT, Katoaka K, Nishizawa M. Two new members of the maf oncogene family, maβK and maβF, encode nuclear b-Zip proteins lacking putative transcription activator domain. Oncogene 1993; 8(9): 2371–2380.
11. Katoaka K, Igarashi K, Itoh K, et al. Small Maf proteins heterodimerize with Fos and may act as competitive repressors of the NF-E2 transcription factor. Mol Cell Biol 1995; 15(4): 2180–2190.
12. Takagi Y, Kobayashi M, Li L, et al. MaβT, a new member of the small Maβ family protein in zebrafish. Biochem Biophys Res Commun 2004; 320(1): 62–69.
13. Blank V. Small Maf proteins in mammalian gene control: more dimerization partners or dynamic transcriptional regulators? J Mol Biol 2008; 376(4): 913–925.
14. Mitchell PJ, Tjan R. Transcriptional regulation in mammalian cells by sequence-specific DNA binding proteins. Science 1999; 245(496): 371–378.
15. Yoshida T, Ohkumo T, Ishibashi S, et al. The 5-AF-rich half-site of Maβ recognition element: a functional target for bZIP transcription factor Maβ. Nucleic Acids Res 2005; 33(11): 3465–3478.
16. Kawauchi S, Takahashi S, Nakajima O, et al. Regulation of lens fiber cell differentiation by transcription factor c-Maf. J Biol Chem 1999; 274(27): 19254–19260.
17. Oshida K, Imai J, Koyama Y, et al. Differential expression of maβ1 and maβ2 genes in the developing rat lens. Invest Ophthalmol Vis Sci 1997; 38(12): 2679–2683.
18. Xie Q, Cvekl A. The orchestration of mammalian tissue morphogenesis through a series of coherent feed-forward loops. J Biol Chem 2011; 286: 43269–43271.
19. Ring BZ, Cordes SP, Overbeek PA, et al. The 5-AT-rich half-site of Maf recognizes nucleotide motifs with AT diads. Acta Histochem 2006; 107(6): 469–472.
20. Kase S, Yoshida K, Sakai M, et al. Immunolocalization of cyclin D1 in the developing lens of c-maf−− mice. Acta Histochem 2006; 107(6): 469–472.
21. Kim JI, Li T, Ho IC, et al. Requirement for the c-Maf transcription factor in crystallin gene regulation and lens development. Proc Natl Acad Sci U S A 1999; 96(7): 3781–3785.
22. Liu FY, Tang XC, Deng M, et al. The tumor suppressor p53 regulates c-maf and Prox-1 to control lens differentiation. Curr Mol Med 2012; 12(8): 917–928.
23. Imaki J, Tsuchiya K, Mishima T, et al. Developmental contribution of c-Maf in the kidney: distribution and developmental study of c-maf mRNA in normal mice kidney and histological study of c-maf knockout mice kidney and liver. Biochem Biophys Res Commun 2004; 320(4): 1323–1327.
24. Nakamura M, Hamada M, Hasegawa K, et al. c-Maf is essential for the F4/80 expression in macrophages in vivo. Gene 2009; 445(1–2): 66–72.
25. Shirota S, Yoshida T, Sakai M, et al. Correlation between the expression level of c-maf and glutathione peroxidase-3 in c-maf−− mice kidney and c-maf overexpressed renal tubular cells. Biochem Biophys Res Commun 2006; 348(2): 501–506.
26. Blonska M, Joo D, Nurieva RI, et al. Activation of the transcription factor c-Maf in T cells is dependent on the CARMA1-IRAK signaling cascade. Sci Signal 2013; 6(306a): 1–12.
27. Buat et al, Jin H, Paterson K, et al. The stimulatory molecule ICOS regulates the expression of c-Maf and IL-21 in the development of follicular T helper cells and TH-17 cells. Nat Immunol 2009; 10(2): 167–175.
28. Pat C, Jin H, Awasthi A, et al. Cutting edge: IL-27 induces the transcription factor c-Maf, cytokine IL-21, and the coordinulatory receptor ICOS that coordinately act together to promote differentiation of IL-10-producing Th1 cells. J Immunol 2009; 183(2): 797–801.
29. Sato K, Miyoshi F, Yokota K, et al. Marked induction of c-Maf protein during Th17 cell differentiation and its implication in memory Th cell development. J Biol Chem 2011; 286(17): 14963–14971.
30. Cao S, Liu J, Song L, et al. The proto-oncogene c-Maf is an essential transcription factor for IL-10 gene expression in macrophages. J Immunol 2005; 174(6): 3484–3492.
31. Ho IC, Hodge MR, Rooney JW, et al. The proto-oncogene c-maf is responsible for tissue-specific expression of interleukin-4. Cell 1996; 85(7): 973–983.
32. Elias D, Mallin A, Ablamunits V, et al. Hsp60 peptide therapy of NOD mouse diabetes induces a Th2 cytokine burst and downregulates autoimmunity to various beta-cell antigens. Diabetes 1997; 46(5): 758–764.
33. Tisch R, Wang S, Serreze DV. Induction of glutamic acid decarboxylase 65-specific TH2 cells and suppression of autoimmune diabetes at late stages of disease is epitope dependent. J Immunol 1999; 163(3): 1178–1187.
34. Kusakabe M, Hasegawa K, Hamada M, et al. c-Maf plays a crucial role for the definitive erythropoiesis that accompanies erythroblastic island formation in the fetal liver. Blood 2011; 118(5): 1374–1385.
35. Wende H, Lechner SG, Birchenmeier C. The transcription factor c-Maf in sensory neuron development. Transcription 2012; 3(6): 285–289.
36. Wende H, Lechner SG, Cheret C, et al. The transcription factor c-Maf controls touch receptor development and function. Science 2012; 335(6074): 1373–1376.
37. Katoaka K, Shiota S, Ando K, et al. Differentially expressed Maβ family transcription factors, c-Maf and Maβ, activate glucagon and insulin gene expression in...
pancreatic islet α- and β-cells. J Mol Endocrinol 2004; 32(1): 9–20.

38. Gosmain Y, Marthinet E, Cheyssac C, et al. Pax6 controls the expression of critical genes involved in pancreatic (alpha) cell differentiation and function. J Biol Chem 2010; 285(43): 33381–33393.

39. Gosmain Y, Avril I, Mamin A, et al. Pax-6 and c-Maf functionally interact with the alpha-cell-specific DNA element G1 in vivo to promote glucagon gene expression. J Biol Chem 2007; 282(48): 35024–35034.

40. Pauza ME, Nguyen A, Wolfe T, et al. Variable effects of transgenic c-Maf on autoimmune diabetes. Diabetes 2001; 50(1): 39–46.

41. Cameron MJ, Arreaza GA, Zucker P, et al. IL-4 prevents insulitis and insulin-dependent diabetes mellitus in nonobese diabetic mice by potentiation of regulatory T helper-2 cell function. J Immunol 1997; 159: 4686–4692.

42. Leavenworth JW, Ma X, Mo YY, et al. SUMO conjugation contributes to immune deviation in nonobese diabetic mice by suppressing c-Maf transactivation of IL-4. J Immunol 2009; 183: 1110–1119.

43. Lai CY, Lin SY, Wu CK, et al. Tyrosine phosphorylation of c-Maf enhances the expression of IL-4 gene. J Immunol 2012; 189(4): 1545–1550.

44. Katz LS, Geras-Raaka E, Gershengorn MC. Reprogramming adult human dermal fibroblasts to islet-like cells by epigenetic modification coupled to transcription factor modulation. Stem Cells Dev 2013; 22(18): 2551–2560.

45. Miyashita K, Miyatsuka T, Matsuoka TA, et al. Sequential introduction and dosage balance of defined transcription factors affect reprogramming efficiency from pancreatic duct cells into insulin-producing cells. Biochem Biophys Res Commun 2014; 444(4): 514–519.

46. Zhang XL, Gu YY, Zhou WZ, et al. Expression of Maf genes in pancreatic duct and pancreatic islet. Prog Biochem Biophys 2008; 35(4): 431–436.

47. Tsuchiya M, Taniguchi S, Yasuda K, et al. Potential roles of large mafs in cell lineages and developing pancreas. Pancreas 2006; 32(4): 408–416.

48. Hurt EM, Westner A, Rosenwald A, et al. Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. Cancer Cell 2004; 5(2): 191–199.

49. Nishimura W, Kondo T, Salameh T, et al. A switch from MafB to MafA expression accompanies differentiation to pancreatic beta-cells. Dev Biol 2006; 295(2): 526–539.