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Multiple Mechanisms and Functions of Maf Transcription Factors in the Regulation of Tissue-Specific Genes

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Maf family transcription factors are regulators of tissue-specific gene expression and cell-differentiation in a wide variety of tissues and are also involved in human diseases and oncogenic transformation. To establish tissue-specific expression, Maf binds to Maf-recognition elements (MAREs) in the regulatory regions of target genes, and functionally interacts with other transcription factors. For example, L-Maf and c-Maf, which are specifically expressed in developing lens cells, act synergistically with Sox proteins to induce lens-specific crystalline genes. MafA, a β-cell-specific member of the Maf family, activates the insulin gene promoter synergistically with Pdx1 and Beta2 to establish β-cell specific expression. Furthermore, in β-cells, MafA activity is regulated at both the transcriptional and post-translational levels by glucose and oxidative stress. This review summarizes the functions and roles of Maf in various biological processes and recent progress in elucidating the mechanisms whereby Maf proteins regulate transcription.

Key words: basic-leucine zipper structure, cell differentiation, oncogenic transformation, tissue-specific gene expression, transcriptional network.

Abbreviations: bZip, basic leucine zipper; EHR, extended homology region; PLE, presumptive lens ectoderm; MAREs, Maf-recognition elements; bHLH, basic helix-loop-helix; MODY, maturity-onset diabetes of the young; HMG, high mobility group.

BASIC CHARACTERISTICS OF MAF TRANSCRIPTION FACTORS

The Maf family is a subgroup of the basic leucine zipper (bZip) transcription factors with homology to the v-Maf oncoprotein, the founding member of the Maf family, which was originally identified in the genome of the AS42 chicken musculoaponeurotic sarcoma retrovirus in 1989 (*1*). To date, genes encoding Maf family proteins have been isolated from vertebrate (mammals, birds, frogs and fish) and from invertebrate (*Drosophila*) species (Fig. 1A and B) [summarized in (*2*)]. The Maf family members are unique among the bZip factors in that they contain a highly conserved extended homology region (EHR), or ancillary DNA binding region, in addition to a typical basic region, and both regions are involved in target DNA sequence recognition (Fig. 1A).

The members of the Maf family are subdivided into two groups, large Maf and small Maf proteins (Fig. 1A), based on their structure and function. The small Maf proteins (MafK, MafF, MafG, MafT and Maf-S) lack the transactivation domain and repress transcription when they form homodimers. In contrast, when these proteins form heterodimers with Cap'n'collar (CNC) or Bach family bZip proteins, they can activate or repress transcription of genes regulating many aspects of cellular function, including erythroid-differentiation and oxidative stress responses [for review, see (*3*, *4*)].

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This review will focus in the second subgroup, the large Maf proteins (v-Maf/c-Maf, MafB/Kreisler/Valentino, MafA/L-Maf/S-Maf1, S-Maf2/Krml2, Nrl and DMaf/Traffic Jam) (Fig. 1B) (*1*, *5–15*), which have a conserved amino-terminal domain related to transactivator function (Fig. 1A). This domain is rich in Asp (D), Glu (E), Ser (S), Thr (T) and Pro (P) residues, and recent findings suggest that phosphorylations within this domain regulate the biological activity of Maf proteins (*16*, *17*). The region between the D/E/S/T/P-rich domain and the bZip domain is relatively divergent among the family members and is referred to as the hinge region, because, with the exception of Nrl, this region contains stretches of polyglycine or polyhistidine, which can form a flexible hinge in the protein.

The large Maf proteins (hereafter referred to simply as Maf proteins) form homodimers through their leucine zipper domains and bind to relatively long consensus DNA sequences termed Maf-recognition elements (MAREs) (Fig. 1A) (*18*, *19*). The T-MARE element (TGCTGACTCAGCA) contains a phorbol 12-*O*-tetradecanoate-13-acetate (TPA)-responsive element (TRE: TGACTCA) and the C-MARE element (TGCTGACGTCAGCA) contains a cyclic AMP-responsive element (CRE: TGACGTCA), to which the AP-1 and the CREB/ATF families of bZip proteins bind, respectively. Previous reports have shown that Maf family proteins have the ability to form heterodimers with AP-1 (Fos and Jun family) proteins *in vitro* and bind to MAREs (*18*, *19*). However, heterodimers between Maf and the other bZip factors have not as yet been detected *in vivo*. Therefore, the large Maf proteins are thought to function as

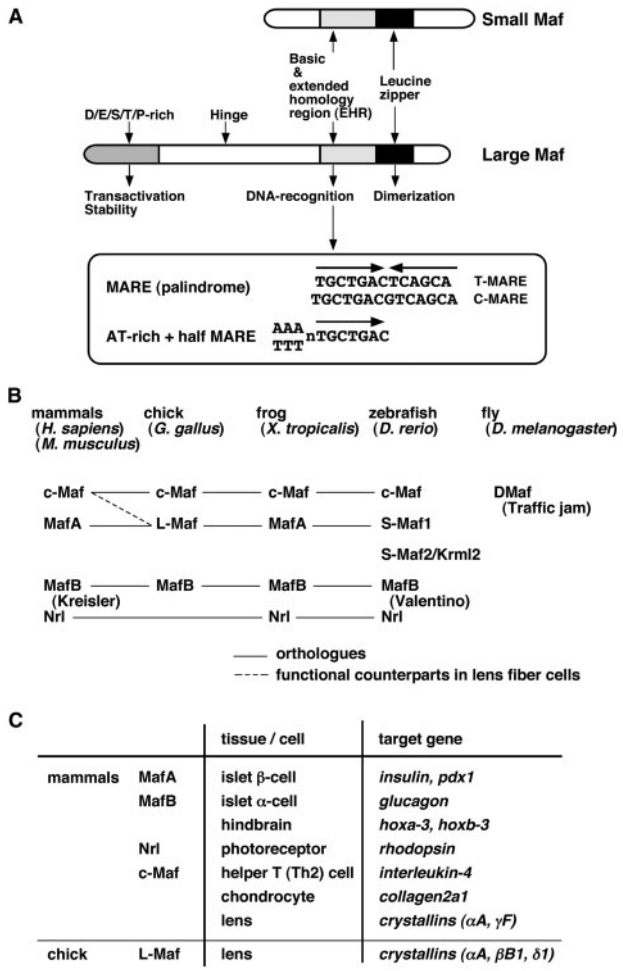

Fig. 1. **Schematic structures, DNA recognition sequences, and target genes of Maf family transcription factors.** (A) Schematic structures and functions of small and large Maf proteins. MARE: Maf-recognition element. (B) Members of large Maf family proteins identified in various species (*Homo sapiens, Mus musculus, Gallus gallus, Xenopus tropicalis, Danio rerio and Drosophila melanogaster*). Note that chicken L-Maf is an orthologue of mammalian MafA, but its function in lens fibre cells to activate crystallin genes seems to be replaced by c-Maf in mammals. (C) A partial list of target genes of mammalian (MafA, MafB, Nrl, and c-Maf) and chicken (L-Maf) large Maf factors.

homodimers, although more extensive studies may be needed to confirm this conclusion.

The typical bZip proteins, such as Fos, Jun and ATF/CREB family members, bind palindromic DNA sequences of 7–8 bp in length, and X-ray crystallography has shown that a single α-helix of one monomer contacts the half site of the DNA in the major groove (*20*). In contrast, the Maf recognition sequence is relatively long (13–14 bp in length). Some base mismatches from the consensus recognition sequence are allowed in Maf homodimer binding to the palindromic MAREs, but GC residues flanking the central TRE or CRE seem to be critical for binding (*18*, *19*). Dlakic *et al*. (*21*) have shown that upon binding to DNA, the Maf EHR undergoes a conformational change, suggesting a unique mode of DNA-binding by Maf proteins. Recently, Yoshida *et al*. (*22*) showed that Maf homodimers also bind efficiently to MARE half-site preceded by an AT-rich sequence (AT-rich plus half MARE) (Fig. 1A), indicating that AT-rich sequences flanking MAREs are also important for binding. Therefore, Maf is unique among bZip proteins in that it can bind to several types of target sequences including palindromic MAREs and AT-rich plus half MARE. The DNA-sequences of regulatory elements of well-characterized Maf target genes have been shown to be related to these sequences (*22*, *23*).

MAF PROTEINS ARE REGULATORS OF TISSUE-SPECIFIC GENE EXPRESSION AND CELL DIFFERENTIATION

Physiological functions of the Maf transcription factors have been elucidated by a variety of approaches, *e.g*. forward or reverse genetics, biochemical and molecular identification of *cis*- and *trans*-regulatory components of specific genes, and bioinformatics. Although Maf was first identified as a retroviral transforming protein, it is now widely accepted that Maf family proteins are regulators of a wide variety of cell- and tissue-specific gene expression and also play a role in cell differentiation during development (Fig. 1C). The cellular counterpart of viral Maf (v-Maf), c-Maf was rediscovered as a T helper 2 (Th2) lineage-specific gene product and was shown to regulate Th2-specific *interleukin-4* expression (*24*). Nrl, which was isolated as a gene product specifically expressed in photoreceptor cells in the retina (*13*), is a regulator of photoreceptor specific rhodopsin gene expression (*25*, *26*). Knockout mice have revealed that Nrl is required for development of rod photoreceptor cells (*27*), and missense mutations in human *nrl* are associated with autosomal dominant retinitis pigmentosa (*28*).

Analysis of the mouse mutant *kreisler* has identified physiological function and target genes of MafB. In this mutant, organization of the 5th and 6th rhombomeres (r5/r6), the segmental compartments in the developing hindbrain, is abnormal, and *mafB* was identified as the gene responsible for this defect. MafB is expressed in r5/r6 during embryogenesis (*6*) and has been shown to regulate the expression of the *hoxa-3* and *hoxb-3* genes in r5/r6 and r5, respectively, by binding to their r5/r6- and r5-specific enhancer elements (*29*, *30*).

Analysis of tissue-specific enhancer elements has identified additional roles for Maf. For example, chicken L-Maf (the counterpart of mammalian MafA) was identified as a transcription factor which binds to the lens-specific enhancer of the chicken *αA-crystallin* gene (*9*). L-Maf also activates other crystallin genes, chicken *βB1-*, chicken *δ1-*, mouse *αA-*, and mouse *γF-crystallin*, by binding to MARE sequences located in the promoter or enhancer regions of these genes (*9*). In the developing chick embryo, L-Maf expression is initiated in the presumptive lens ectoderm (PLE), where *δ-crystallin* expression follows. L-Maf expression persists in the lens placode and, subsequently, lens vesicle where *αA-crystallin* gene expression is activated. Furthermore, gain- or loss-of-function experiments of L-Maf in the developing chick embryo revealed that L-Maf is a key regulator of lens development (*9*).

In the developing lens of vertebrates, Maf family members are expressed in different spatio-temporal

patterns [(*31*) and references therein], suggesting similar but distinct roles of Maf family members in lens development. In mice, for example, c-Maf and MafB are expressed in lens fiber and lens epithelial cells, respectively (*32*). The essential role of c-Maf in lens fiber cell differentiation has been shown using *c-maf* knockout mice, which exhibit microphthalmia due to substantial reduction or loss of expression of α-, β-, and γ-*crystallins* (*32–34*). Furthermore, missense mutations in the DNA-binding domain of c-Maf were identified in individuals from a family affected by autosomal dominant cataract formation (*35*) and also in *opaque flecks in lens (Ofl)* mutant mice, which exhibit cataracts in the heterozygous state (*36*). Curiously, role of MafA in lens fiber development is, if any, very small (*37*), in spite that MafA is the mammalian orthologue of chicken L-Maf. Therefore, roles of Maf family members are not necessarily conserved among species. At least for lens fiber development, mammalian c-Maf seems to be the functional counterpart of L-Maf (Fig. 1B).

A partial list highlighting key Maf target genes identified thus far is shown in Fig. 1C. Comprehensive analyses of the developmental expression patterns of Maf family members in the chicken indicate that these proteins are expressed in a wide variety of different tissues and cells (*38*). Therefore, the roles and target genes of Maf transcription factors largely remain to be elucidated. Given the role of Maf proteins in cell differentiation, it is likely that some of these target genes may be related to human diseases or developmental disorders.

ROLE OF MAFA IN INSULIN GENE EXPRESSION IN PANCREATIC β-CELLS

Recently, an important advance in understanding the roles of Maf transcription factors has been made. MafA, the mammalian homologue of chicken L-Maf, was identified as a regulator of insulin gene expression (*11*, *12*, *39*, *40*).

Insulin is a polypeptide hormone that critically regulates blood glucose levels and is exclusively produced by β-cells in the islets of Langerhans in the pancreas. Previous efforts have revealed that the promoter region of about 350 bp can direct β-cell specific expression of insulin, and functionally important *cis*-regulatory elements and *trans*-acting factors have been identified (Fig. 2) [for review, see (*41*)]. Pdx1 is a homeodomain-containing transcription factor and binds to the insulin promoter A1, GG2 and A3 elements. Beta2 is a basic helix-loop-helix (bHLH) transcription factor and binds to the E1 element by forming a heterodimer with the ubiquitous bHLH factor E47. Both Pdx1 and Beta2 are expressed in islet endocrine cells, and gene ablation experiments in mice have demonstrated that these proteins play critical roles in insulin gene expression, as well as in islet development and function. Pdx1 and Beta2 are responsible for the maturity-onset diabetes of the young (MODY) type 4 and 6, respectively, and mutations in these proteins have also been found in some cases of type 2 diabetes mellitus. Genes responsible for other types of MODY, HNF1α(MODY3), HNF1βMODY5) and HNF4 (MODY1), have been shown to regulate insulin gene expression either directly by binding to the promoter or indirectly by regulating other insulin transcription factors.

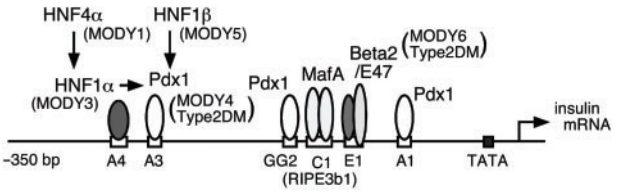

Fig. 2. **Key regulators of the insulin gene promoter.** Important *cis*-elements and *trans*-factors required for β-cell-specific insulin gene expression are shown. MODY, maturity-onset diabetes of the young; Type2DM, type2 diabetes mellitus.

The C1/RIPE3b element also plays a critical role in β-cell-specific insulin gene expression, as well as in glucose-regulated expression of insulin (*42*). Previous studies have identified a β-cell-restricted C1-binding factor that appeared in response to glucose in pancreatic β-cell nuclear extracts (*43*). The C1-binding factor was recently purified biochemically and identified as MafA (*11*, *39*). Our bioinformatics approach searching MARE-related sequences in the GenBank database has also identified the C1 element as a target of MafA (*12*, *18*).

MafA, Pdx1 and Beta2 are only weak transactivators for the insulin promoter when expressed alone, but when co-expressed, these three factors synergistically and strongly activate the promoter (*44–47*). MafA is expressed in β-cells, but not in α-, γ- or δ-cells, in adult pancreatic islets (*39*, *48*, *49*). In contrast, expression of Pdx1 and Beta2 is not restricted to β-cells. Therefore, β-cell-restricted expression of the insulin gene seems to be established by the synergistic action of these transcription factors. Furthermore, simultaneous expression of these three factors in non-β-cells, such as liver cells, induced expression of the endogenous insulin gene, as well as other β-cell specific genes such as glucokinase and the potassium channel subunits, Kir6.2 and SUR1. These data indicate that MafA, Pdx1 and Beta2 are excellent potential targets for gene therapy methods to treat diabetes (*45*).

SYNERGISTIC ACTION OF MAF AND OTHER TRANSCRIPTION FACTORS

Synergy in transcriptional activation by Maf and other transcription factors is also observed in other cells and tissues. For example, Nrl is specifically expressed in rod photoreceptor cells and, together with Crx, a cone and rod photoreceptor cell-specific homeodomain transcription factor, synergistically activates the rod cell-specific rhodopsin promoter (*50*).

The Sox1, Sox2 and Sox3 proteins are important regulators of lens development and contain high mobility group (HMG) box DNA-binding domains. They are expressed in developing lens and regulate the δ-*crystallin* gene in chicken and the γ*F-crystallin* gene in mouse. L-Maf and Sox2 synergistically induce expression of the δ-*crystallin* gene in chicken (*51*), and c-Maf acts synergistically with Sox1, Sox2 and Sox3 to activate the

γF-crystallin gene in mouse (*52*). Similarly, Sox9, a Sox protein which regulates chondrocyte differentiation, acts synergistically with c-Maf to activate the type II collagen gene *Col2a1* by binding to an enhancer element (*53*). In addition, c-Maf induces *interleukin-4* gene expression in cooperation with NF-AT and NIP45 factors in Th2 cells (*54*).

The molecular mechanisms of the synergistic actions of Maf and these factors are not yet well understood. In the examples cited here, the binding sites of Maf and the other transcription factors are located in close proximity to each other within enhancer region. In the case of MafA activation of the insulin promoter, a direct interaction with both Pdx1 and Beta2 has been demonstrated (*44*). Generally, such protein–protein interactions enhance the affinity of the *trans*-factors for their respective *cis*-elements and/or co-activators, and, thus, stabilizes the DNA–protein complexes. However, the binding of c-Maf and Sox2 to the *γF-crystallin* enhancer is not cooperative (*52*). An important and interesting finding is that a mutation in c-Maf is found in some cataract patients. This point mutation, R288P, is located within the conserved EHR of c-Maf, but did not affect its DNA-binding activity. Rajaram and Kerppola (*52*) have demonstrated that this mutation eliminated the ability of c-Maf to act synergistically with Sox proteins to stimulate the *γF-crystallin* gene promoter. These results indicate the functional importance of the synergistic action of Maf proteins in gene regulation *in vivo*, and highlight a key aspect of the molecular mechanism of Maf protein function that will require further investigation.

TARGET GENE SELECTIVITY OF MAF FAMILY MEMBERS

As described above, c-Maf and MafB are expressed in lens fibre and lens epithelial cells, respectively (*31*). Similarly, distinct members of the Maf protein family are, in some cases, expressed in different types of cells in the same tissue. For instance, MafA is specifically expressed in β-cells in adult pancreatic islets (*37*, *39*, *48*, *49*), and it has recently been shown that MafB is exclusively expressed in α-cells in the islets and regulates glucagon gene expression (*49*, *55*). c-Maf seems to be expressed both in α- and β-cells (*39*, *48*, *49*). Do these proteins have a unique function in each cell types, or are they functionally interchangeable?

Gel mobility shift analysis has shown that the DNA-binding specificities of the Maf family members are very similar (*5*, *19*). Furthermore, luciferase assays have shown that not only MafA but also MafB and c-Maf can activate the insulin promoter, and that MafA and c-Maf can activate the glucagon promoter with an efficiency similar to MafB (*39*, *40*, *49*). Therefore, it seems that the three Maf factors regulate the same target genes and are functionally interchangeable.

Interestingly, however, they exhibit clear differences in their ability to induce endogenous target genes. L-Maf is the first Maf family member to be expressed in the PLE in chicken and is the master regulator of lens differentiation. Only L-Maf can efficiently induce endogenous δ-crystallin expression, when ectopically expressed in cultured primary retina cells, although c-Maf and MafB are similarly potent activators of the crystallin gene promoter in luciferase assays (*56*). The molecular mechanism underlying the selectivity of specific Maf members toward endogenous target genes is currently unknown. One factor may be the compatibility of Maf with other transactivators. For example, we have shown that, among Maf family members, only MafA can synergistically activate the insulin promoter with Pdx1 and Beta2 (*46*), suggesting that only MafA may be structurally and functionally compatible to interact with Pdx1 and Beta2. Considering that expression patterns of Maf family members are also temporally regulated in both developing lens and islet cells, sequential changes in their expression may thus contribute to proper execution of cell-differentiation programs and establishment of specific gene expression in terminally differentiated cells.

REGULATION OF *mafA* EXPRESSION AND MafA PROTEIN LEVELS IN β-CELLS

In pancreatic β-cells, insulin secretion as well as insulin gene expression is regulated by a variety of extracellular stimuli, including glucose, under physiological and pathological conditions. Insulin gene transcription is stimulated by short-term exposure to high glucose. However, long-term or chronic exposure to high glucose, as in the hyperglycaemic conditions ocurring in type 2 diabetes, leads to β-cell dysfunction and decrease in insulin production. The molecular mechanism of this β-cell failure (glucotoxicity) is not well understood, but oxidative stress caused by excess glycolytic reactions may play a role. Previously, C1/RIPE3b-binding activity in β-cells, which plays a critical role in the regulation of β-cell-specific and glucose-regulated expression of the insulin gene, was shown to increase in response to short-term glucose exposure, and decrease in response to chronic glucose exposure or oxidative stress (*43*, *57*). As indicated above, MafA was identified as the C1/RIPE3b-binding factor, which has enabled us to examine the underlying molecular mechanisms of these responses to glucose exposure.

As illustrated in Fig. 3, recent data indicates the involvement of both transcriptional and post-translational processes in the regulation of MafA by acute and chronic glucose exposure of β-cells. Levels of *mafA* mRNA as well as MafA protein are increased under high glucose conditions (*12*, *44*). Recently, Kitamura *et al*. (*58*) showed that glucose and oxidative stress regulate *mafA* expression at the transcriptional level through FoxO1, a forkhead transcription factor involved in oxidative stress responses and metabolism. Raum *et al*. (*59*) have identified a *cis*-regulatory region of *mafA* approximately 8 kb upstream of the transcription start site, which regulates its β-cell-specific expression. Pdx1, FoxA2 and Nkx2.2, which are all important transcriptional regulators of β-cell formation and function, are able to regulate transcription of *mafA* by binding to this *cis*-regulatory region (*59*).

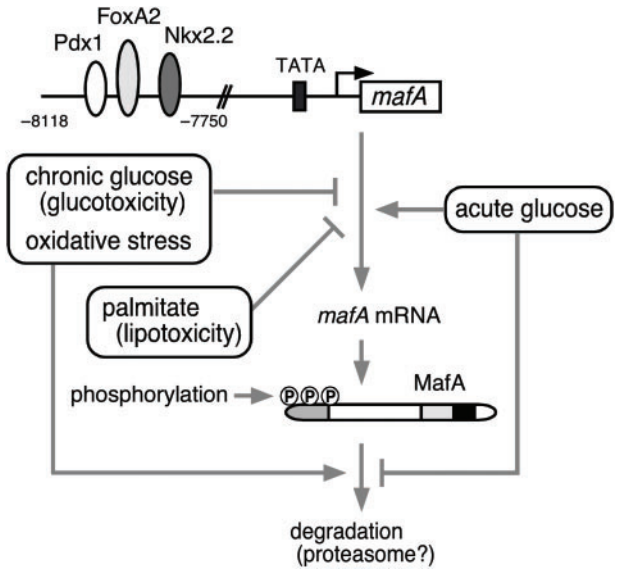

Fig. 3. **Multiple modes of MafA regulation in β-cells.** Transcription of the *mafA* gene, as well as MafA protein stability, in β-cells, is regulated by acute and chronic exposure to glucose, oxidative stress and fatty acids.

Harmon *et al*. (*60*) have shown that chronic exposure of a β-cell line to high glucose leads to a decrease in MafA protein without a corresponding change in *mafA* mRNA level, indicating a post-translational control of MafA protein stability by oxidative stress. Avian MafA/L-Maf is phosphorylated by MAP kinases at multiple sites, and the phosphorylation of MafA, especially at Ser65, induces degradation of MafA by the proteasome (*17*). Similar mechanism may be active in β-cells, and we have recently found that MafA is phosphorylated at multiple serine and threonine residues in the amino-terminal region and undergoes proteasomal degradation in β-cells in response to glucose concentration (unpublished results).

In obesity, or in type 2 diabetes, prolonged exposure of β-cells to fatty acids also causes dysfunction of β-cells (lipotoxicity), including defects in glucose-induced insulin secretion and insulin transcription. The molecular mechanism underlying lipotoxicity has been unknown, but recently, exposure of β-cells to palmitate was demonstrated to decrease insulin expression through reduction of *mafA* mRNA expression, as well as nuclear exclusion of Pdx1 (*61*).

Investigation of the molecular mechanisms of gene regulation by MafA has just recently begun. Close examination and elucidation of MafA regulation in β-cells will enable us to develop a comprehensive understanding of the pathophysiology of β-cells and the molecular mechanisms of glucotoxicity and lipotoxicity.

CONCLUSION AND FUTURE PROSPECTS

Since identification of the founding member v-Maf in 1989, many aspects of the physiological roles of Maf family transcription factors have been elucidated. Maf factors are accepted as regulators of tissue-specific gene expression and cell differentiation. However, Maf is also involved in cell transformation. When overexpressed, c-Maf, MafB and MafA induce transformation of chicken embryo fibroblasts (*62*), and c-*maf* or *mafB* is frequently overexpressed in multiple myeloma caused by chromosome translocations or by unknown mechanisms (*63*).

Why do Maf factors have such opposing activities, i.e. cell differentiation and oncogenic transformation? Recently, Pouponnot *et al*. (*64*) demonstrated that the roles of Maf in cell transformation and differentiation are cell context-dependent. Furthermore, according to the recent analysis of *mafA* knockout mice, MafA seems to be involved not only in insulin gene transcription but also in proliferation and survival of β-cells in the adult pancreas (*37*). In order to depict the entire regulatory network involving Maf transcription factors in various tissues and in cell transformation, it will be necessary to identify target genes and to elucidate crosstalk with other classes of transcription factors, interactions with co-activators, transcriptional regulation and regulatory mechanisms of post-translational modifications.

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