



Review

ANDOH-TAJIMA Award

Functional analysis of large MAF transcription factors and elucidation of their relationships with human diseases

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Abstract: The large MAF transcription factor group is a group of transcription factors with an acidic region, a basic region, and a leucine zipper region. Four types of MAF, MAFA, MAFB, c-MAF, and NRL, have been identified in humans and mice. In order to elucidate the functions of the large MAF transcription factor group *in vivo*, our research group created genetically modified MAFA-, MAFB-, and c-MAF-deficient mice and analyzed their phenotypes. MAFA is expressed in pancreatic β cells and is essential for insulin transcription and secretion. MAFB is essential for the development of pancreatic endocrine cells, formation of inner ears, podocyte function in the kidneys, and functional differentiation of macrophages. c-MAF is essential for lens formation and osteoblast differentiation. Furthermore, a single-base mutation in genes encoding the large MAF transcription factor group causes congenital renal disease, eye disease, bone disease, diabetes, and tumors in humans. This review describes the functions of large MAF transcription factors *in vivo* and their relationships with human diseases.

Key words: gene engineering, genetically modified mouse, human disease model, large MAF transcription factor

Introduction

The MAF transcription factor group is a group of transcription factors identified as cellular homologues of v-MAF, an oncogene product protein discovered in AS42, which is a virus that causes musculoaponeurotic fibrosarcoma in chickens [1]. These transcription factors bind to DNA sequences called MAF recognition elements (MAREs) through a basic region involved in DNA binding and a leucine zipper structure (bZip domain) required for dimer formation (Fig. 1). The MARE sequences are relatively long (13 or 14 bp); however, even half of the sequences (half MARE) have been reported to function. The MAF family is divided into two sub-families: large MAF transcription factors with a bZip domain and a transcriptional activation domain and small MAF transcription factors with only a bZip domain [2,

3]. Large MAF transcription factors are generally considered to form homodimers and bind to the MARE sequence to activate transcription of target genes in the vicinity. On the other hand, the small MAF transcription factors are reported to form homodimers that suppress the transcription of target genes as well as heterodimers with transcription factors possessing a transcriptional activation domain to activate transcription [4]. Four types of large MAFs—MAFA, MAFB, c-MAF, and NRL—have been identified in mice and humans, while three types of small MAFs—MAFF, MAFG, and MAFK—have been reported. c-MAF is a cell-related gene product of v-MAF. Since they are transcriptional regulators, MAFs are considered important for carcinogenesis, cell differentiation, and cellular functions; however, their functions and relationships with diseases remain unclear. The present review focuses on the members

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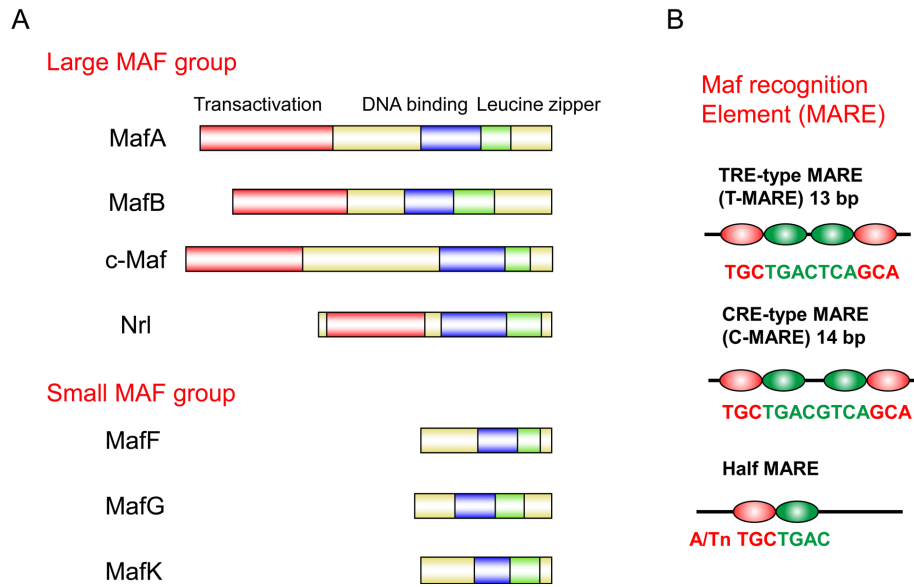


Fig. 1. Structural features of MAF proteins. A. Schematic diagrams of four large MAF and three small MAF protein structures. Large MAF proteins contain a transactivation domain, DNA binding basic domain, and leucine zipper domain, while the small MAF proteins do not have a transactivation domain. B. MAF proteins bind as homodimers to three types of target sequences, two classical Maf recognition element (MARE) sites and the 5'-AT-rich MARE half-site.

of large MAF transcription factor group and describes their functions *in vivo* and their associations with human diseases, including carcinogenesis.

Functional Analysis of Large MAF Transcription Factors *in Vivo*

MAFA

MAFA has been identified as a transcription factor that induces lens development from the epidermis in chickens [5]. Subsequent analysis revealed it to be a transcription factor that binds to the C1 element of the insulin promoter region that is important for insulin expression in pancreatic β cells [6, 7] (Fig. 2). In order to elucidate the function of MAFA *in vivo*, we generated *Mafa*-deficient ICR mice by replacing the *Mafa* with *nls-LacZ* and analyzed the phenotype [8]. Although *Mafa* homo-deficient mice were born normally, they gradually showed mild fasting hyperglycemia. A glucose tolerance test showed abnormal glucose tolerance, and analysis of isolated pancreatic islets revealed an abnormal insulin secretory mechanism in pancreatic β cells. Moreover, gene expression analysis confirmed decreased expression of *Ins1*, *Ins2*, *Pdx1*, *Neurod1*, and *Glut2*. Interestingly, regulatory regions of *Ins1*, *Ins2*, *Pdx1*, and *Glut2* have MARE sequences, and these genes were identified as direct targets of MAFA [8]. In addition, Granuphilin, which is important for fusion of insulin granules to the pancreatic β cell plasma membrane, was reported to be a direct

	In vivo functions	Human diseases
MafA	β cell function Insulin transcription	Multiple myeloma Diabetes mellitus Insulinoma
MafB	Rhombomere segmentation Podocyte development Macrophage function α and β cell development Parathyroid development Lymphangiogenesis Keratinocyte differentiation	Multiple myeloma MCTO FSGS Duane Syndrome
c-Maf	Lens fiber cell development IL-4 transcription in T cells IL-10 transcription in macrophages Osteoblast development Pacinian corpuscle development	Cataract, iris coloboma Ayme-Gripp syndrome Multiple myeloma AILT
Nrl	Rod cell development	Retinitis pigmentosa

Fig. 2. Functions of large MAF transcription factors *in vivo* and their association with human diseases.

target of MAFA [9]. Although MAFA is essential for postnatal β cell function in mice, no apparent abnormality was observed in fetal pancreatic β cells [8]. Nishimura *et al.* suggested that MAFB is expressed along with MAFA in murine fetal pancreatic β cells and may compensate for the functional deficiency of MAFA [10] and stated that it is reportedly important along with MAFA in fetal pancreatic β cells. Thus, MAFA is an essential transcription factor for maintaining adult pancreatic β -cell function in mice. Subsequent studies revealed MAFA expression to be an important indicator for assessing pancreatic β -cell function in humans. Further-

more, direct reprogramming of insulin-producing pancreatic β cells can be achieved by forced overexpression of *Pdx1*, *Ngn3*, and *Mafa* in pancreatic exocrine cells *in vivo* [11]. Although there are contradicting reports on direct reprogramming of pancreatic β cells, it is clear that MAFA is important for insulin transcription.

Although MAFA is a transcriptional activator, its transcriptional activity is regulated by phosphorylation of multiple sites in the transcriptional activation domain by GSK3 β [12, 13]. These phosphorylation sites are conserved in the large MAF transcription factors, and their association with human disease development is described below.

MAFB

Mafb was identified as the causative gene in *Kreisl* (*Kr*) mice exhibiting turning behavior due to radiation-induced inner ear developmental defects. Analysis of *Kr* mice revealed that it is important for segment formation in the hindbrain, and its defect causes dysplasia in the inner ear [14]. Kataoka *et al.* independently isolated MAFB by homology screening of v-MAF [15]. Sieweke *et al.* reported that it suppresses ETS1 function and inhibits erythroid differentiation using the chicken hematopoietic system [16]; MAFB overexpression stimulates monocyte and macrophage differentiation [17]. Moreover, an analysis of the mouse *Kr* (*enu*) mutation, a mouse point mutation in the DNA-binding domain by ENU, revealed that MAFB is essential for the formation of renal glomerular epithelial cells (podocytes) [18]. On the other hand, a detailed analysis of *Kr* and wild-type mice revealed that the expression of *Mafb* was maintained in many tissues in *Kr* mice, indicating a partial defect only in the hindbrain [19]. Therefore, to elucidate MAFB function, *Mafb*-deficient mice were constructed by targeted gene disruption; *Mafb* homo-deficient mice died due to respiratory failure immediately after birth as a result of hypoplasia of the neuronal respiratory center [20]. We created *Mafb-Gfp* knock-in/knock-out mice in which *Mafb* was replaced with *Gfp* to identify MAFB function *in vivo*; the mice died soon after birth due to hindbrain abnormality, renal abnormality, and respiratory failure, as previously reported, but had unexpectedly normal macrophage numbers. A further detailed analysis revealed that the expression of F4/80, a macrophage cell surface antigen, was decreased [21]. In line with this finding, Sieweke's group reported that although the generation of macrophages was not abnormal, the actin formation in macrophages was abnormal [22]. In addition, parathyroid gland formation was abnormal in heterozygous mice, and homozygous mice lacked parathyroid hormone [23].

Since *Mafb* homo-deficient mice die immediately after birth, it is difficult to analyze MAFB function in adults. Therefore, we constructed a *Mafb* conditional knockout mouse to analyze MAFB function *in vivo*. We identified that MAFB regulates the expression of apoptosis inhibitor of macrophage (AIM) that regulates macrophage apoptosis, thereby suppressing foam cell apoptosis in atherosclerotic lesions, which is important for the formation of atherosclerotic lesions [24]. In addition, the MafB regulated the phagocytic function of macrophages by controlling the expression of C1q, a complement component important for phagocytosis of dead cells and foreign substances, and scavenger receptor MSR1 [25, 26]. MafB functions in macrophages were reviewed by Hamada *et al.* [27]. Furthermore, it was revealed that MAFB is essential for the maintenance of glomerular podocytes in adult mice [28].

MAFB was reportedly expressed in α and β pancreatic cells in embryonic mice, and the development of these cells was impaired in *Mafb* homo-deficient mice [29]. Analysis of *Mafb* conditional knockout mice revealed that MAFB is required for the development of fetal pancreatic β cells but is not functional under normal conditions in the adult mouse. However, it is essential for pancreatic α cell development and function throughout the mouse life span [30, 31].

In addition, MAFB is reportedly involved in the myeloid commitment of hematopoietic stem cells and macrophage proliferation [32, 33], thymus development [34], hair cuticle formation [35], skin keratinocyte differentiation [36], urethral formation [37], and lymph-angiogenesis [38, 39].

c-MAF

As mentioned above, c-MAF was identified as a cellular gene product of v-MAF. Subsequently it was reported to be a transcription factor essential for IL-4 expression in helper T (Th) cells of the immune system [40]. Since then, it has been reported to be important for regulating the functions of various immune cells, in particular T cells [41] and functional analysis of it in the immune system has progressed. We generated *c-Maf*-deficient mice to elucidate its functions in other organs [42]. *c-Maf* homo-deficient mice began to die during the late embryonic period, and none survived. The lens formation in the eyes of these animals was abnormal, and analysis of it confirmed that the proteins that constituted the lens, crystallins, were not expressed. The crystallin genes have MARE sequences, and c-MAF was found to directly control their expression. These results indicate that c-MAF is a transcription factor essential for lens formation [42, 43]. Further, fetal analysis revealed that

c-Maf is an important transcription factor for bone formation [44]. *c-Maf* homo-deficient mice exhibited embryonic lethality, but the cause of death was unknown; fetal analysis revealed the condition of anemia beginning in the mid-embryonic stage, suggesting death due to anemia. A detailed analysis of hematopoiesis in the fetal liver revealed that c-MAF was expressed in central macrophages that form blood islands, the sites of erythropoiesis in the fetal liver [45]. This finding is considered to identify the first transcription factor involved in blood island formation. c-Maf has also been reported to regulate F4/80 expression in macrophages [46].

As described above, since the *c-Maf* homo-deficient mouse exhibited embryonic lethality, it was not possible to analyze the function in adults. Therefore, conditional knockout mice were created by genome editing using CRISPR/Cas9 to elucidate its function in adults. Systematic deletion of *c-Maf* in adult mice resulted in survival of the mice but caused cataracts in the long term. Analysis of the lens revealed that lens epithelial cells could not differentiate into lens fiber cells and exhibited structural abnormalities causing cataract development [47]. Thus, although c-MAF is not essential for survival in adults, it seems to be involved in maintaining the functions of various organs.

NRL

NRL is specifically expressed in the retina [48] and is reported to be one of the causative genes for human autosomal dominant retinitis pigmentosa. This transcription factor is specifically expressed in rod photoreceptors of the retina and is predicted to be important for its differentiation. Therefore, in order to analyze the function of NRL *in vivo*, *Nrl*-deficient mice were created [49]. In *Nrl*-deficient mice, rod photoreceptor and normal S-cone photoreceptor function were lost. Rod photoreceptors in the *Nrl*-deficient retina had short, sparse outer segments with a cone-like nuclear morphology and abnormal discs. Moreover, gene expression of rod photoreceptors was similar to that of the S-cone photoreceptors. These results suggest that NRL induces the differentiation of rod photoreceptors by inducing expression of genes specific to rod photoreceptors and activating Nr2e3 to suppress the differentiation of S-cone photoreceptors [49].

Large MAF Transcription Factors in Human Diseases

MAFA

Although MAFA has been shown to be important for the transcription of insulin in pancreatic β cells, it was only reported to be involved in a single human disease,

multiple myeloma, prior to 2018. However, in 2018, two unrelated families with familial diabetes and insulinoma were reported. Analysis of the causative gene mutation revealed a point mutation in the nucleotide sequence for the transcriptional activation domain of MAFA (Fig. 3). The serine next to the first phosphorylated serine is replaced by phenylalanine, and this mutation prevents phosphorylation of the transcriptional activation domain. Interestingly, such abnormal phosphorylation has also been reported in mutations of MAFB and c-MAF in human diseases as described below. Among these families, cases with this mutation in the hetero and homo form were reported. The incidence of diabetes in MAFA mutants is more common in men, while the incidence of insulinoma in MAFA mutants is more common in women, and gender differences have been reported in the development of these diseases [50].

MAFB

Since *Mafb* homo-deficient mice die due to respiratory failure immediately after birth, it was suspected that MAFB deficiency-related human diseases do not exist. However, in 2012, Zankl *et al.* identified *MAFB*, based on the whole exome sequence of patients, as the causative gene for multicentric carpo-tarsal osteolysis (MCTO) syndrome, which results in osteolysis of bones that form the palm and foot [51]. It has been reported that patients with MCTO have mutations in the phosphorylation sites of the transcriptional activation domain and show abnormal phosphorylation, which is similar to that in cases with MAFA mutations. Moreover, MCTO cases are reportedly complicated by hereditary focal segmental glomerulosclerosis (FSGS). Further, MAFB was identified as a causative gene for abnormal abduction of the eye in Duane syndrome. In a case of Duane syndrome, the truncated MAFB protein was suspected to be expressed by the mutated gene [52]. We collaborated with clinicians to identify Japanese cases with a new *MAFB* mutation showing FSGS and Duane syndrome. We identified a mutation in which the highly conserved leucine in the DNA-binding domain of *MAFB* was replaced with proline, which made its binding to the MARE sequence impossible (Fig. 4). To validate the identified mutation as the direct cause, the same mutation was introduced into mice by genome editing, where it induced lesions similar to those observed in human cases [53]. Thus, mutations in *MAFB* have been identified as causative genes for bone, eye, and kidney diseases.

c-MAF

As lens malformation was observed in c-MAF-deficient mice, it was suspected to be associated with eye

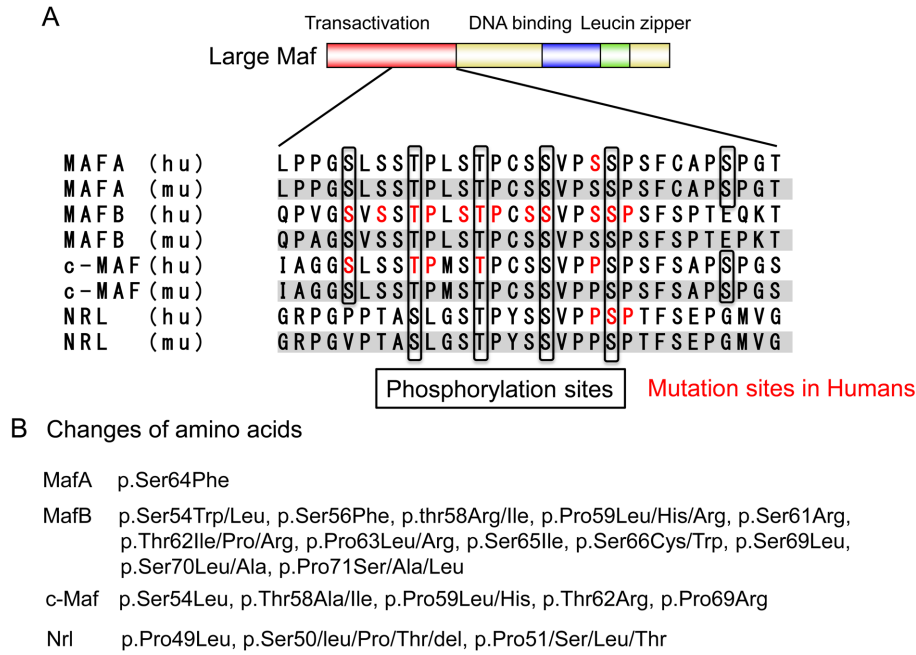


Fig. 3. Mutation sites in the transactivation domain of large MAF proteins identified in human patients. A. Red color indicates the amino acid substitutions observed in patients. Boxes indicate phosphorylation sites. (hu) indicates human amino acid sequence and (mu) indicates mouse. B. Detailed information about amino acid substitutions.

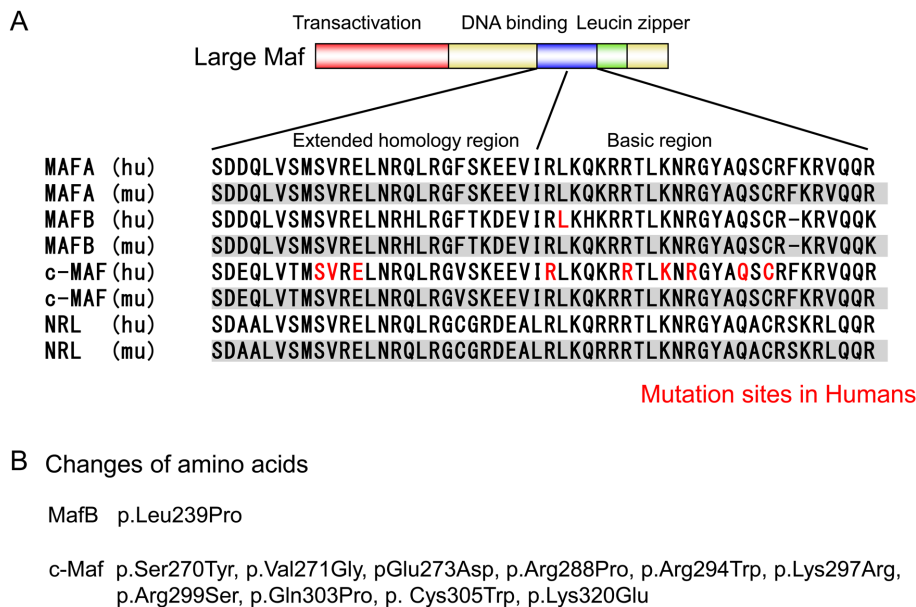


Fig. 4. Mutation sites in the DNA-binding domain of large MAF transcription factors identified in human patients. A. Red color indicates the amino acid substitutions observed in patients. (hu) indicates human amino acid sequence and (mu) indicates mouse. B. Detailed information about amino acid substitutions. Each position indicates the amino acid substitution for the observed mutations in patients.

diseases. In 2002, a point mutation in *c-MAF* was reported to be the cause for human congenital cataract and iris coloboma. In this case, the conserved arginine in the DNA-binding domain of c-MAF was replaced by proline; as a result of this mutation, it could not bind to the

MARE sequence [54]. Since then, several published studies have determined that the occurrence of a point mutation in *c-MAF* is relatively frequent and that *c-MAF* is a causative gene for human congenital cataract and iris coloboma. In addition, analysis of *c-Maf*-deficient

mice revealed that c-MAF is required for the formation of Pacinian corpuscles that sense skin vibrations. Furthermore, analysis of human cases of congenital cataract revealed that the vibration sensation decreased. These results clearly indicate that c-MAF is essential for the formation of Pacinian corpuscles [55]. In 2015, Niceta *et al.* revealed that *c-MAF* is the causative gene for Ayme–Gripp syndrome with concomitant cataracts, deafness, mental retardation, epilepsy, and skeletal dysplasia. In cases of Ayme–Gripp syndrome, mutations in the phosphorylation sites of the transcription activation domain of *c-MAF* were reported [56].

NRL

As described above, NRL was reported to be a retina-specific bZIP-type transcription factor, but it was subsequently identified to be a causative gene for retinitis pigmentosa [57]. Of the multiple mutations reported so far, mutations with dominant inheritance have been identified at the conserved phosphorylation sites in the transcriptional activation domain, while mutations with recessive inheritance have been identified at other sites [58]. In addition, NRL has also been identified as the cause of enhanced S-cone syndrome [59].

Relationship with carcinogenesis (multiple myeloma)

The large MAF transcription factor group is a group of transcription factors identified as oncogene cellular homologues, and therefore, its association with human carcinogenesis has received attention. Multiple myeloma is a tumor in which plasma cells proliferate monoclonally in the bone marrow. Approximately 70% of cases of multiple myeloma reportedly have immunoglobulin H chain (*IGH*) gene translocations [60]. These translocations cause overexpression of the translocation partner gene in B cells. In the late 90s, *c-MAF* was discovered to be one of the translocation partner genes [60, 61], and similar translocations were observed for *MAFB* [62], and *MAFA* [63]. Hunt *et al.* performed a microarray analysis of 27 human multiple myeloma cells and found significantly high expression of cyclin D2, integrin β 7, and CCR1 in cells strongly expressing *c-MAF*. Cyclin D2 is a cell cycle regulator that has been previously reported to cause multiple myeloma. The MARE sequence was identified in the promoter region of cyclin D2, and the gene is directly regulated by c-MAF [64]. Furthermore, AMPK-related kinase 5 (*ARK5*), which is involved in tumor malignancy, was identified downstream of *c-MAF* and *MAFB*, and large MAFs were found to comprehensively affect cell survival, proliferation, and carcinogenesis [65]. In our laboratory, we generated mice with *c-Maf* overexpression in B cells using the *Igh* promoter

and enhancer. Breeding of these mice over a long period of time revealed that B cell lymphoma accompanied by the production of a monoclonal M protein develops, although infrequently. Gene expression analysis of the lymph node infiltrating this lymphoma by RT-PCR identified high expression of integrin β 7 and cyclin D2 as observed in human multiple myeloma cells. Thus, c-MAF has a role in the development of lymphoma in mice via a mechanism similar to that in humans [66].

Summary

This review summarizes the essential functions of the large MAF transcription factor group in the development of various organs and maintenance of their functions. However, several aspects need further elucidation and thus future research. In particular, multiple large MAF transcription factors are expressed in several organs, and the functions of MAFs in these organs cannot be determined by studying a single gene-deficient mouse model. Further analysis of compound mutant mice is needed. In addition, although MAFs have been identified as the causative genes for human diseases, such as diabetes, MCTO, Duane syndrome, FSGS, cataract, and Ayme–Gripp syndrome, understanding of their functions is expected to lead to the identification of new diseases as well. Furthermore, the importance of the large MAF transcription factor group in the development of multiple myeloma and insulinoma has been established, and it may be potentially involved in the development of other cancers as well. We look forward to further analyses of human cases.

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