Large Maf Transcription Factors: Cousins of AP-1 Proteins and Important Regulators of Cellular Differentiation

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ABSTRACT

A large number of mammalian transcription factors possess the evolutionary conserved basic and leucine zipper domain (bZIP). The basic domain interacts with DNA while the leucine zipper facilitates homo- and heterodimerization. These factors can be grouped into at least seven families: AP-1, ATF/CREB, CNC, C/EBP, Maf, PAR, and virus-encoded bZIPs. Here, we focus on a group of four large Maf proteins: MafA, MafB, c-Maf, and NRL. They act as key regulators of terminal differentiation in many tissues such as bone, brain, kidney, lens, pancreas, and retina, as well as in blood. The DNA-binding mechanism of large Mafs involves cooperation between the basic domain and an adjacent ancillary DNA-binding domain. Many genes regulated by Mafs during cellular differentiation use functional interactions between the Pax/Maf, Sox/Maf, and Ets/Maf promoter and enhancer modules. The prime examples are crystallin genes in lens and glucagon and insulin in pancreas. Novel roles for large Mafs emerged from studying generations of MafA and MafB knockouts and analysis of combined phenotypes in double or triple null mice. In addition, studies of this group of factors in invertebrates revealed the evolutionarily conserved function of these genes in the development of multicellular organisms.

INTRODUCTION

Tissue-specification and formation of organs during the development of multicellular organisms is under the control of transcriptional programs that simultaneously decide which genes are to be expressed and which genes will be shut down. Before cells reach a terminally differentiated state, characterized by a unique pattern of gene expression, earlier populations of the cells are subjected to external signals that restrict their developmental potential. To generate the full complexities of multicellular organisms, an extensive network of transcription factors is needed. At present, 1962 human genes, representing nearly 9 percent of whole gene content, are thought to code transcription factors (Messina et al., 2004). Tissue-specific and tissue-preferred gene expression is regulated by a combinatorial use of transcription factors with tissue-restricted patterns of expression that interact with cis-acting elements comprising the genomic regulatory regions, e.g. promoters, enhancers, and locus control regions.

A Superfamily of bZIP Proteins Regulate Cellular Differentiation

The large Maf proteins form a distinct group of bZIP transcription factors (Blank and Andrews, 1997). The bZIP structural motif, comprised of a basic region and a leucine zipper, harbors an 18 amino acid long basic peptide that is considered the simplest structural motif for specific DNA recognition (Dlakic et al., 2001). A leucine zipper domain (Landschulz et al., 1988) allows formation of homo- or hetero-dimers of mutually compatible bZIP proteins (Kataoka et al., 1994b; Kerppola and Curran, 1994a). Other families of bZIP proteins are AP-1 (Shaulian and Karin, 2002), CREB/ATF (Andrisani, 1999; Hai and Hartman, 2001), CNC (Motohashi et al., 2002; Motohashi et al., 1997), C/EBP (Ramji and Foka, 2002; Zahnow, 2002), and PAR (Cowell, 2002). Several human herpes viruses also encode bZIP proteins, including the well-characterized Epstein-Barr virus-encoded transcriptional activator Zta (Hicks et al., 2003; Liu and Kung, 2000).

An extensive number of studies on bZIP, including transcription factor analyses, have shown their critical function in the regulation of cellular differentiation by their association with a variety of signal transduction pathways. The hallmark of the AP-1 protein complex c-Fos/c-Jun is its role in regulation of proliferative responses (Jochum et al., 2001). CREB proteins regulate signal transduction using cAMP as a second messenger and play specific functions in managing long-term memory (Izquierdo et al., 2002). The heterodimeric protein NF-E2 (p45/p18), from the CNC/small Maf group, regulates expression of βA-globin and other genes activated during erythropoiesis (Andrews et al., 1993).

Molecular studies of a group of large Maf proteins comprised of MafA, MafB, c-Maf, and NRL provided novel insights into the mechanism of *in vivo* gene regulation. Based on the strong conservation of their basic regions, it was initially suggested that binding of Mafs to DNA was similar to Mafs binding to AP-1 proteins; however, present data points to novel mechanisms employing cooperative interactions between the conserved basic region and an adjacent region specific for large Mafs. The expression pattern of MafA, MafB, c-Maf, and NRL suggests that they play a role in brain, eye, kidney, and pancreas development. This hypothesis was confirmed by a number of studies; however, it also raised issues regarding the functional specificity of each Maf gene.

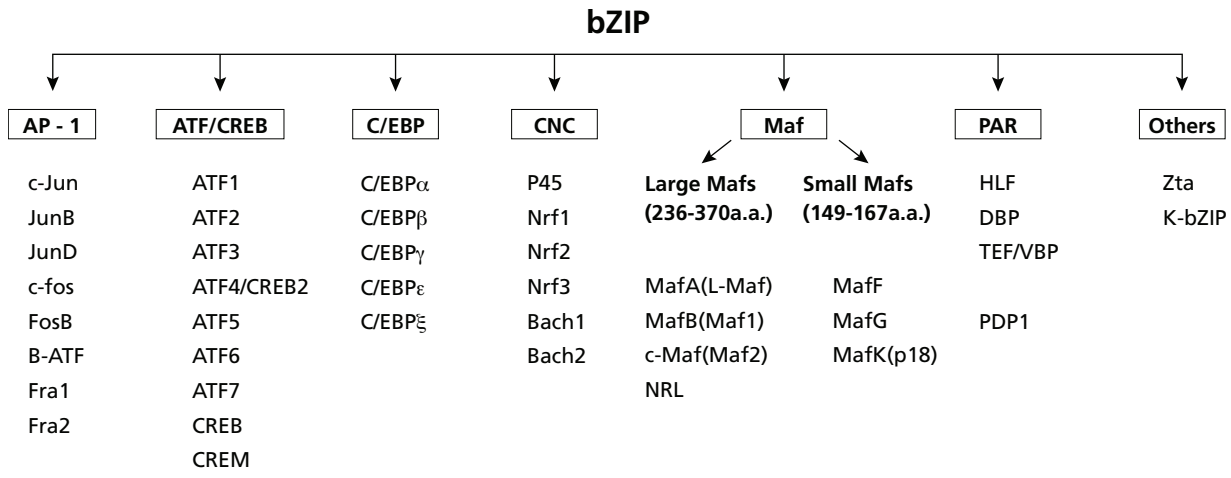

FIGURE 1 | Transcription Factors Comprising the bZIP Superfamily. The individual families are given in alphabetical order. For the most complete list of 53 human bZIP proteins excluding MafA, see Vinson et al. 2002.

More recent studies were aimed at dissecting the signal transduction pathways during terminal cell differentiation that may involve modification of large Mafs. The aim of this review is to summarize the recent advances made in the field of molecular biology and genetics on this intriguing family of transcription factors.

History and Nomenclature of Mafs

The founding member of the Maf family, v-maf, was identified in 1989 from natural musculo-aponeurotic fibrosarcoma of chicken in a gag-maf locus from the replication-defective retrovirus AS42 (Nishizawa et al., 1989). Using a probe containing a v-maf sequence, cellular counterparts, c-Mafs, were cloned from a number of vertebrate genomes (Nishizawa et al., 1989). In contrast to the AP-1 proteins c-Jun and c-Fos, endogenous c-Maf expression is not induced by mitogens (Nishizawa et al., 1989). The protein encoded by c-Maf possesses a bZIP domain close to its C-terminus. Molecular dissection studies identified additional functional domains, (see Figure 2) including the ancillary DNA binding region, hinge domain, and acidic transcriptional activation domain (Blank and Andrews, 1997; Kataoka et al., 1993). A retinal-specific cDNA related to Maf sequences was isolated by screening a subtractive library and named the neural retina leucine zipper (NRL) (Swaroop et al., 1992). The NRL domain structure is similar to c-Maf (see Figure 2), though its internal regions are shorter.

MafB was cloned as an abundant gene expressed in the developing caudal hindbrain and was shown to match with the disease causing gene in the mouse strain Kreisler (Krml1) (Cordes and Barsh, 1994). Additional clones encoding MafK, MafF (Fujiwara et al., 1993), MafB (see Figure 2), and MafG (Kataoka et al., 1994a; Kataoka et al., 1995; Kataoka et al., 1994b) were isolated by Nishisawa and associates using c-Maf as a probe and low stringency hybridization conditions. Rat homologues of MafB and c-Maf were obtained from screening the liver cDNA library using a v-maf probe and were called Maf1 and Maf2, respectively (Sakai et al., 1997). In contrast to c-Maf, the genes MafK, MafF, and MafG encode shorter proteins lacking the transcriptional activation domains. These proteins, which act as transcriptional repressors, were called small Mafs. Nevertheless, small Mafs can form heterodimers with cap'n'collar (CNC) proteins that harbor transcriptional activation domains.

The Drosophila cap'n'collar, the founding member of the CNC group, regulates head segment identity (Mohler et al., 1991). The erythroid-specific transcription factor NF-E2 is a heterodimer of CNC-like p45 and p18/MafK (Andrews et al., 1993) and serves as a key regulator of the β-globin locus via binding to both specific promoters and to the locus control region (LCR) (Motohashi et al., 2002; Motohashi et al., 1997). Other members of the CNC group are listed in Figure 1.

The remaining large Maf protein, MafA/L-Maf, was independently discovered in the quail retina (Benkhelifa et al., 1998) and chicken lens library (Ogino and Yasuda, 1998). Mammalian homologues of MafA were cloned based on the prediction of a novel human Maf gene on chromosome 8q24 by PCR, and independently by analysis of proteins interacting with a key regulatory region RIPE3b in the insulin promoter (Kataoka et al., 2002; Olbrot et al., 2002).

Phylogenetic analysis of 38 genomic large Maf sequences

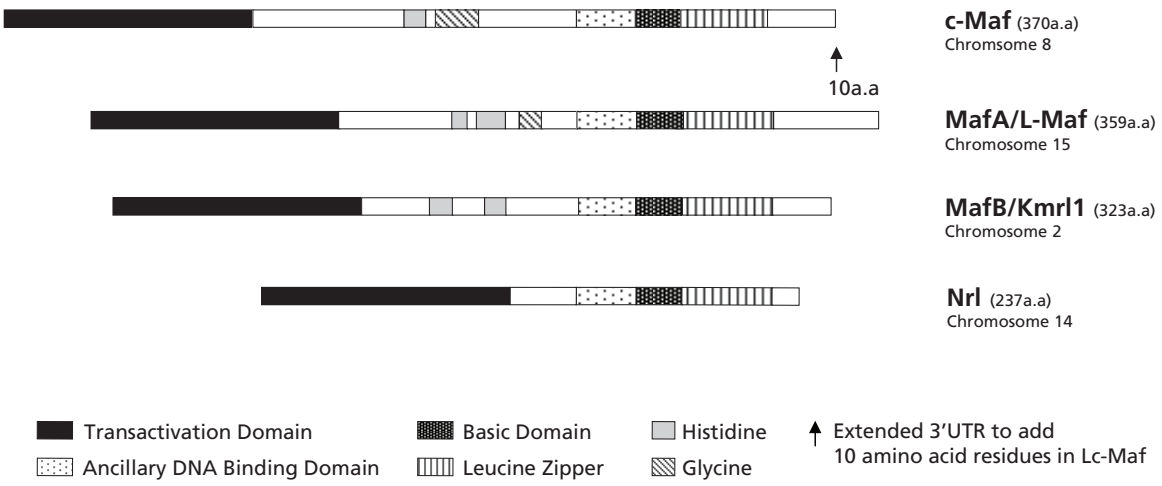

FIGURE 2 | A Diagrammatic Representation of Molecular Structure of Human Large Mafs. The structural domains including the transactivation domains, ancillary DNA binding domains (ADBDs), basic regions, leucine zippers, histidine- and glycine-rich domains are shown in boxes.

are in agreement with the single origin of the large Maf gene precursor (Coolen et al., 2005). This study assigned the *Xenopus laevis* XlMaf gene, previously considered a MafA orthologue, to the NRL class. This analysis also identified a separate line of three MafL genes in *Drosophila melanogaster*, *Ciona intestinalis* and *Strongylocentrotus purpuratus*. The function of these single-copy large MafL genes in evolutionary distinct species is thought to provide information regarding the ancestral function of the XlMaf gene.

Structure and DNA-binding of Large Mafs

The bZIP domain of MafA, MafB, c-Maf, and NRL is located near the C-terminus and is highly homologous to a similar domain in the AP-1 and CREB/ATF proteins. However, all large Mafs possess an adjacent homologous region, initially termed the extended homology region. This region was subsequently shown to mediate DNA binding and was named the ancillary DNA-binding domain (ADBD) (Dlakic et al., 2001). Large Mafs share an N-terminal transcriptional domain, consisting of approximately 100 amino acid residues rich in serine, proline, and tyrosine. The linker region between these domains is of variable length (Figure 2). MafA, MafB, and c-Maf contain histidine repeats between the transactivation domain and the ancillary DNA-binding domain. Another feature of this linker is the presence of a domain rich in glycine residues between the histidine repeats and ADBD. MafA, MafB, and c-Maf lack introns, while NRL is encoded by four exons.

The leucine zipper allows the formation of Maf homo- and heterodimers with other compatible bZIP proteins (Kataoka et al., 1995; Kataoka et al., 1994b; Kerppola and Curran, 1994a; Kerppola and Curran, 1994b). The "compatibility code" is not fully understood; however, a method to assess possible complex formation is based on the evaluation of hydrophobic, electrostatic, and Van der Waal's interactions inside the dimerized leucine zipper domains (Vinson et al., 2002). Experimentally, heterodimers of c-Maf and NRL with c-Fos and c-Jun were observed in vitro (Kerppola and Curran, 1994a; Kerppola and Curran, 1994b). MafA, but not MafB, also can heterodimerize with c-Jun (Benkhelifa et al., 1998; Kerppola and Curran, 1994a). It has been proposed that large Mafs can heterodimerize with each other (Vinson et al., 2002). Since a number of bZIP proteins are alternatively spliced, including CREB, CREM, and c-Maf, the number of potential heterodimers consisting of at least 54 cellular members of this family (Figure 1) is enormous.

The DNA-binding mechanism of large Mafs represents a novel paradigm in gene regulation. Early studies of c-Maf resulted in a concept that c-Maf binding sites, called Maf recognition elements (MAREs), are derivatives of sites recognized by AP-1 and ATF/CREB proteins. *In vitro* selection of the optimal binding sites for c-Maf generated two 13 and 14 base pair palindromic sequences, TGCTGACTCAGCA (T-MARE) and TGCTGACGTCAGCA (C-MARE) (Kataoka et al., 1994b). In support of this, T-MARE and C-MARE contain AP-1 (TPA-responsive element) and CRE consensus motifs in the middle region, respectively

(see Figure 3). Similar studies of c-Maf and NRL homodimers also identified binding to palindromic recognition sites with the consensus sequences TGC$(N)_{6-7}$GCA (Kerppola and Curran, 1994a), but they lack the internal AP-1 site. In addition, Fos/NRL, Jun/NRL, and Fos/c-Maf heterodimers recognized the nonpalindromic consensus sequence TGAC$(N)_{3-4}$GCA. However, a compilation of natural Maf-binding sites shows that the 5′-half binding sequence TGCTGA, comprised by a Maf-motif TGC and an AP-1 motif TGA, is almost perfectly conserved in these sites (see Figure 3). A detailed biochemical study of c-Maf binding to DNA resulted in a model based on cooperative binding mediated by the basic and ancillary regions. The ancillary region is thought to adopt a helix-turn-helix structural-recognition motif (Dlakic et al., 2001), which is found in other classes of vertebrate DNA-binding proteins including homeodomain, paired domain, and winged helix/Ets proteins (Sato, 2001; Underhill, 2000; Xu et al., 1999). This model fully explains the extended 13 and 14 base pair Maf recognition sequences and the critical roles of the two TGA repeats at positions -6/-5/-4 and +4/+5/+6 (see Figure 3). However, as mentioned previously, sequence analysis of the Maf binding sites found in rhodopsin, crystallin, and other genes showed high conservation of 5′-TGCTGA-3′ only in the 5′-half region. In the 3′-half site, the GCA motif is less frequent than the opposite TGC motif (see Figure 3). Hence, it is sometimes complicated to predict the Maf protein recognition sites *in vivo* as it is necessary to consider the flexibility of Maf binding that reduces the stringency of "consensus" sequences (Andrews et al., 1993; Kataoka et al., 1994b; Kerppola and Curran, 1994a; Kurschner and Morgan, 1995).

Expression Pattern of Large Mafs in Developing Vertebrate Embryos and Adult Tissues

MafA, the human/mouse homologue of chicken L-Maf (Ogino and Yasuda, 1998) and quail MafA (Benkhelifa et al., 1998), is expressed in the insulin producing β-cells

Chicken	αA-crystallin	**TGC**TGACCACGTT	MafA
Mouse	insulin	**TGC**AGCTTCAGCC	
Mouse	αB-crystallin	TGAGTACCGGGTA	MafB
Mouse	αA-crystallin	**TGC**TGACGGT**GCA**	c-Maf
Mouse	γF-crystallin (rev)	**TGC**TGACGGT**GCA**	
Mouse	βB2-crystallin	**TGC**TGACCCGGGC	
Mouse	L7 (-22)	GTCTGAGCCTCCC	
Mouse	p53	TCCTGACTCT**GCA**	
Mouse	Collagen II (rev)	TACAGAGCCCGAT	
Mouse	IL-4	**TGC**TGAAACCAAG	
Human	rhodopsin	**TGC**TGATTCAGCC	NRL
Human	PDE-6a	CACTGATCCTCAT	
Mouse	β-PDE	AGCTGACTCACTC	

	-6 -5 -4 -3 -2 -1 • +1+2+3+4+5+6
"consensus"	T**GC**T**G**AN $^{T}_{C}$CNGNN
AP-1	TGA $^{G}_{C}$T $^{C}_{A}$A
Type V-Mare	TGCNNNNNNNGCA
T-Mare	TGCTGACTCAGCA
ARE	TGACNNNGC

FIGURE 3 | A Compilation of DNA-Binding Sites Recognized by Large Mafs. Thirteen Maf binding sites were aligned and a "consensus" sequence was derived. Nucleotides with 90 percent conservation are shown in bold. A consensus binding site for AP-1 proteins is shown for comparison. Type V-MARE was derived from studies of c-Maf and NRL homodimers (Kerppola and Curran, 1994a; Kerppola and Curran, 1994b), and T-MARE was generated from a random pool of oligonucleotides (Kataoka et al., 1994b). A 10 base pair consensus antioxidant responsive element (ARE) recognized by CNC-bZIP factor Nrf2 can also bind c-Maf (Dhakshinamoorthy and Jaiswal, 2002).

of the pancreas as well as in the eye. In contrast, its expression is not detected in the α-cells of the pancreas (Kataoka et al., 2004). Northern blot analysis using RNA from adult mouse tissues did not identify additional sites of expression, though expression of chicken MafA was detected in the developing brain, eye, ear, muscle, pancreas, peripheral nervous system, and spinal cord (Lecoin et al., 2004). In chick lens, MafA/L-Maf is first detected when the evaginating optic vesicle makes contact with the overlaying surface ectoderm (Ogino and Yasuda, 1998; Yoshida and Yasuda, 2002). Expression of this gene persists both in embryonic chicken lens epithelium and fibers. MafA is expressed in the developing quail neuroretina and its peak expression coincides with its differentiation (Benkhelifa et al., 1998). Additional studies of MafA in the developing mouse embryo are necessary to clarify its possible expression outside the eye and pancreas. Based on the UniGene databank, human MafA is also expressed in kidney, lung, and blood.

The expression of MafB has been studied in mice, rats, chicken, and zebrafish. In mice, the analysis focused on the eye and brain. MafB expression at the mRNA level was detected from E10.5 in mouse lens vesicle (Kawauchi et al., 1999) following the onset of c-Maf expression. *In situ* hybridizations pointed to high levels of MafB expression in lens epithelial cells (Cordes and Barsh, 1994; Kawauchi et al., 1999; Kim et al., 1999; Reza and Yasuda, 2004; Sakai et al., 1997; Yoshida et al., 1997; Yoshida and Yasuda, 2002). MafB has a well-established role in hematopoiesis as it is expressed only in myelomonocytic cells and can suppress erythroid differentiation (Sieweke et al., 1996; Eichmann et al., 1997). The significance of MafB expression in mouse brain and kidney is described below. Zebrafish MafB is identical to a mutation called valentino (Val) (Moens et al., 1998). The hindbrain of Val mutants is shortened by the length of one rhombomere.

In the mouse embryo, c-Maf is dynamically expressed in multiple tissues with different onsets of expression. In the lens, c-Maf mRNA was first detected in the lens placode at E9 - 9.5 during the process of lens invagination (Kawauchi et al., 1999). A parallel study found onset of its expression in lens vesicle at E10.5 (Ring et al., 2000). Its expression is evenly maintained in lens vesicle, but is dramatically upregulated in primary lens fiber cells (Ring et al., 2000). Mouse c-Maf is also widely expressed outside of the eye in regions such as the spinal cord, cartilage, spleen, kidney, heart, lung, intestine, muscle, uterus, and liver (Ring et al., 2000; Sakai et al., 1997). In rat lens, c-Maf/Maf2 mRNA was detected mainly in lens fiber cells, with the strongest expression occurring in cells that form the lens equator and then differentiate into secondary lens fiber cells (Yoshida et al., 1997). In chicken, ocular c-Maf expression pattern is still unclear. The onset of c-Maf expression was reported in lens at stage HH14 (Yoshida and Yasuda, 2002); however, the same authors later concluded that expression starts at stage HH12, about four hours after the onset of MafA/L-Maf in the invaginating lens placode, and appears to be more abundant than MafA/L-Maf in five day old chick embryo (Reza and Yasuda, 2004).

Expression of NRL is restricted to the retina with weak expression in the lens (Liu et al., 1996), blood, liver, muscle, and testis. In contrast to other large Mafs expressed during the early stages of lens development, NRL is detected in the mouse lens from E14.5 both in the secondary fiber cells and the lens epithelium (Liu et al., 1996). RT-PCR from various stages of postnatal mouse lenses showed its weak but persistent expression in the lens (Yang and Cvekl, 2005).

The most intriguing aspect of large Maf genes is the variability of their expression in mouse, chicken, and quail embryonic lenses. Two recent studies of Maf expression in *Xenopus laevis* (Ishibashi and Yasuda, 2001) and *Xenopus tropicalis* (Coolen et al., 2005) further confirmed distinct expression patterns of Maf paralogous genes. For example, both *Xenopus* MafB genes are expressed in the presumptive lens ectoderm followed by the expression of Xtc-Maf (Coolen et al., 2005). However, this Xtc-Maf expression is transient and the invaginating lens placode later expresses XtMafB and XtNrl. Thus, expression domain shuffling, rather than evolutionary conservation, marks lens development (Coolen et al., 2005).

Developmental Abnormalities and Diseases Caused by Mutations in MafB, c-Maf, and NRL

The Kreisler (Krml1) X-ray-induced viable mutation in MafB is linked to segmentation abnormalities in the caudal hindbrain and defective inner ear development in homozygous mice (Cordes and Barsh, 1994), though no eye abnormalities are observed in the Krml1 mice. It has been suggested that the Krml1 does not represent a null mutation (Eichmann et al., 1997), as the mutation specifically abolishes MafB expression in early hindbrain. Mutagenesis with ethylnitrosourea generated a lethal krenu allele and revealed the critical function of MafB for cellular differentiation of podocytes (Sadl et al., 2002). Recent inactivation of MafB resulted in fatal central apnea, demonstrating the essential role of MafB in central respiratory control, possibly due to its expression in rhythmogenic preBotC neurons (Blanchi et al., 2003).

The major phenotype of the c-Maf null mouse model is defective lens fiber cell differentiation (Kawauchi et al., 1999; Kim et al., 1999; Ring et al., 2000). No gross abnormalities were observed in c-Maf heterozygous mice, though null mice died within a few hours after birth. Lens development was normal during the early stage of invagination, but loss of both c-Maf alleles prevented fiber cell elongation at E12.5. Expression of Sox2, Eya1, 2, and Pax6 is not affected in the lens, demonstrating that c-Maf does not regulate these lens lineage-specifying factors. However, virtually all crystallins are expressed at reduced levels. For example αA-crystallin expression

is reduced to one percent of the mRNA level present in the wild type lens. Furthermore, no detectable expression of βB2-, βA3/A1-, βA4-, or γD-crystallin was shown (Ring et al., 2000). In contrast, expression of the lens-specific proteins CP49 and filensin were not impaired in c-Maf-/- lenses (DePianto et al., 2003). Recent studies analyzing the c-Maf null model have shown that c-Maf facilitates the initial phase of chondrocyte terminal differentiation during bone development (MacLean et al., 2003).

A natural heterozygous point mutation in the mouse c-Maf (R291Q) basic domain results in mild pulverulent cataracts named "opaque flecks in lens" (Ofl), although heterozygous c-Maf+/- lenses described above show no cataract (Lyon et al., 2003). This mutation can have a dominant effect in a selective alteration of DNA-binding specificity of the c-Maf (R291Q) homodimers containing one or both mutated forms. In addition, Ofl/Ofl mice develop renal tubular nephritis contributing to early lethality. The human c-MAF mutation, R288P, also in the basic region causes a similar type of cataract with variably associated microcornea and iris coloboma (Jamieson et al., 2003).

Missense mutations in the human NRL are associated with autosomal dominant retinitis pigmentosa (Bessant et al., 1999; Mitton et al., 2000). NRL null mice completely lose rod function while the heterozygous retina appear normal. No lens phenotype was reported in this study (Mears et al., 2001).

Mechanism of Gene Regulation by Mafs: Signal Transduction, Target Genes, and Protein-Protein Interactions

The specificity of the action of Mafs depends on their expression pattern, relative abundance, regulation via post-translational modifications, protein stability, and interactions with other transcription factors. The biological function of quail MafA is dependent on the phosphorylation of two serine residues, S14 and S65, in the transcriptional activation domain (Benkhelifa et al., 2001). Site-directed mutagenesis of these residues resulted in reduced but not abolished activities in the process of ectopic induction of α-, β, and δ-crystallins in chicken embryonic neuroretina. Additional studies have shown that p38α and p38b MAP kinases phosphorylate MafA (Sii-Felice et al., 2005), and that MafB and c-Maf are also phosphorylated by these systems. NRL forms at least six distinct phosphorylated variants in rod photoreceptor nuclei (Swain et al., 2001). Interestingly, serine 50 in NRL appears to be homologous to serine 65 in MafA (Benkhelifa et al., 2001). This serine 50 to threonine substitution in NRL is implicated in retinal pigmentosa (Bessant et al., 1999).

Primary lens fiber cell differentiation is regulated by fibroblast growth factors (FGFs) originating from the retina (Lang, 2004; McAvoy et al., 1991). A connection between the activity of chicken L-Maf and FGF2 signaling suggested that MEK1/ERK mediates FGF-2 signaling, but the outcome was repression of the chicken αA-crystallin promoter activity in transiently transfected lens cells (Ochi et al., 2003). Phosphorylation of threonine 57 and serine 65 residues appeared to control L-Maf activity, and this modification reduced its stability in lens cells. Activated ERK is found in lens epithelium where it may degrade L-Maf (Ochi et al., 2003). Since this possibility is inconsistent with the presumptive role of L-Maf in lens placode formation and its key role in the chicken αA-crystallin expression (Ogino and Yasuda, 1998), additional work is needed to clarify this problem.

The number of known genes directly regulated by large Mafs is in its infancy. Mammalian MafA has been shown to regulate insulin expression in β-cells of the pancreas in two ways: via direct binding to DNA in the promoter, and in concert with other DNA-binding factors including NeuroD, Pdx1, Nkx2.2, and Pax6 (Cissell et al., 2003). Chicken L-Maf interacts with a single MARE in the -162 to +77 promoter region of the chicken αA-crystallin (Ogino and Yasuda, 1998) and requires additional lens lineage specifying factors including Pax6, to direct lens-specific expression (Cvekl et al., 1994). Other chicken crystallins, namely βB1- and δ-crystallins, are also regulated by MafA/L-Maf (Cui et al., 2004; Shimada et al., 2003).

Transfection studies demonstrated that MafB could activate several crystallin genes including the mouse αA-, αB- and γF-, chicken βB1-, and rat βB2-crystallin promoters (Cui et al., 2004; Doerwald et al., 2001; Yang et al., 2004; Yang and Cvekl, 2005). However, none of these genes demonstrated the specificity of MafB action. Certain genes regulated by MafB demonstrate a different paradigm as MafB is recruited to the promoter by other DNA-binding factors. MafB has been shown to act as an interaction partner and repressor of Ets-1, which represses transcription of the transferrin receptor (Sieweke et al., 1996). During megakaryocyte differentiation, extracellular signal-regulated kinase (ERK) induces expression of MafB and controls transcription of platelet GPIIb integrin (CD41) using DNA-binding GATA1 and Ets factors (Sevinsky et al., 2004).

c-Maf has been shown to regulate transcription of the L7 gene expressed in cerebellar Purkinje cells via two binding sites in the 5'-promoter (Kurschner and Morgan, 1995). These sites were both specific to c-Maf and NRL and were not activated by Fos or Jun. Tissue-specific expression of the interleukin-4 gene in CD4+ T helper (Th2) cells is regulated by synergism between c-Maf and the nuclear factor for activated T cells (NF-ATp), interacting with two sites in the proximal promoter region (Ho et al., 1996). In contrast, repression by c-Maf of the CD13/APN promoter in myeolid cells is mediated by c-Maf interaction with c-Myb (Hedge et al., 1998), consistent with c-Maf's role in hematopoietic development. Mouse p53 promoter is

also regulated by a promoter-proximal c-Maf-binding site (Hale et al., 2000). A long form of c-Maf (Lc-Maf) (see Figure 2) together with Sox9 synergistically activates type II collagen in developing chondrocytes (Huang et al., 2002). Finally, promoter studies of the mouse αA-, αB-, βB2, and γF-crystallin promoters are activated by c-Maf in the lens and non-lens cultured cells (Chauhan et al., 2004; Chen et al., 2002; Yang et al., 2004; Yang and Cvekl, 2005). *In vivo* interaction of c-Maf with the mouse αA-crystallin locus further demonstrates its key role in αA-crystallin gene expression (Yang et al., unpublished data). Considering the low expression of crystallins in the mouse retina (Xi et al., 2003), it is likely that the expression of MafA and NRL in the retina contributes to the expression of crystallins in this tissue. The increased presence of αB- and other crystallins in the drusen of patients with age-related macular degeneration (AMD) raises the possibility that the pathology of AMD is linked to the abnormal expression of crystallins (Crabb et al., 2002).

While a positive role of c-Maf has emerged in lens biology, its high level of expression may interfere with the expression of genes encoding antioxidative and detoxifying enzymes regulated via the antioxidant responsive elements (AREs) (see Figure 3). It has been shown that c-Maf negatively regulates NAD(P)H: quinoneoxidoreductase (NQO1) and the glutathione S-transferase Ya subunit genes have AREs in their promoters that are normally regulated by CNC-bZIP factor Nrf2 (Dhakshinamoorthy and Jaiswal, 2002). Since oxidative stress is thought to play a significant role in the formation of lens cataract, studies on the expression levels of c-Maf and Nrf2 in aging lenses deserve special attention.

Initial studies of NRL have shown that it regulates three photoreceptor-specific genes: rhodopsin, and the cGMP phosphodiesterase α and β subunits (Lerner et al., 2001; Pittler et al., 2004; Rehemtulla et al., 1996). Expression profiling of the mouse NRL-/- retina revealed batteries of genes downstream of NRL in rods with a number of candidates for a direct regulation by NRL (Yoshida et al., 2004).

Four common themes have emerged from studies of gene regulation by large Maf proteins. First, Maf proteins can act both as transcriptional activators and repressors (Yoshida et al., 2004). For example, a comparable number of up- (83) and down-regulated (78) genes were found in NRL null retinas. Second, large Mafs functionally interact with Pax6 proteins in crystallin gene regulation. Depending on the mutual position of their binding sites, both synergism and repression are found (Yang et al., 2004; Yang and Cvekl, 2005). Similarly, c-Maf synergistically regulates gene expression with Sox factors (Rajaram and Kerppola, 2004; Yang et al., 2004). Third, some function of Maf proteins does not require the presence of MAREs in the promoter. MafB and c-Maf can enter the transcription complex via other DNA-binding proteins including Ets-1, c-Myb, and Pax6 (Hedge et al., 1998; Planque et al., 2001; Sevinsky et al., 2004; Sieweke et al., 1996). Fourth, Mafs interact with both general transcription factors and common co-activators. MafA and c-Maf recruit CREB binding protein CBP and its cousin p300 into the promoters (Chen et al., 2002). MafA, c-Maf and NRL directly interact with TBP/TFIID (Friedman et al., 2004).

CONCLUDING REMARKS

The large Mafs form an important group of transcriptional regulators. Historically, they were classified as a subgroup of oncogenic AP-1 proteins and modifiers of AP-1 activity. Indeed, chromosomal translocations of MafB and c-Maf result in multiple myelomas (Bergsagel and Kuehl, 2001). Both MafA and MafB can induce cellular transformation upon overexpression in chicken embryonic fibroblasts (Nishizawa et al., 2003). The present data support their independent classification within the bZIP superfamily along with their distinct primary functions and complex mechanisms of binding to DNA. A compilation of natural Maf binding sites supports that MARE sites are asymmetric, with the 5′-half of the 13 base pair recognition sequence being more conserved than the 3′-half.

Genetic studies of c-Maf and NRL revealed specific functions of these genes in individual tissues; nevertheless, similar MafA and null MafB mutation studies remain to be published. Analyses of MafA/c-Maf and MafB/c-Maf double knock-outs is also critical to fully address potentially redundant roles of these factors in the brain, eye, pancreas, and kidney development, as well as in hematopoiesis. Studies of the only large Maf factor in *Drosophila*, traffic jam (tj) (Fassler et al., 2002), which is most closely related to MafB, revealed its role in gonad morphogenesis (Li et al., 2003). Since MafB and c-Maf are both expressed in mouse reproductive systems, further studies of these genes may point to novel evolutionary conserved regulatory pathways. As large Mafs function in the mammalian eye, it is of general interest to establish their functions in the invertebrate visual systems. A microarray analysis of the *Drosophila* eye identified expression of cap-n-collar (CNC, see above) in the ectopically induced eyes (Michaut et al., 2003). This protein is present in three isoforms of 532, 805, and 1383 amino acid residues with variable N-termini. Its role in *Drosophila* eye development remains to be determined. A large Maf homologue, MafL, has been recently cloned from hydrozoan jellyfish (Seipel et al., 2004). Putative Maf binding sites were shown in the invertebrate squid SL11 and SL12, jellyfish J3-, and scallop omega-crystallin promoters (Carosa et al., 2002; Kozmik et al., 2003; Tomarev et al., 1994). These sites might associate with cnidarian MafL and function together with PaxB to regulate expression of these crystallins in invertebrate lenses.

The identification of additional genes regulated by Mafs

using educated guesses, differential gene expression, and chromatin immunoprecipitations (ChIPs) will provide novel clues into the molecular mechanism of this group of proteins. Equally important is the identification of differentiation signals and integration of FGF, Wnt, Shh, and BMP/TGFβ signaling pathways into the regulation of expression and modulation of activities of Mafs at specific stages of development and organogenesis.

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