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The transcription factor c-Maf in sensory neuron development

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The proto-oncogene c-Maf has been shown to be an important transcriptional regulator in the differentiation of a number of cellular contexts, like the eye and hematopoietic system. Here we discuss the recent progress made in understanding c-Maf function in the nervous system.

Keywords: c-Maf, Ret, touch, mechanoreceptors, development, skin innervation, pacinian corpuscles, sensory neuron

Abbreviations: bZIP, basic-leucine-zipper; MARE, Maf recognition element; c-Maf, musculoaponeurotic fibrosarcoma oncogene homolog; MafA, musculoaponeurotic fibrosarcoma oncogene homolog A; MafB, musculoaponeurotic fibrosarcoma oncogene homolog B; Nrl, neural retina leucine zipper; Ngn1, neurogenin 1; Ngn2, neurogenin 2; TrkA, tropomyosin receptor kinase A; TrkB, tropomyosin receptor kinase B; TrkC, tropomyosin receptor kinase C; Ret, ret proto-oncogene; Brn3a, Brain-specific homeobox/POU domain protein 3A; DRG, dorsal root ganglion; Isl1, islet-1; Cre, Cre recombinase; Kcnq4, potassium voltage-gated channel, KQT-like subfamily, member 4; NF200, Neurofilament 200

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Introduction

Maf was first identified in the late 1980s as a retroviral oncogene encoded by the avian musculoaponeurotic fibrosarcoma virus AS42.[1] The corresponding proto-oncogene c-Maf has cell transforming activity when overexpressed in fibroblasts, and chromosomal translocations of the *c-Maf* locus that result in overexpression occur in human tumors, particularly in multiple myeloma.[2,3] *c-Maf* encodes a transcription factor that binds DNA directly and recognizes a sequence motif that is known as Maf Recognition Element (MARE). c-Maf contains a basic-leucine-zipper (bZIP) domain, an evolutionary conserved sequence located N-terminal to the basic domain, called extended homology region/ancillary DNA binding domain, and an acidic transactivation domain. The basic domain and the evolutionary conserved ancillary DNA binding domain located N-terminal to the basic domain participate in DNA binding.[2,4] The leucine-zipper, a part of the bZIP domain, is responsible for dimerization of c-Maf and is present also in other transcription factors like Jun and Fos. c-Maf forms homo- and heterodimers with other bZIP factors, expanding its regulatory repertoire. In mammals, further paralogs of c-Maf exist; the large Maf proteins MafA, MafB (mutated in the kreisler mouse) and Nrl have a similar domain structure as c-Maf, whereas the small Maf proteins MafF, MafG and MafK lack the N-terminal transactivation domain and act as dimerization partners of other bZIP factors.

Maf transcription factors have been shown to be important transcriptional regulators in a number of cellular contexts, like the eye and lens (c-Maf), hindbrain (MafB), bone (c-Maf) and the hematopoietic system (c-Maf and MafB). Their role in hematopoietic cells has received considerable attention, for instance, the fact that MafB/c-Maf co-operate to suppress self-renewal in terminally differentiated, mature monocytes and macrophages.[5,6] Thus, in the absence of MafB/c-Maf, the typical link between cell cycle exit and terminal differentiation is revoked. c-Maf is also expressed in several neuronal cells (**Fig. 1**) and we recently identified the first function of c-Maf in the development of sensory neurons that we will discuss in depth below.

Development of Sensory Neurons

Sensory neurons are part of the peripheral nervous system and are located in dorsal root ganglia (DRG). Many functionally distinct sensory neuron subclasses exist that detect a remarkable variety of physical and chemical stimuli, like force, temperature or acid. Sensory neurons are classified into (1) low-threshold mechanoreceptors that end in specialized anatomical structures (e.g., Pacinian and Meissner corpuscles, Merkel cells, laceolate and circumferential endings) and detect innocuous touch, (2) nociceptors that terminate as free nerve endings and

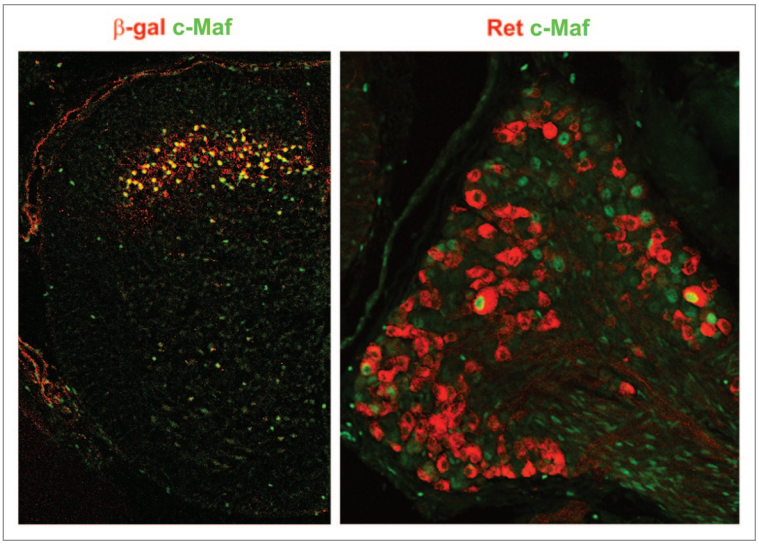

Figure 1. c-Maf expression in the spinal cord and sensory neurons. Analysis of c-Maf expression in the dorsal spinal cord (left) and dorsal root ganglia (right). In the dorsal spinal cord, c-Maf (green) is expressed in layer III neurons that receive mechanosensory information from the periphery. In dorsal root ganglia, c-Maf (green) is expressed in large diameter neurons that co-express Ret (red). For the analysis shown on the left, mice that carry a heterozygous *c-Maf*^{lacZ} allele were used. In *c-Maf*^{lacZ} mice, *LacZ* is expressed under the control of the *c-Maf* locus, and expression of the *LacZ* gene product, β-galactosidase, is useful to follow the expression of the allele.

sense noxious (i.e., potentially harmful physical, chemical or thermal stimuli) and (3) proprioceptors that innervate muscles and tendons to provide information about their movement and position. According to their electrophysiological properties, mechanoreceptors are classified as rapidly adapting mechanoreceptors that sense for instance vibration, and slowly adapting mechanoreceptors that detect stimuli like indentation and stretch of the skin. Neurotrophin receptors provide classical markers that distinguish sensory neuron subtypes:[7] Mechanoreceptors express the neurotrophin receptor TrkB and/or Ret (early Ret+ neurons), proprioceptive neurons express TrkC, and nociceptive neurons express TrkA. TrkA is expressed in all nociceptive neurons during early development, but during maturation subpopulations of nociceptors extinguish TrkA and begin to express Ret.

The developmental mechanisms that generate the functional and anatomical diversity of sensory neurons are incompletely understood. Sensory neurons derive from neural crest cells that delaminate from the dorsal neural tube and migrate to condense into dorsal root ganglia. It is now clear that sensory neurons are generated in two major neurogenic waves. During the first wave (E9.5) neural crest cells express the transcription factor neurogenin 2 (*Ngn2*), which drives formation of mechanoreceptors and proprioceptors. A second wave of neurogenesis (E11-E13) depends on neurogenin 1 (*Ngn1*) and mostly generates nociceptors.[8] Most or all sensory neurons express the homeobox transcription factors Islet1 and brain-specific homeobox/POU domain protein 3A (Brn3a) after they exit the cell cycle and begin to differentiate. Islet1 and Brn3a are essential for the correct expression of many markers of the sensory neuron lineages.[9,10] Interestingly, sensory ganglia of Islet1 mutant mice ectopically express transcription factors that are normally found in the central nervous system, indicating that Islet1 suppresses inappropriate differentiation programs.[10]

The diversification into specialized mechanoreceptor and nociceptor subtypes, however, begins once neurogenesis is completed. For instance, diversification and maturation of nociceptors start around E15.5 and are only completed after birth and depend on the neurotrophin NGF, the transcription factor Runx1 and the tyrosine kinase receptor Met.[11-13] Compared with nociceptors, mechanoreceptor mature faster.[14] Mechanoreceptors represent a small population of sensory neurons and, until recently, few markers for this lineage were known. The scarcity of molecular data had made it difficult to analyze the development of mechanoreceptors and to define the basis of their diversity and function.

Molecular Mechanisms of Mechanoreceptor Development

The first genes found to drive development and differentiation of mechanoreceptive and proprioceptive neurons were the tyrosine kinase receptor Ret, and the transcription factors Shox2 and Runx3. Ret expression appears early during development of mechanoreceptors, and in the absence of Ret, cutaneous mechanoreceptive end-organs are underdeveloped and Pacinian corpuscles are absent.[15,16] The transcription factor short stature homeobox 2 (Shox2) promotes TrkB expression in mechanoreceptors, and Shox2 is required for formation of most TrkB+ neurons. Consistent with this, Shox2 mutants have a deficit in a subset of mechanoreceptors that terminate in Meissner corpuscles and Merkel cells, and light touch sensation is strongly impaired.[17,18] Conversely, Runx3 blocks inappropriate gene expression programs in prospective proprioceptive neurons. Runx3 is expressed in TrkC+ proprioceptive neurons, promoting TrkC and suppressing Shox2 in these cells.[17,19] The molecular identity of signals controlling Ret, Shox2 and Runx3 expression in early-born sensory neurons is unclear, leaving it open how the diversification of mechanoreceptive and proprioceptive neurons is initiated. Similarly, little is known about the genes that execute the differentiation program of mechanoreceptive neurons.

c-Maf Controls Development and Function of Cutaneous Mechanoreceptors

We identified c-Maf as a transcription factor expressed in mechanoreceptive neurons shortly after their birth (E11). c-Maf expression in sensory neurons is conserved in evolution and is detected in rodents, birds and humans.[20] c-Maf expression defines two main subgroups

of sensory neurons: (1) neurons that co-express c-Maf, Ret and MafA (about 7% of all sensory neurons; these correspond to rapidly adapting mechanoreceptors) and (2) c-Maf-positive neurons that do not express Ret and MafA (about 15% of all sensory neurons; these correspond to slowly adapting mechanoreceptors, proprioceptors and a small subpopulation of nociceptors). Mice lacking c-Maf die in the perinatal period. To study the role of c-Maf in sensory neurons, conditional mutant mice were generated. These *Isl1*^{Cre} *c-Maf*$^{flox/-}$ mice are hereafter called *c-Maf* mutants.[20]

Anatomical analysis showed that a lack of c-Maf primarily affects the morphology of rapidly adapting mechanoreceptors, whereas slowly adapting mechanoreceptors and D-hair mechanoreceptor morphologies are left intact. Several types of rapidly adapting mechanoreceptors that innervate the skin are disrupted in the mutants. Meissner corpuscles—the end organs of rapidly adapting mechanoreceptors in the non-hairy skin—and a substantial proportion of lanceolate endings that associate with hair follicles showed an aberrant morphology. The fact that not all lanceolate endings were altered indicated that these endings are heterogeneous, which was verified by the use of a battery of neurochemical markers. This analysis revealed that neurochemically distinct neuron types, some of which are dependent on c-Maf, innervate the same hair follicle.[20] Consistent with recent observations by others,[21] three types of lanceolate endings could be distinguished. Lanceolate endings that express Calbindin and NF200 correspond to rapidly adapting mechanoreceptors and require c-Maf for development.[20] Those that express high levels of TrkB do not depend on c-Maf and most likely represent D-hair mechanoreceptors.[20,21] A third subpopulation is also not c-Maf-dependent and does not expresses Calbindin, NF200 or TrkB, and appears to correspond to C-fiber low threshold receptors.[20,21] Finally, circumferential endings are altered in morphology in *c-Maf* mutant mice. Interestingly, despite the dramatic effects on the morphology of the peripheral nerve terminals in the skin, cell death of the corresponding neurons was not observed. However, the changed morphology was accompanied by sensory dysfunction.

Sensory function was assessed by electrophysiology using the in vitro skin-nerve preparation. This technique allows qualitative and quantitative characterizations of subtypes of mechanoreceptors, such as rapidly adapting, slowly adapting, and D-hair mechanoreceptors, which are distinguished by firing patterns, force sensitivities, and action potential conduction velocities.[22] Rapidly adapting mechanoreceptors of *c-Maf* mutant mice had a reduced conduction velocity and aberrant firing properties, i.e., action potentials were increased and fired in a prolonged manner. At first glance, it is counterintuitive that a morphological disruption of rapidly adapting mechanoreceptors results in increased and prolonged firing. However, c-Maf controls the expression of many genes, including several voltage-gated ion channels that control neuronal excitability. Thus, it is unlikely that morphological changes solely account for the altered firing properties. Slowly adapting mechanoreceptors were only mildly affected in *c-Maf* mutants and showed a reduction of thresholds to mechanical stimulation and reduced conduction velocities, but their firing pattern was not significantly changed. D-hair mechanoreceptors remained fully functional.

The *c-Maf* mutation affects the expression of many downstream genes. Interestingly, c-Maf is essential for appropriate expression of Ret, and the morphology of rapidly adapting mechanoreceptors in Ret mutant mice resemble those observed in *c-Maf* mutants.[15,16,20] Several deregulated genes encode potassium channels; among these Kcnq4 is already known to affect firing properties of rapidly adapting mechanoreceptors and contributes to the changes observed in *c-Maf* mutants.[20,23] MafA is co-expressed with c-Maf in rapidly adapting mechanoreceptors and the two closely related factors might act redundantly. The fact that c-Maf regulates MafA expression explains the dominating c-Maf function in these neurons.[16,20] Interestingly, genes like Netrin G1 and G2, whose ligand (Lrrc4) is expressed in spinal cord lamina III/IV were also deregulated; these receptors/ligands might participate in the establishment of the mechanoreceptive sensory circuitry and the formation of synapses.

c-Maf Function and the Detection of High Frequency Vibration

The electrophysiological characterization described above was restricted to sensory neurons innervating the mouse hairy skin and thus did not assess Pacinian corpuscles. Pacinian corpuscles are found at high densities in rodent periostea, the membranes covering bones, but they are abundant in human skin. These structures are particularly sensitive to high frequency vibration.[24] Ablation of c-Maf in mice leads to a pronounced loss of Pacinian corpuscles, and the few remaining had an abnormal morphology. Furthermore, in contrast to the axons of cutaneous mechanoreceptors, axons innervating Pacinian corpuscles were lost. Thus, among all mechanoreceptive neuron types, those that end in Pacinian corpuscles react particularly sensitive to a loss of c-Maf function.

In addition to its important role in sensory neurons, c-Maf controls eye and lens development in mice and humans.[25,26] c-Maf is highly expressed in the lens where it controls the transcription of crystallin genes encoding structural lens proteins. The lack of c-Maf in mice abrogates crystallin gene expression and causes microphthalmia due to a failure in differentiation of lens fibers.[27] Ocular abnormalities and cataracts have been reported in families that carry dominant mutations in the c-MAF gene. These patients suffer from juvenile cataract, microcornea and a malformation of the iris (coloboma). All known mutations that cause such dysfunctions locate to sequences encoding the c-MAF ancillary DNA binding domain, and all act dominantly and thus affect heterozygous carriers.[25,28,29] The evolutionary conservation suggested a function in sensory neuron development of humans, and therefore a family comprising four carriers of the dominant Arg^{288}→Pro^{288} (R288P) mutation was tested for touch sensitivity. The function of Meissner and Pacinian corpuscles was assessed by applying a vibrational stimulus of increasing amplitude to the nail bed of the little finger, and the subjects were asked to signal

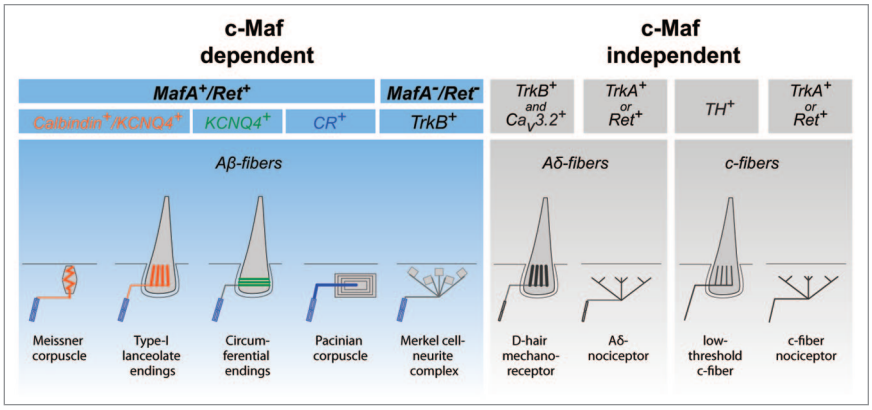

Figure 2. Schematic representation of low threshold mechanoreceptor endings and their dependence on c-Maf. Aβ-fibers depend on c-Maf. The *c-Maf* mutation affects strongly the development and function of rapidly adapting mechanoreceptors like Meissner corpuscles, type-I lanceolate endings and Pacinian corpuscles.

the detection of the stimulus by pressing a button. A wide range of frequencies (5–240 Hz) covering the detection range of Pacinian corpuscles and other mechanoreceptors was tested. All four carriers were strongly impaired in their ability to detect high frequency vibrations, but not low frequencies, indicating that Pacinian corpuscles are affected by the dominant *c-MAF* mutation.[20] However, it cannot be ruled out that other mechanisms might contribute, for instance abberant processing of sensory information in the central nervous system. For instance, c-Maf is also present in neurons of dorsal horn layers III/IV, which are known to receive mechanosensory input, and was recently found to regulate gene expression in these neurons.[30] We conclude that c-MAF/c-Maf is critical for mechanoreception in humans and in mice.

Conclusion

The richness of our touch percepts requires integration of signals from various types of mechanically sensitive end-organs. Depending on the stimulus quality and strength, distinct combinations of end-organs respond to tactile stimuli. The diversity of mechanoreceptors and the scarcity of molecular data had made it difficult to analyze the development of mechanoreceptors and to define the basis of their functional heterogeneity. c-Maf is a useful marker for mechanoreceptors and the analysis of c-Maf functions provided a wealth of information about ion channels and other genes expressed by mechanosensory neurons. Rapidly adapting mechanoreceptors are particularly dependent on c-Maf function, but it is also clear that other cutaneous Aβ-fibers are affected, albeit to a lesser extent, in *c-Maf* mutant mice (summarized in **Fig. 2**), indicating that c-Maf functions extends beyond rapidly adapting mechanoreceptors.

Interestingly, in the central nervous system, c-Maf is expressed by neurons thought to integrate mechanoreceptive information, indicating that c-Maf marks a neuronal circuit that participates in touch sensation. To unravel c-Maf function in the processing of the peripheral signals will be one of the intriguing challenges lying ahead.

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