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Emerging Roles for MEF2 in Brain Development and Mental Disorders.

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Abstract

The MEF2 family of transcription factors regulates large programs of gene expression important for the development and maintenance of many tissues, including the brain. MEF2 proteins are regulated by neuronal synaptic activity, and they recruit several epigenetic enzymes to influence chromatin structure and gene expression during development and throughout adulthood. Here, we provide a brief review of the recent literature reporting important roles for MEF2 during early brain development and function, and we highlight emerging roles for MEF2 as a risk factor for multiple neurodevelopmental disorders and mental illnesses, such as autism, intellectual disability, and schizophrenia.

Introduction

Proper brain wiring and experience-dependent synaptic remodeling during development require activity-dependent gene expression, and MEF2 proteins play a key role in this process [1, 2]. In the nervous, muscle and immune systems, the four vertebrate *Mef2* (Myocyte Enhancer Factor 2) genes (*Mef2a-d*) code for transcription factors that are expressed in distinct yet overlapping patterns during development and throughout adulthood (Fig. 1) [3–8, 9**, 10–14]. They possess highly conserved N-terminal regions that encode the DNA binding and dimerization functions, and C-terminal regions involved in regulating transcription and nuclear localization (Fig. 2) [14, 15]. Homo- or heterodimers of MEF2s can bind directly to DNA regions possessing the consensus sequence, YTA(A/T)4TAR (termed the MEF2 Response Element (MRE)) [14, 16, 17]. MEF2s undergo alternative splicing at the mRNA level [6, 18–20] (Sciabica et al 2016, SCIEX) and post-translational modifications at the protein level (phosphorylation/dephosphorylation [21–33], sumoylation [23, 34, 35], acetylation [34, 36, 37], cleavage [38, 39**, 40, 41]. S-nitrosylation [42]) that modulate their interactions with other proteins and regulate their functions (Fig. 2). MEF2s can act as activators or repressors of gene expression depending upon the association with co-factor complexes, including epigenetic enzymes that alter chromatin state and/or recruit

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the polymerase complex [15]. MEF2s are regulated by neuronal activity through several calcium-sensitive enzymatic pathways, positioning MEF2s as critical regulators of activity-dependent neural epigenetics [15]. Under basal activity levels, MEF2s often associate with class Ha HDACs (histone deacetylases) that recruit other repressors to induce chromatin condensation and repression of gene expression [14, 15]. However, following high levels of neuronal activity and increased intracellular calcium, CaMKinase-dependent phosphorylation of HD AC results in MEF2-HDAC dissociation [15]. Subsequently, MEF2s can switch from repressors to activators by recruiting HATs (histone acetyl transferases), including CBP and p300, or by recruiting SWI-SNF complexes containing the Brg1 ATPase, to promote chromatin remodeling and polymerase complex recruitment [15, 43]. Additionally, calcium-dependent MEF2 dephosphorylation by calcineurin (protein phosphatase 2B; PP2B) stimulates MEF2 transcription activity [12, 34, 44]. MEF2s are also regulated by other relevant stimuli, including neurotrophin signaling, oxidative stress and excitotoxicity [15].

MEF2s are critical for proper nervous system development and function. MEF2s are reported to regulate neuronal migration [45], activity-dependent cell survival [22, 25, 40, 41, 46, 47], neuronal differentiation [45, 47–50], axon guidance and pruning [51], and dendrite formation and remodeling [39**, 52**, 53, 54]. In addition, gene expression analyses identify a wide array of MEF2-regulated genes linked to synapse development and function, and neuronal excitability [9**, 51,55, 56]. Over a decade ago, two key studies revealed that MEF2s can function as activity-dependent regulators of developmental synapse elimination [34, 44], followed by numerous studies confirming critical roles of MEF2 in synaptic connectivity regulation (Table 1) [9**, 43, 45, 57, 58, 59*, 60**, 61**, 62*, 63*, 64]. Multiple proteins have been associated to MEF2-induced synapse elimination, including the RNA-binding protein, FMRP (Fragile × mental retardation protein), calcineurin, Arc (activity-regulated cytoskeleton-associated protein), group I metabotropic glutamate receptors (mGluRl/5), PCDH10 (protocadherin 10) and Nur77 [57, 58, 65–70], as well as MCH1 [71], and potentially Homer1 [43, 55, 72]. Interestingly, MEF2-dependent synaptic regulation could be synapse-specific as MEF2s act upstream of proteins like NPAS4 and Arc [55], that can selectively modulate specific synapses within a given cell [73, 74]. Consistent with this breadth of neurobiological functions, MEF2 proteins, directly or indirectly, influence the expression of hundreds of genes – many of whom are important for neurotypical development [9**].

MEF2s regulate activity-dependent synapse plasticity

Emerging studies demonstrate that MEF2s can translate sensory experiences into structural and functional alterations of neural connectivity, particularly during developmental critical periods (Fig. 3) – restricted windows of time early in development when sensory experiences sculpt highly-plastic neural circuits. In the developing vertebrate visual cortex, ocular dominance columns represent clustered groups of neurons that respond preferentially to visual stimulation of one eye over the other. Ocular dominance plasticity (ODP) occurs via brief monocular deprivation during a postnatal critical period, and it leads to decreased responses to stimulation of the previously deprived eye in visual cortical neurons (depression component) and increased responses to stimulation of the spared eye (potentiation

component). Brief visual deprivation stimulates an increase in MEF2 expression in cat visual cortical neurons in the lesion projection zone [75], and reduction of MEF2 function in the mouse visual cortex attenuates the ODP depression component, suggesting a critical role for MEF2 in ODP long-term synaptic depression [76**]. Interestingly, monocular deprivation in adult monkeys induces a MEF2-dependent increase in the secreted factor, Osteocrin, in cortical neurons receiving inputs from the spared, but not the deprived, eye. Osteocrin is involved in dendritic growth, suggesting a role for the MEF2-Osteocrin pathway in sensory-dependent plasticity [52**]. Interestingly, Osteocrin expression is induced in primate (but not mouse) neurons, indicating that MEF2 has evolved primate-specific gene targets and brain functions.

In the developing mouse somatosensory cortex, MEF2C regulates synaptic transmission and remodeling during critical periods. Conditional embryonic knockout of *Mef2c* in Emxl-lineage forebrain cells reduces glutamatergic synaptic strength and increases GABAergic inhibitory synaptic transmission when measured in layer II/III pyramidal neurons of the somatosensory cortex – a function dependent upon MEF2C's role as a transcriptional repressor [9**]. Sparse postnatal deletion of *Mef2c* in layer II/III neurons within only one cortical hemisphere also produces a decrease in glutamatergic synaptic strength, but it also produces an increase in glutamatergic synaptic transmission from the wild-type contralateral cortical inputs, indicating that MEF2C can differentially regulate local versus long-range synaptic transmission in a cell autonomous fashion [61**]. In wild-type mice, whisker trimming during a critical period decreases evoked layer IV to layer II/III glutamatergic synaptic responses in the deprived barrel field [61**]. This synaptic weakening is absent in layer II/III neurons lacking MEF2C expression, suggesting that MEF2C could be important for this activity-dependent circuit plasticity [61**].

MEF2 is also linked to a process called metaplasticity (or "plasticity of plasticity"), which refers to alterations in the thresholds required for inducing synaptic changes as a result of the recent history of neuronal activity [77]. This process is believed to be particularly important during highly plastic critical periods to avoid plateau-like limitations and to maintain neuronal responses within a physiological range that allows for further plasticity. In tadpole tectal neurons, MEF2A and MEF2D regulate a metaplastic process that switches an activity-induced synaptic potentiation into a synaptic depression as a result of previous exposure to unpatterned white noise (WN) visual stimuli. This WN visual stimuli induced a transient caspase-dependent degradation of MEF2, which enabled the synaptic response switch [39**].

Multiple studies have assessed the role of MEF2s in learning and memory in mice [78]. *Mef2a/Mef2d* double knockout mice exhibit normal fear learning and memory [79]. However, under subthreshold learning conditions, experimental reduction of MEF2A and MEF2D in the hippocampus facilitates spatial learning and memory [80]. These data are consistent with the fact that in the mature hippocampus, MEF2A and MEF2D levels reduce during fear-related contextual learning and memory experiences [80]. Interestingly, embryonic deletion of *Mef2c* in the brain produces profound fear learning and memory deficits [9**], while postnatal deletion of *Mef2c* from CaMKII-lineage forebrain excitatory neurons fails to produce fear learning and memory deficits [81]. The specific hippocampal

role of *Mef2c,* where its expression is highly-restricted to the dentate gyrus, has yet to be tested with regards to learning and memory. Interestingly, expression of a constitutively-active form of MEF2 (MEF2-VP16) in the adult anterior cingulate cortex after a contextual fear conditioning task prevents fear memory consolidation [82], while MEF2-VP16 expression in the adult nucleus accumbens increases cocaine conditioned place preference, a drug reward learning and memory test [12], suggesting brain region- and task-selective influences of MEF2 activity. Lastly, chronic nicotine exposure during early development increases cortical MEF2C levels, which in turn alters cortical synaptic transmission and produces hypersensitive passive avoidance learning [59*].

MEF2C as a risk gene for neurodevelopmental and mental disorders

Recent human genome-wide association studies (GWAS) and genome sequencing studies of patient populations reveal that *MEF2C* is a candidate risk gene for several common mental disorders, including bipolar disorder [83, 84], schizophrenia [63*, 85, 86], attention deficit and hyperactivity disorder (ADHD) [87, 88], major depressive disorder [89, 90], and Alzheimer's Disease [11, 91–94]. In most of these studies, the impacts of the disease-linked single nucleotide polymorphisms on *MEF2C* expression or function is unknown, but it emphasizes the emerging importance of MEF2C in healthy human brain function. Recently, microdeletions or coding-region missense or nonsense mutations in the *MEF2C* gene associate with a newly described neurodevelopmental disorder, *MEF2C* Haploinsufficiency Syndrome (MCHS), which is characterized by varying degrees of intellectual disability (ID), absence of speech, autism symptoms, variable seizures and various motor abnormalities including hyperactivity [95–98]. In addition, mutations in *MEF2C* were detected in a small subset of patients with idiopathic ID [99]. Interestingly, conditional deletion of mouse *Mef2c* exon 2, which encodes a large portion of the DNA binding domain, in various neuronal subpopulations in the developing brain produces mice with numerous behavioral, synaptic and brain structural abnormalities [9**, 45, 64]. Moreover, global $Mef2c^{\Delta\ exon\ 2/+}$ heterozygous mice display abnormalities in social- and anxiety-related behaviors, deficits in learning and memory, motor hyperactivity, and increased repetitive behavior [60**] (unpublished observations, AJH and CWC). *Mef2c* heterozygous mutant mice also show changes in excitatory (E) and inhibitory (I) synaptic transmission in hippocampal circuits, suggesting an altered hippocampal E/I balance [60**]. Chronic treatment with a NMDA receptor antagonist reverses the reported behavioral and synaptic phenotypes in the *Mef2c* mutant mice [60**]. Together, these studies suggest that reduced MEF2C function in humans or mice throughout early development has a profound impact on brain development and neurotypical behavior.

So why is MEF2C so essential for neurotypical development? Perhaps the answer is that MEF2C regulates the expression, directly and indirectly, of more than a thousand genes in the developing brain. Indeed, analysis of differentially-expressed genes in the cortex of *Mef2c* conditional knockout mice reveals a significant overlap with genes linked to synaptic transmission, axon guidance and membrane excitability [9**]. Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder characterized by impairments in social behavior and communication and increases in restricted or repetitive patterns of behavior [100], and ASD has a strong genetic underpinning [100]. MEF2C-regulated genes display a

significant overlap with scores of candidate autism risk genes, perhaps explaining the observed deficits in social behaviors in *Mef2c* mutant mice and the presence of autism-related symptoms in some patients with MCHS [9**]. MEF2C is linked to *Mecp2* [96, 101–103] and *Ube3a* [104], which are involved in Rett [105] and Angelman syndromes, respectively. Schizophrenia – a neurodevelopmental disorder characterized by complex symptoms including psychosis, disorganized thought, paucity of speech, social isolation and flat affect – is also a genetically-linked disorder, and SNPs in the vicinity of the *MEF2C* gene emerged from a large GWAS meta-analysis study as conferring significant disease risk [63*]. It's interesting to note that the behavior phenotypes in *Mef2c* mutant mice, including social interaction deficits, reduced ultrasonic vocalizations, learning and memory deficits, etc. [9**], could be viewed as schizophrenia-like symptoms as much as ASD or MCHS symptoms.

Fragile × syndrome (FXS) is a neurodevelopmental disorder characterized by ID, ADHD, anxiety symptoms, epilepsy and autism-related symptoms [106]. FXS is caused by epigenetic silencing of the *FMR1* gene promoter (or missense mutations in a few rare cases), and it is the most common inherited cause of ID in males and the most common genetic cause of ASD [106]. Similar to *Mef2c* mutant mice, the male *Fmrl* knockout mice exhibit social interaction and communication deficits, hyperactivity, altered anxiety, some repetitive behaviors and learning and memory deficits [106]. The protein product of the *Fmrl* gene, FMRP, functions to bind and regulate the subcellular localization and protein synthesis of >1000 neuronal mRNAs in the brain, a subset of whom are MEF2-regulated genes [9**]. Interestingly, MEF2-induced synapse elimination is absent in *Fmr1* knockout neurons [66], suggesting that some of the pathophysiology and symptoms of FXS could be related to dysregulation of overlapping MEF2 and FMRP target mRNAs, such as *Pcdh10* [58]. Another possible common pathway between MEF2 and FMRP could be the regulation of protein synthesis mediated by non-coding microRNAs (miRNAs). Indeed, MEF2 proteins control the transcription of a subset of miRNAs [53], and FMRP interacts with miRNAs to regulate protein synthesis of associated mRNAs [107].

Conclusion

MEF2 proteins play pivotal roles in the development and maintenance of the nervous system by regulating the expression of hundreds of gene targets. Since its initial discovery as a muscle cell differentiation factor, MEF2 proteins have emerged as critical neurodevelopment factors that participate in neuronal differentiation, synaptic connectivity and transmission, and neuronal survival. MEF2s can regulate activity-dependent synaptic remodeling during critical periods, and SNPs near, or mutations in, the *MEF2C* gene are linked to risk for numerous neurodevelopmental disorders and mental illnesses (Fig. 3). However, we have only begun to understand the mechanisms by which MEF2 genes govern healthy brain development and function. Additionally, the role of MEF2s in other brain cells, such as microglia [11] and interneuron populations [10, 45, 108], are just beginning to be explored and might provide new insights into MEF2's role in healthy brain function. Understanding MEF2's various contributions to typical brain development represents a tremendous challenge going forward, but a challenge that is likely to reveal important principles of

neural development and function and possible treatment strategies that could impact multiple common mental disorders.

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Highlights:

- MEF2s control gene expression in the developing and adult brain.
- MEF2s regulate synaptic plasticity during critical periods of brain development.
- Sensory experiences influence MEF2-dependent synapse remodeling.
- Mutations affecting MEF2 are linked to multiple neurological disorders.

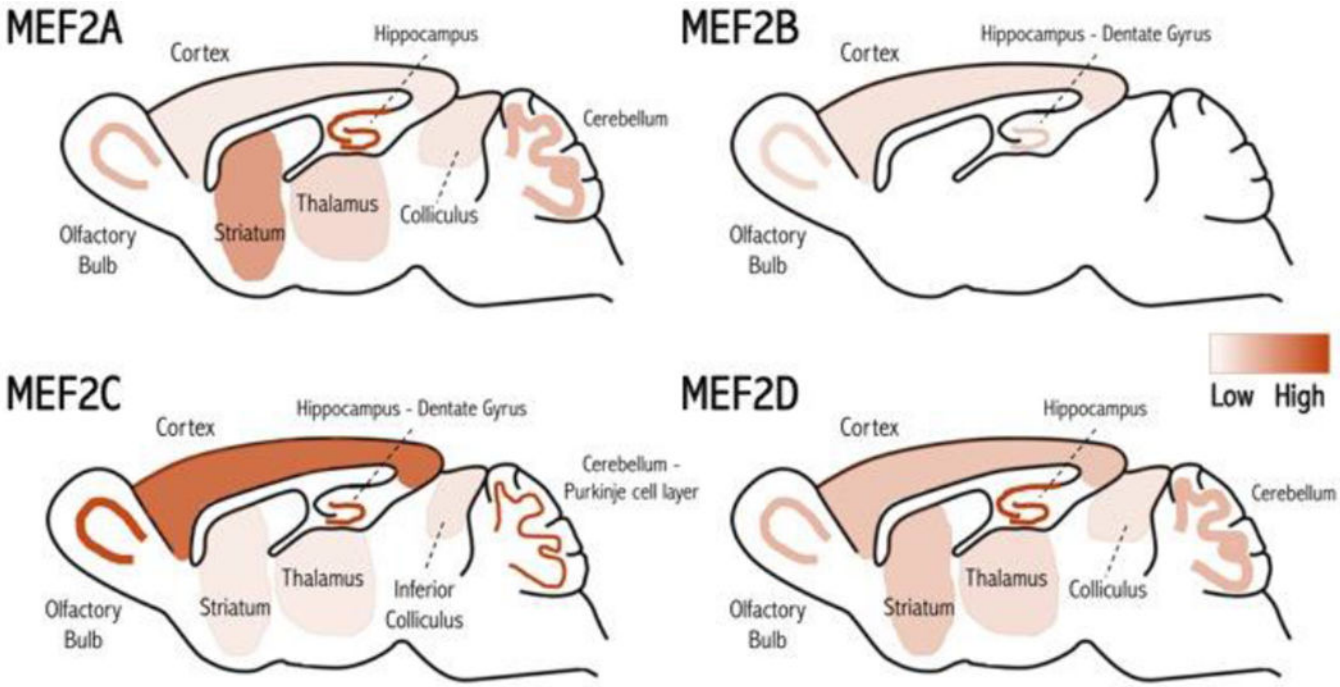

Figure 1. MEF2 expression in the mouse brain.

The four MEF2 proteins (A-D) are differentially expressed in unique but overlapping regions in the postnatal and adult mouse brain [3–14], suggesting that these proteins may have specific functions in different areas. Heatmap denotes relative expression.

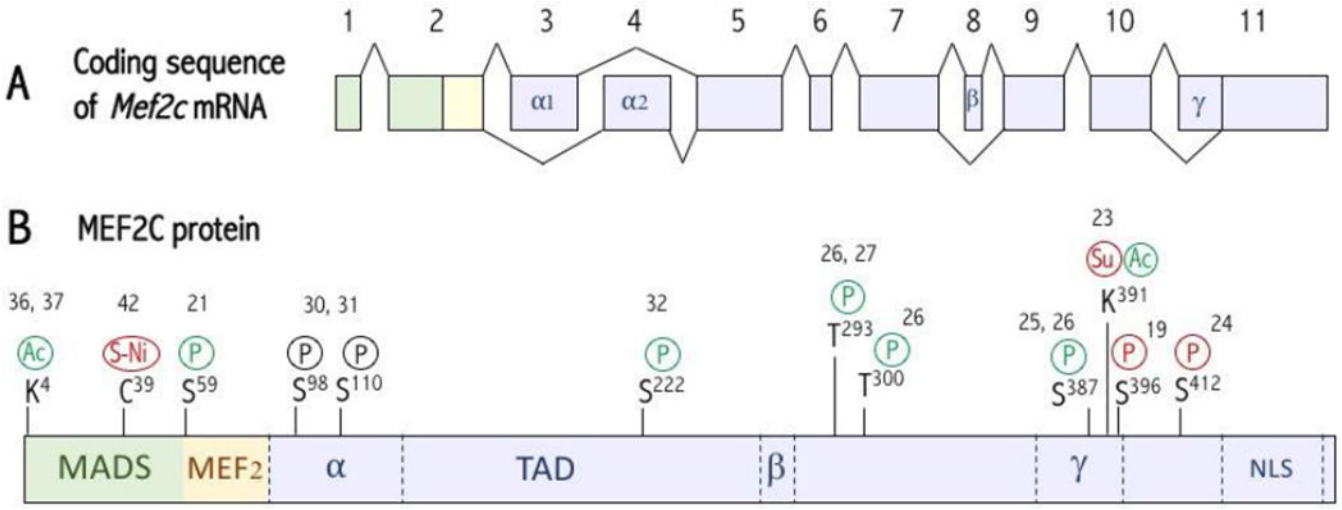

Figure 2. Transcriptional variants and post-translational modifications of MEF2C.

(A) *Mef2c* mRNA splicing. *Mef2* transcripts undergo tissue-specific alternative mRNA splicing at different sites [6, 18–20]. All transcripts will contain either the α1 or α2 (exon 3) domain, and ~50% of the transcripts will also contain the γ domain (located within exon 9). The mouse brain MEF2C protein possesses the α1 and β domains, while mouse muscle/heart tissues contain MEF2C variants that include α1 or α2, but they exclude β (Sciabica et al 2016, SCIEX). (B) Domains and post-translational modifications of MEF2C. The MADS and MEF2 domains mediate MEF2 dimerization and DNA binding as well as co-factor recruitment, and the TAD recruits co-factors to regulate transcription activity (TA). Multiple forms of posttranslational modifications occur on MEF2C, including phosphorylation, acetylation and sumoylation, that regulate its activity, stability or DNA binding affinity [21–42]. Modifications in green increase TA, in red decrease TA, and in black induce protein degradation. NLS: Nuclear Localization Signal. P: Phosphorylation. Su: Sumoylation. Ac: Acetylation. S-Ni: S-Nitrosylation. TAD: Transactivation Domain.

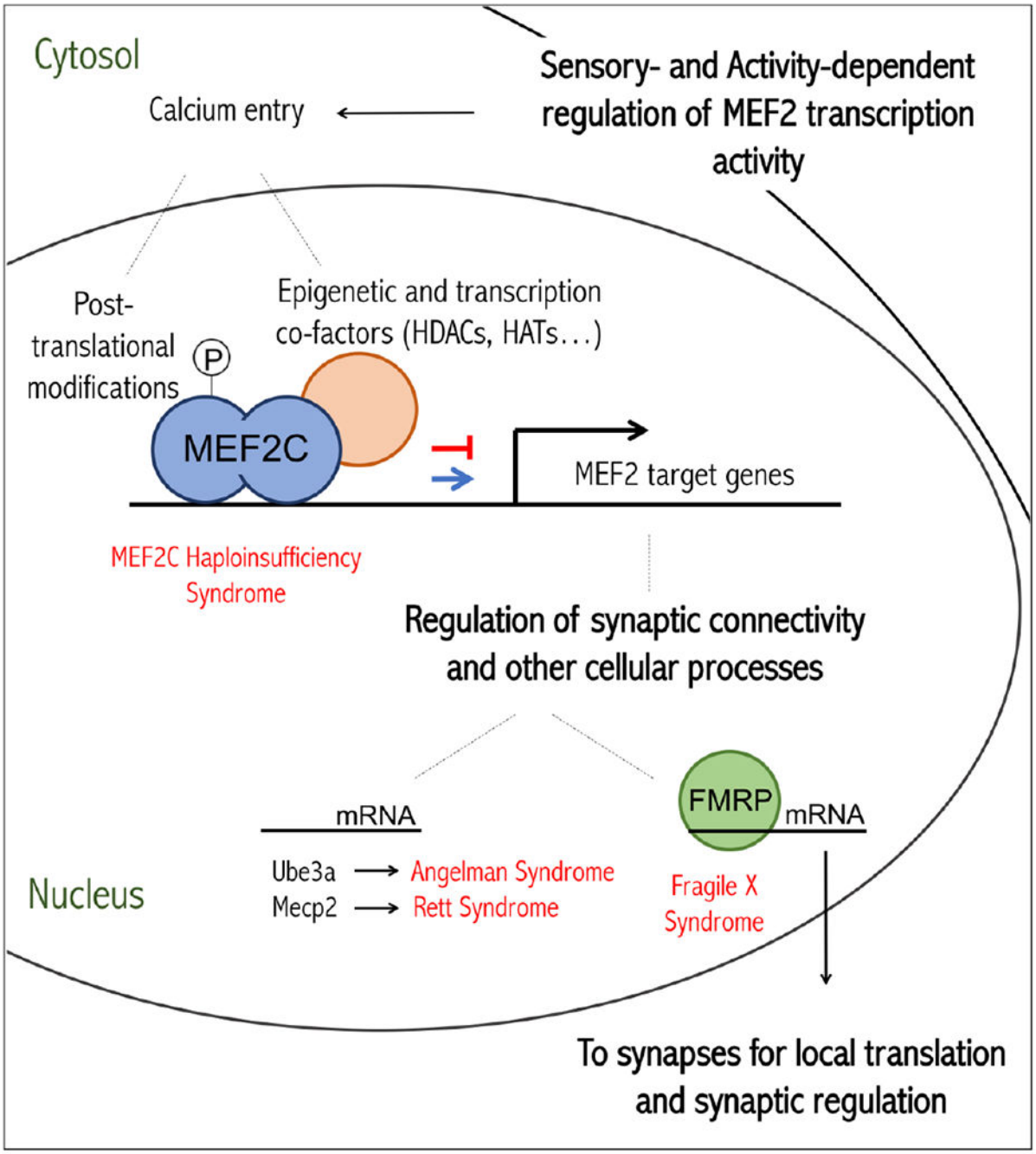

Figure 3. Model for MEF2 regulation and function in neurons.

Sensory experiences lead to neuronal depolarization that results in an increase in intracellular calcium and subsequent changes in MEF2 transcriptional activity by altering posttranslational modifications on MEF2 and affecting co-factor interactions. MEF2s bind to DNA as homo- or heterodimers and can either activate or repress specific target genes that have numerous downstream functions, including synaptic connectivity regulation. The RNA-binding protein, FMRP, transports a subset of the MEF2-regulated mRNAs into dendrites. FMRP can control local protein synthesis of common MEF2-FMRP target mRNAs to

regulate synapse elimination. Neurodevelopmental disorders associated with MEF2 are labeled in red.

Table 1.

Summary of phenotypes produced by manipulation of MEF2.

***Mef2* manipulation**	**Neural circuit phenotype**	**Behavior phenotype**	**References**
Embryonic *Mef2c* deletion from **most forebrain** excitatory neurons in mice (*EmxCre* × *Mef2c* flox/flox)	Decreased E/I ratio in the cortex Organotypic slices at 3 week old in the somatosensory cortex : Decreased cortical UP states (layer IV) Decreased mEPSC amplitude (layer II/III) Increased mIPSC frequency and amplitude (layer II/III) On cultured cortical pyramidal neurons: Decreased spine density Increased GABAergic synapses	Decreased ultrasonic vocalizations in pups and adults, decreased social preference, decreased sucrose preference, increased locomotor activity and stereotypy, fear learning and memory deficits	9**
Embryonic downregulation of ***Mef2c*** from a **mosaic of pyramidal cortical neurons** by shRNA *in utero* electroporation of one hemisphere in mice	At postnatal day 21 on pyramidal cortical neurons: Basal increased spine density Attenuation of increased spine density after nicotine exposure Abolition of increased dendritic complexity after nicotine exposure	Attenuation of nAChR-dependent hypersensitive passive avoidance learning, induced by nicotine exposure during critical periods	59*
Embryonic overexpression of ***Mef2c*** from a **mosaic of pyramidal cortical neurons** by *Mef2c in utero* electroporation of one hemisphere in mice	At postnatal day 21on pyramidal cortical neurons: Basal increased spine density Basal increased dendritic complexity	–	59*
Postnatal *Mef2c* deletion from a **sparse population of cortical neurons** by Cre-expressing virus injections into the ventricles of postnatal day 1 floxed *Mef2c* in mice	Recordings from somatosensory cortex layer II/III pyramidal neurons in organotypic slides at ~ 1month old: Increased mEPSC frequency and amplitude Decreased locally evoked EPSC amplitude (layer IV to II/III; layer V to layer II/III) Increased contralaterally evoked EPSC amplitude (contralateral layer II/III to layer II/III) MEF2C regulation of synapses is input-specific	–	61**
Global ***Mef2c* heterozygous** mice, as a model of the genetic human haploinsufficiency syndrome	Increased E/I ratio in the hippocampus Recordings from dentate gyrus neurons in hippocampal slices at 1 to 6 month old mice: Decreased mIPSC amplitude Decreased mIPSC frequency Increased mEPSC frequency Decreased mEPSC amplitude	Cognitive impairments, social interaction deficits	60**
Embryonic *Mef2c* deletion from the brain (human *gfap*-Cre × *Mef2c* flox/KO) in mice	Recordings from granule cells in the dentate gyrus in hippocampal slices at postnatal 12-21 days: Increased mEPSC frequency Increased evoked perforant path synaptic transmission Increased number of spines	Fear learning and memory deficits	64
Downregulation of *Mef2a/d* in cultured **hippocampal neurons** by shRNA transfection	Increased mEPSC frequency Increased number of excitatory synapses	–	44
Expression of a constitutive ***Mef2c*** transcriptional activator (MEF2C-VP16) in wild-type **cultured cortical** pyramidal neurons	On cultured cortical pyramidal neurons: Decreased spine density Increased GABAergic synapses	–	9**
Expression of a constitutive ***Mef2c*** transcriptional activator (NSE-MEF2C-VP16 transgenic mice)	Decreased mEPSC frequency in dentate granule cells	–	64
Expression of a constitutive ***Mef2c*** transcriptional repressor (MEF2C-Engrailed) in *Mef2c* knock-out **cultured cortical** pyramidal neurons	On cultured cortical pyramidal neurons: Rescue of spine density and GABAergic synapses in *Mef2c* knock-out neurons MEF2C acts as a transcriptional repressor	–	9**
Downregulation of ***Mef2c*** in **cultured neural progenitor cells** by shRNA transfection	At 4 days post-transfection:	–	59*

***Mef2* manipulation**	**Neural circuit phenotype**	**Behavior phenotype**	**References**
	Basal decreased spine density		
Intrastriatal injection of HSV-Cre-GFP virus in ***Mef2C*** flox/flox mice **at P2**	Increased number of spines in striatal projecting neurons at P8	–	62*
Intrastriatal injection of HSV-Cre-GFP virus in ***Mef2C*** flox/flox mice at **P14-15**	Normal number of spines in striatal projecting neurons at P19-20	–	62*
In utero electroporation of a constitutive ***Mef2c*** transcriptional activator (*Mef2C*–VP16) at E12.5 in wild-type *embryos*	Decreased number of spines in striatal projecting neurons at P14	–	62*
Up-regulation of **MEF2C in the adult prefrontal cortex (PFC)** by AAV-*Mef2c* virus injections	Decrease in mushroom spines proportion in layer III of the PFC with no difference in total spine density	Improved cognition	63*