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ΔFOSB: A Potentially Druggable Master Orchestrator of Activity-Dependent Gene Expression

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Abstract

ΔFOSB is a uniquely stable member of the FOS family of immediate early gene AP1 transcription factors. Its accumulation in specific cell types and tissues in response to a range of chronic stimuli is associated with biological phenomena as diverse as memory formation, drug addiction, stress resilience, and immune cell activity. Causal connections between ΔFOSB expression and the physiological and behavioral sequelae of chronic stimuli have been established in rodent and, in some cases, primate models for numerous healthy and pathological states with such preclinical observations often supported by human data demonstrating tissue-specific ΔFOSB expression associated with several specific syndromes. However, the viability of ΔFOSB as a target for therapeutic intervention might be questioned over presumptive concerns of side effects given its expression in such a wide range of cell types and circumstances. Here, we summarize numerous insights from the past three decades of research into ΔFOSB structure, function, mechanisms of induction, and regulation of target genes that support its potential as a druggable target. We pay particular attention to the potential for targeting distinct ΔFOSB isoforms or distinct ΔFOSB-containing multiprotein complexes to achieve cell type or tissue specificity to overcome off-target concerns. We also cover critical gaps in knowledge that currently limit the exploitation of ΔFOSB's therapeutic possibilities and how they may be addressed. Finally, we summarize both current and potential future strategies for generating small molecules or genetic tools for the manipulation of ΔFOSB in the clinic.

Graphical Abstract

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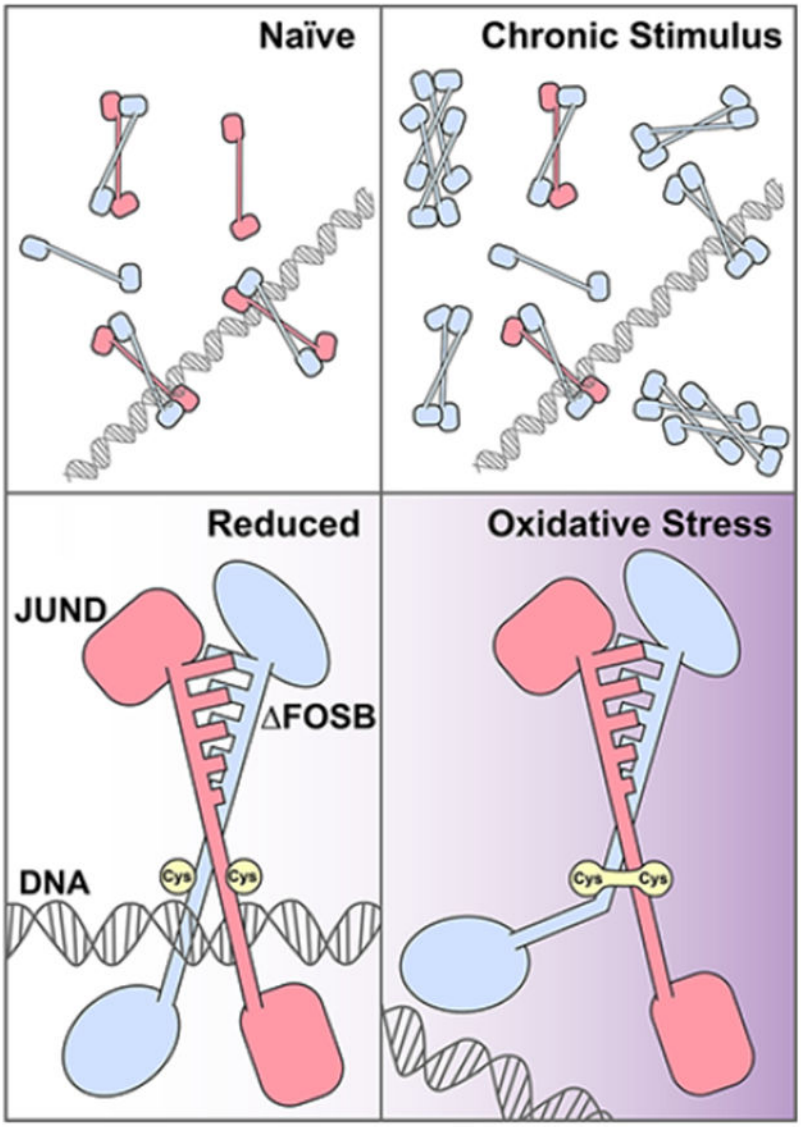

Keywords

AP1; transcription; addiction; Alzheimer's disease; depression; stress; learning and memory; protein structure; drug design

INTRODUCTION

Complex organisms have distinct organs and tissues that are composed of many different cell types varying enormously in form and function, yet all cells in a given organism contain essentially identical DNA. During development, the differentiation of these cells depends upon exquisitely regulated changes in gene expression controlled by cell-to-cell signaling, environmental cues, and presumably random factors.[1] Likewise, regulation of gene expression occurs within cells of adult organisms to mediate adaptation to the environment

throughout life, such as learned behaviors as well as critical oscillatory functions like daily sleep or seasonal mating or migration.[2–4] Many complex and interlocking mechanisms contribute to the expression of a particular gene within a eukaryotic cell, including modification of chromatin structure, noncoding RNAs, and a large class of proteins called transcription factors (TFs) that bind to DNA in a sequence-specific manner to control RNA transcription. There are many families of TFs, which bind to the proximal promoter regions of genes to regulate RNA polymerase binding and initiation of transcription as well as to more distant regulatory (e.g., enhancer) sequences to stimulate or repress the expression of genes thousands of base pairs away, potentially even on different chromosomes.[5]

Activator Protein-1 (AP1) is a prototypical family of TFs critical in virtually every eukaryotic cell.[6] Dimeric AP1 protein complexes are master regulators of transcription, responding to a wide variety of extracellular signals to modulate myriad physiological functions, and have been implicated in dozens of diseases from cancer to drug addiction.[3,7] Genes encoding AP1 proteins are classified as immediate early genes, a superfamily characterized by their rapid (minutes) expression in response to many forms of cell activation, for instance, viral regulatory proteins that are synthesized following viral infection of a host cell or homeostatic regulators of excitability expressed after rapid firing of neurons.[8,9] AP1 complexes expressed transiently in neurons following activation are typically formed as heterodimers of one FOS family and one JUN family protein (see details below). Of the many AP1 proteins, this current Review focuses on ΔFOSB, which is unique among AP1 proteins due to its remarkable stability in the brain.[3,10] In neurons, all AP1 proteins, like FOS, are rapidly and robustly induced following high-frequency firing with a half-life ranging from minutes up to a couple of hours.[11–13] FOS-containing AP1 complexes are hypothesized to target a variety of genes associated with cell differentiation, cell and synapse development, synaptic plasticity, and learning.[14,15] ΔFOSB, on the other hand, has an unusually long half-life, up to 8 days *in vivo*,[16–18] and though it is primarily expressed in neurons of the central nervous system, it is also found in other cells, including microglia in brain[19] as well as in osteoblasts in bones, where it functions as an oncoprotein and directly associates with tumorigenesis.[7] In the brain, long-lasting ΔFOSB induction in distinct types of neurons is directly linked to addiction,[20–22] stress susceptibility, resilience, and antidepressant action,[23,24] L-DOPA-induced dyskinesias in Parkinson's disease,[25,26] Alzheimer's disease (AD) and memory formation,[27–29] and sexual behavior,[30] among others, with each function linked to the specific brain regions and cell types in which ΔFOSB accumulates.

Although ΔFOSB has been studied extensively for decades and bidirectional genetic manipulation of ΔFOSB expression in the brains of mice, rats, and monkeys has provided causal links between ΔFOSB expression and many physiological responses and behaviors linked to disease, ΔFOSB has yet to be effectively targeted with pharmacological tools. Viral vectors or inducible genetic mutant mice that increase or decrease ΔFOSB function in specific brain cells and circuits have proven effective in reversing animal behaviors relevant to human disease,[24,31–33] but these viral and genetic tools are not readily translatable to humans.[34] This gap highlights the critical need to develop small molecules that target ΔFOSB, a prospect that appears more feasible than in past years with the recent development of drugs targeting other AP1 TFs.[35,36] Here, we review the circumstances

and effects of ΔFOSB induction and the current understanding of ΔFOSB structure and function, and we highlight recent discoveries that indicate the suitability of ΔFOSB as a pharmacological target. We also cover the strategies currently being used to uncover compounds that modulate its function and tools that will provide greater understanding of activity-dependent regulation of long-term gene expression and may become vital new treatments for diseases ranging from addiction to AD to cancer.

ΔFOSB INDUCTION IN THE BRAIN AND PERIPHERY

ΔFOSB Induction and Function in Nucleus Accumbens.

ΔFOSB is induced in response to a wide range of stimuli in many different tissues and cell types. For many years, we and others have studied the mechanism and circumstances of ΔFOSB induction in discrete regions of the brain in response to stimuli associated with neurological and psychiatric disease. We originally characterized 35–37 kDa proteins, which we termed “chronic FRAs” (FOS-related antigens) induced in rodent brain after chronic exposure to psychostimulants.[22,37,38] We further found that these proteins persisted for weeks after exposure to chronic cocaine, an effect that was especially prominent in the nucleus accumbens (NAc), a key site of dopaminergic signaling modulated by cocaine and critical for the rewarding effects of drugs and other pleasurable stimuli. These FRAs were resolved as unique isoforms of ΔFOSB,[38,39] and we went on to demonstrate that ΔFOSB accumulates in medium spiny neurons (MSNs) of the mouse NAc in response to chronic exposure to virtually all drugs of abuse.[40–43] This accumulation occurs preferentially in MSNs expressing D1-type dopamine receptors (D1-MSNs) for all drugs of abuse except for opioids, which also induce ΔFOSB in D2-type MSNs (D2-MSNs).[44–48] Critically, ΔFOSB is induced in the NAc of human drug addicts,[21] indicating that this phenomenon may indeed underlie certain addiction behaviors.

In support of this idea, overexpression of ΔFOSB specifically in D1-MSNs of the NAc and dorsal striatum of mice causes increased locomotor sensitivity to cocaine,[20,49] increased cocaine and morphine conditioned place preference,[20,49,50] and increased cocaine self-administration and relapse.[51,52] Although the downstream mechanisms underlying the effects of NAc D1-MSN ΔFOSB on drug responses are still not fully understood, ΔFOSB is critical for cocaine-dependent changes in D1-MSN dendritic spine shape and number,[21,32,49] which are reflected in the altered function of glutamatergic synapses onto D1-MSNs.[49] Plasticity at these synapses involving altered AMPA-type glutamate receptor (AMPAR) insertion and activity underlies cocaine reward, seeking, withdrawal, and incubation of craving in rodents,[53,54] and indeed, ΔFOSB target genes in the NAc include those that encode certain AMPAR subunits,[20,24] Ca^{2+}/calmodulin-dependent protein kinase IIα (CaMKIIα),[21,23] and cyclin-dependent kinase 5 (CDK5),[55] all critical regulators of glutamatergic synaptic strength. It is important to note that constitutive knockout of the *Fosb* gene in mice also results in increased sensitivity to the behavioral effects of cocaine.[38] Because this knockout is global and occurs at the earliest stages of development, a variety of adaptive changes may occur driving this drug-sensitivity phenotype that may be independent of the acute or chronic adult effects of ΔFOSB specifically in NAc MSNs. Moreover, in other cells like hippocampal CA1 pyramidal neurons, both overexpression and inhibition

of ΔFOSB in adulthood can cause a similar impairment in spatial learning,[27] suggesting that there is a range of ΔFOSB expression that drives normal behavioral outcomes with a deviation above or below this range causing cellular and behavioral abnormalities.

ΔFOSB is likewise induced in rodent NAc by other stimuli, including many forms of chronic stress.[24,48,56–61] Transgenic reporter mice allowing visualization of MSN subtypes revealed that chronic social defeat stress (CSDS) induces ΔFOSB in NAc D2-MSNs of animals that are susceptible to depression-like behaviors following stress, while mice that were stressed in the same manner but were behaviorally resilient showed ΔFOSB accumulation only in D1-MSNs.[48] Using a novel neuroepigenome-editing approach, it was shown that induction of endogenous ΔFOSB in D1-MSNs of NAc drives the resilient phenotype, whereas such induction in D2-MSNs promotes susceptibility with neuroepigenomic suppression of endogenous ΔFOSB expression having the opposite effects.[57] These opposite actions of ΔFOSB in D1- vs D2-MSNs are consistent with the opposite effects seen upon optogenetic activation of these MSN subtypes in controlling resilience vs susceptibility to CSDS.[62] Antidepressants like fluoxetine and tranylcypromine also induce ΔFOSB in mouse NAc,[22,24,58] and NAc ΔFOSB function is necessary for antidepressant reversal of behavioral deficits after CSDS.[24] Chronic electroconvulsive seizures, which are antidepressant in humans as well, induce ΔFosB in this and other brain regions (see below). Meanwhile, ΔFOSB expression levels are reduced in the NAc of depression patients.[24,63] It is likely this finding in humans is mediated via D1-MSNs although this remains to be demonstrated directly. The identification of the target genes of ΔFOSB in D1- and D2-MSNs that mediate these various effects is a high priority of current research; known target genes such as those encoding the GLUA2 AMPAR subunit[24] and CaMKIIα,[23] plus many others that control functional and morphological plasticity of NAc glutamatergic synapses, are plausible candidates.[24,64,65]

In addition to drugs, stress, and antidepressants, other stimuli that affect the brain's reward circuitry induce ΔFOSB accumulation in NAc. For instance' natural rewards like high fat diet increase ΔFOSB protein in NAc,[66] potentially in a subregion-specific manner.[67,68] However, chronic mild food restriction can also induce ΔFOSB in NAc,[60] suggesting that metabolic changes in either direction can affect expression, which likely occurs in different cell types as discussed above. Nevertheless, ΔFOSB expression in NAc appears critical for motivation to consume food, as overexpression of ΔFOSB in NAc enhanced food-reinforced instrumental performance and the progressive ratio response in rats[69] and drove the preference for sucrose in mice.[70] Nonfood rewards also induce ΔFOSB in NAc, including sexual experience,[71,72] and blocking the ΔFOSB function in NAc prevents the acquisition of sexual proficiency in adult male rats,[71] while overexpression of ΔFOSB in NAc of female hamsters enhances sexual reward.[73] Moreover, ΔFOSB is induced in NAc by exercise, and overexpression of ΔFOSB in NAc D1-MSNs increases voluntary wheel running, while overexpression in D2-MSNs decreases it.[74] Taken together, these studies establish cell type-specific ΔFOSB expression in NAc as a key indicator of reward circuit activation and an essential requirement for proper processing of virtually all forms of reward.

ΔFOSB Induction in Other Brain Regions.

ΔFOSB is induced by chronic neuronal activation and, as such, it is induced in many other brain regions upon repeated exposure to stimuli driving regional activity. For instance, chronic exposure to many drugs of abuse, including psychostimulants, ethanol, delta(9)-tetrahydrocannabinol, and morphine, induce ΔFOSB in brain regions as diverse as dorsal striatum, prefrontal cortex, and hippocampus in rodents, and many of these effects have been found in human drug users as well.[40,63,75,76] ΔFOSB is also induced throughout the rodent brain by both chronic stress[58,61] and chronic antidepressant exposure,[58,77] and ΔFOSB is elevated in the prefrontal cortex of depression patients.[78] Additionally, antipsychotics induce ΔFOSB throughout the rodent brain, as covered in detail by a recent review,[79] and its induction in the prefrontal cortex has been associated with negative behavioral outcomes.[80] Along those lines, ΔFOSB induction in response to repeated L-DOPA administration in a dopamine-lesioned rodent or nonhuman primate has been linked directly to abnormal dyskinetic movements that clinically limit L-DOPA therapy.[25,26]

ΔFOSB induction in the hippocampus has become an important topic in recent years. ΔFOSB accumulates in the hippocampus in response to externally induced electroconvulsive seizures in rats[55,81] and multiple mouse genetic and physiological models driving repeated seizures.[28,82–84] More recently, our groups have demonstrated that, in glutamatergic pyramidal neurons of the dorsal and ventral hippocampus, ΔFOSB accumulation decreases pyramidal cell excitability.[31,85] Importantly, we demonstrated that viral overexpression of ΔFOSB reduces neuronal excitability and that viral expression of a dominant negative construct or knockout of the *Fosb* gene increases neuronal excitability, indicating that the native ΔFOSB protein is actively engaged in controlling hippocampal neuronal excitability.[31,85] Together, these data suggest that ΔFOSB expression in response to high levels of neuronal activity may represent a critical negative feedback mechanism to reduce excitability, as in traditional homeostatic scaling,[86] and that ΔFOSB dysfunction could potentially contribute to pathological states of hippocampal hyperexcitability, such as epilepsy. Indeed, *Fosb* knockout mice are prone to seizures.[87]

ΔFOSB expression in the dorsal hippocampus is critical for normal learning and memory. We have demonstrated that ΔFOSB is induced in the dorsal CA1 region after spatial learning in both mice and rats and that inhibition of the ΔFOSB function in the hippocampus prevents spatial and contextual learning.[27] Critically, we also showed that viral overexpression of ΔFOSB in dorsal hippocampal neurons prevents learning,[27] and other groups have gone on to demonstrate that ΔFOSB is highly induced in dorsal hippocampus in human AD patients and mouse models of AD and that inhibition of this ΔFOSB can reverse cognitive deficits in AD mice.[28,29,88] The ventral hippocampus, though also important for learning and cognition, is more often correlated with emotional learning and associations between specific experiences and feelings of reward, fear, pain, or pleasure. ΔFOSB is induced in the ventral hippocampus by stress, antidepressants, and drugs of abuse,[31,40,58,61,77] and we and others have shown that ventral hippocampal ΔFOSB expression is critical for resilience to stress[31] and the antidepressant effects of ketamine.[77]

ΔFOSB is induced in many subregions of the cortex under conditions associated with their individual functions. For instance, ΔFOSB is induced in the prelimbic area of the mouse

medial prefrontal cortex by stress, where it appears to promote stress susceptibility through modulation of specific output circuits.[89] In the orbitofrontal cortex, however, ΔFOSB is critical for resilience to cognitive impairments caused by chronic cocaine exposure and impulsivity during subsequent withdrawal.[90–92] ΔFOSB is induced in the infralimbic cortex by sexual experience, and viral overexpression of ΔFOSB in the hamster infralimbic cortex is sufficient to induce sexual proficiency and the attendant changes in dendritic spine morphology.[30] These and other studies of ΔFOSB in cortex indicate that it accumulates in neurons in response to virtually any chronic behavior or stimulus that engages a particular cortical circuit and is often critical for key neuroadaptations in those cells and synapses underlying the long-term behavioral sequelae of these experiences.

ΔFOSB in Non-neuronal Cells.

Many AP1 proteins are critical for embryonic development and organogenesis, including JUN and FRA-1, but ΔFOSB is among the group including JUND and FOS that appear largely dispensable for embryonic development.[7] Although rapidly induced in response to growth factors, ΔFOSB also appears to be dispensable for cell cycle progression, since fibroblasts and embryonic stem cells lacking *Fosb* gene expression have no proliferation defect.[87] However, ectopic expression of ΔFOSB promotes differentiation in osteoblasts and increases bone formation.[93,94] Moreover, *Fosb* is associated with tumorigenesis in bone,[7] and rearrangements of the human *Fosb* gene are found in human bone tumors,[95] though to a much lesser extent than rearrangements of *FOS*.[95] FOSB and ΔFOSB can transform cells in culture,[96] though the mechanism and transforming potential of ΔFOSB remains enigmatic.[7]

It is likely that the *Fosb* gene plays an important role in progenitor cell differentiation in the brain. In the mouse hippocampus, *Fosb* appears important for progenitor cell division and proliferation as *Fosb* null mice have impaired hippocampal neurogenesis and specific deletion of *Fosb* expression in the subgranular zone impairs cell proliferation and migration.[97,98] Moreover, ΔFOSB is expressed in microglia in the hippocampus and is required for microglial activation.[19] Other immune cells also express the *Fosb* gene, including mast cells[99,100] and T cells, and *Fosb* induction in response to T cell activation has been implicated in T cell death.[101,102] However, the gene targets of ΔFOSB and its function in most immune cells remain largely to be determined.

ΔFOSB STRUCTURE AND FUNCTION

AP1 complexes are formed by pairs of proteins derived from multigene families most commonly including one FOS (FOS, FOSB, FRA-1, and FRA-2) and one JUN (JUN, JUNB, JUND) protein as stated earlier. The heterodimer is bound together by complementary basic leucine zipper (bZIP) domains with each protein containing the requisite DNA-binding basic region and more variable transactivation domains (Figure 1A). When the two DNA binding regions are brought together, they bind the AP1 consensus sequence TGA(C/G)TCA most typically found in the promoter regions of target genes but now being identified increasingly in enhancer regions as they are delineated. FOSB and ΔFOSB are FOS family proteins both produced from the *Fosb* gene. ΔFOSB is generated by alternative splicing that does not introduce any novel amino acid residues but rather

encodes a premature stop codon causing truncation of the C-terminal 101 amino acids in the full-length protein. As a result, ΔFOSB lacks two degron domains that are found in full-length FOSB and all other FOS family proteins and that target these proteins for rapid degradation via ubiquitinylation-dependent and -independent mechanisms.[103] The lack of these degron domains is a key factor in ΔFOSB's enhanced stability: unlike other FOS family proteins whose half-lives range from minutes to hours, ΔFOSB has a half-life in the mouse brain of ~8 days as stated earlier.[17,39,104] Thus, while other FOS family members are expressed but quickly degrade after each stimulus, ΔFOSB accumulates in the brain in response to chronic stimuli including drugs, stress, antidepressants, consumption of natural rewards, learning, and seizures, among others[24,27,39,58] (Figure 1B[22]).

ΔFOSB is further stabilized by phosphorylation. Multiple sites of ΔFOSB phosphorylation have been uncovered *in vitro* and *in vivo*, some of which are increased by stimuli like cocaine and may regulate its ability to transactivate gene expression.[105] However, phosphorylation at serine 27 (S27) in the N-terminus of ΔFOSB increases its stability in cells and in the brain.[17,103,106,107] S27 of ΔFOSB can be phosphorylated by casein kinase 2 in cells,[107] and Ca^{2+}/calmodulin-dependent protein kinase IIα can phosphorylate S27 in cells and appears to mediate ΔFOSB stability in the brain.[21] Interestingly, ΔFOSB increases *Camk2a* gene expression in mouse NAc in response to cocaine, suggesting a positive feed-forward loop mediating long-lasting effects of the drug.[21]

In recent years, X-ray crystallography and *in vitro* biochemistry have shed new light on the ΔFOSB structure and potential complex formation. Although most data point to other FOS family proteins requiring a JUN family partner to form a function AP1 complex,[7] ΔFOSB uniquely can form homodimers that bind AP1 consensus sequences *in vitro*.[108] Further, the bZIP domain of ΔFOSB can even form tetrameric structures that defy canonical AP1 arrangements (Figure 2A), and we have provided some evidence that ΔFOSB is found in complexes consistent with tetramers in cultured cells.[109] These observations suggest that, once a chronic stimulus causes induction of the ΔFOSB protein exceeding a threshold within a cell, perhaps swamping ambient concentrations of JUND, its major binding partner *in vivo*,[110] self-assembly occurs generating several noncanonical molecular arrangements whose function and potential gene targets have yet to be determined. Moreover, ΔFOSB complexes may be stabilized by oxidation, as recent *in vitro* (cell-free and cell-based) experiments suggest that ΔFOSB cysteine 172 (C172) can form a disulfide bond with C279 of JUND in the canonical heterodimeric AP1 complex and that ΔFOSB C172 may form a disulfide bond with C172 of a partner ΔFOSB in a noncanonical homodimeric complex.[109,111]

These properties, some unique to ΔFOSB and others shared by FOS/JUN family members, have made ΔFOSB an intriguing target of study in fields ranging from neuropsychiatric disease to oncology for decades. However, to fully elucidate the role of ΔFOSB in physiology and disease and to potentially exploit it as a target for therapeutic intervention, many outstanding questions remain to be addressed.

OUTSTANDING QUESTIONS OF ΔFOSB FUNCTION

Although a great deal has been learned about the functional relevance of ΔFOSB by overexpressing or inhibiting it with transgenic mice or viral vectors and by deleting the *Fosb* gene, our understanding of the mechanism by which ΔFOSB controls cellular function remains largely inadequate due to our incomplete knowledge of ΔFOSB target genes. Early studies of ΔFOSB targets in brain used gene expression microarrays to probe the effects of ΔFOSB overexpression on the profiles of hundreds or thousands of candidate genes in homogenates from a specific brain region. This approach identified targets like *Cdk5* in the hippocampus and *Fos* in the NAc.[33,55] Other early studies used a candidate gene approach, uncovering targets like *Gria2* using Western blotting of its gene product, GLUA2, in NAc of mice overexpressing ΔFOSB with the preexisting rationale that NAc AMPA receptors were already known to be critical for many of the same behavioral responses to cocaine regulated by ΔFOSB.[20] Later studies often confirmed these targets in a brain region-specific manner using chromatin immunoprecipitation (ChIP) and qPCR.[24] An earlier study employed promoter microarrays to identify genomic binding targets of endogenous ΔFOSB in NAc under control and chronic cocaine conditions.[112] However, these approaches were limited as they relied upon preconceived rationales for choosing candidate target genes, were restricted to a very small subset of genomic regions (e.g., proximal promoters) as putative ΔFOSB-binding sites, and lacked the quantitative power of more recently developed sequencing-based technologies.

More recently, ChIP has been combined with next generation sequencing (ChIPseq) to enable an unbiased and genome-wide survey of ΔFOSB targets. This approach yielded some exciting results in the hippocampus in models of seizure and AD,[28,29,88] in one case uncovering *Calb1* (which encodes calbindin-1) as a key gene target in the dentate gyrus mediating the severity of cognitive impairment in a mouse model of AD.[28] However, the use of ChIPseq to determine ΔFOSB targets in other brain regions, most notably NAc, has remained challenging, likely due to the very small amount of tissue available and the lack of selective high-affinity antibodies for ΔFOSB. For this reason, our groups and others have begun to adopt the Cleavage Under Targets and Release Using Nuclease (CUT&RUN) technique,[113] a strategy in which antibody-targeted controlled cleavage by micrococcal nuclease releases the ΔFOSB–DNA complexes such that the specifically bound DNA can then be sequenced and identified. This technique avoids the cross-linking and solubilization issues inherent to ChIP, and we have found that it indeed produces a stronger signal-to-noise ratio requiring much less input chromatin and less sequencing depth than traditional ChIP in both brain samples and cultured cells.[114] For example, it is now possible to obtain high quality CUT&RUN maps of genome-wide binding patterns of endogenous ΔFOSB in isolated D1-MSNs and D2-MSNs of mouse NAc.[114] Critical advances that may arise from these unbiased sequencing approaches include not only determining novel gene targets underlying the biological effects of ΔFOSB but also identifying the sites where ΔFOSB binds to enhancers, other intergenic regions, intragenic regions, or other elements that may be as crucial as gene promoters.

One of the key factors complicating the study of ΔFOSB is that it, like any TF, has different gene targets in different cell types and brain regions. For instance, ΔFOSB regulates *Calb1*

in hippocampus,[28,55,88] but has not been shown to bind this gene in NAc. Conversely, multiple studies have confirmed that ΔFOSB exerts many of its effects on NAc D1-MSNs and subsequent reward behaviors through binding and regulation of *Gria2*,[20,24,115,116] but *Gria2* does not appear to be a ΔFOSB target in hippocampus, a brain region wherein AMPA receptor expression is absolutely central to synaptic function and learning. Such cell type-specific effects of ΔFOSB were highlighted in a recent paper that showed the very different range of target genes induced or suppressed upon induction of endogenous ΔFOSB in D1-MSNs vs D2-MSNs of mouse NAc by use of locus-specific neuroepigenome-editing tools.[117] It is not clear why ΔFOSB or other TFs have different targets in different cell types or brain regions, but the likely explanation is that the chromatin state at those genes is differentially regulated in the different cells, allowing or preventing ΔFOSB (or another TF) access to target sequences in a cell-specific manner. This epigenetic explanation is supported by findings that altered histone acetylation at the promoter region of *Camk2a* in the NAc is required for fluoxetine-dependent regulation of ΔFOSB binding at this site and subsequent behavioral effects of the drug.[23]

Similar questions have arisen from the observation that different stimuli can cause ΔFOSB regulation of distinct target genes in the same cells or brain region. For example, chronic exposure to either cocaine or morphine strongly induces ΔFOSB expression in NAc D1-MSNs, but even within this single cell type, the two drugs cause ΔFOSB transactivation of partly distinct target genes. For instance, *Sirt1* (which encodes the protein deacetylase sirtuin-1), identified originally as a target for ΔFOSB in the context of chronic cocaine exposure in an early ChIP-promoter array study,[112] was found to be similarly induced via ΔFOSB in NAc by chronic cocaine and by chronic morphine, while its isoform *Sirt2* was found to be bound by ΔFOSB and induced in NAc in response to chronic cocaine only.[118] Current research is investigating whether cocaine induces another factor that is required for ΔFOSB binding to *Sirt2* or whether morphine induces a factor that prevents that binding.

It has long been observed that ΔFOSB can function as either a transcriptional activator, as in the case with *Gria2*,[20,24] or a transcriptional repressor, as with *Fos* or *Pdyn*,[28,50,119] but the mechanisms controlling this dichotomy are only partially understood, not only for ΔFOSB but also for most TFs. One potential mechanism could again be epigenetic control of the 3D conformation of chromatin. At the *Cdk5* gene, ΔFOSB recruits the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex as well as histone acetyltransferases with the combined effect of destabilizing DNA–histone interactions and increasing nucleosome spacing along the *Cdk5* gene, which along with other changes render the gene in a conformation permissive for transcription.[120] In contrast, chronic amphetamine drives increased ΔFOSB binding to the *Fos* gene where it recruits specific histone deacetylases, decreasing histone acetylation and presumably shifting the chromatin into a tighter, more repressed structure that reduces *Fos* expression.[118] It will be critical in future studies to overlay RNaseq and DNA regions with altered histone modifications with genome-wide ΔFOSB binding sites, perhaps using CUT&RUN, to determine the specific sites at which ΔFOSB drives permissive vs repressive chromatin modification to control differential gene expression (Figure 3).

For many decades, immunohistochemical staining of immediate early gene products, like FOS, has been used to identify neuronal populations active just prior to the death of an animal, helping to identify cell types or brain regions whose activity is acutely associated with specific stimuli or behaviors. More recently, the *Fos* promoter has been used to drive expression of tools allowing labeling of neuronal ensembles encoding specific memories or behaviors. Critically, these FOS-expressing ensembles can be subsequently manipulated to affect related behavioral outcomes.[121] For instance, disruption of the activity of NAc neurons expressing FOS in response to cocaine prevents locomotor sensitization to the drug.[122] ΔFOSB's unique stability can likewise be exploited to identify cell populations that have been chronically stimulated.[40,58,61] This raises the intriguing possibility that ΔFOSB could be exploited as a molecular handle to identify and then specifically manipulate neuronal ensembles *chronically* activated by specific stimuli, allowing a better understanding of functional regulation over time and causal connection to the behavioral sequelae of chronic conditions. Indeed, there is some evidence that ΔFOSB accumulates in repeatedly activated NAc ensembles that are specifically associated with the environment in which the drug is administered,[123] indicating that functionally manipulating ΔFOSB could selectively affect behaviors associated with these ensembles.

The mechanisms by which ΔFOSB is induced are only partially understood. For instance, we know that ΔFOSB induction in NAc by chronic cocaine is dependent upon three TFs: cAMP response element binding protein (CREB), serum response factor (SRF), and E2F3a.[124,125] In contrast, its induction in the same brain region by chronic stress appears to require only SRF.[126] Moreover, epigenetic control of the chromatin state at the *Fosb* gene plays a clear role in cocaine-mediated ΔFOSB expression in both NAc and hippocampus.[32,75,127] However, the TFs and epigenetic modifiers controlling *Fosb* gene expression at baseline or after stimulation in specific cell types are not known. It may prove critical to uncover cell type-specific upstream pathways driving ΔFOSB expression, as they could be exploited systemically to control the function of specific neurons underlying a syndrome associated with ΔFOSB without affecting the critical functions of ΔFOSB in other, unaffected cells.

ΔFOSB AS A MEDICINAL TARGET

As we have described, ΔFOSB is expressed in many different cell types and tissues in response to stimuli both natural and artificial, and its functions range from mediating responses to psychotropic drugs, to controlling stress susceptibility vs resilience, to facilitating learning and memory, to transforming bone cells to drive tumor growth, and beyond. As such, ΔFOSB has often been questioned as a viable target for therapeutic intervention in the many disease states with which it is associated due to presumptive concerns of side effects in any of these diverse areas of function. However, it has become apparent that TFs with a similar diversity of functions and gene targets are viable pharmacological targets for the treatment of disease.[128] One of the clearest examples of this advance has been the selective inhibition of FOS-containing AP1 complexes by the drug T-5224. This compound has been proven to be effective in reversing arthritis and spinal cartilage degeneration in preclinical mouse models,[35,36] and Toyoma Chemical has entered this compound in Phase II trials for the treatment of rheumatoid arthritis.

One of the key mechanisms allowing the targeting of many proteins previously considered "undruggable" has been the advent of compounds that covalently bind to cysteine residues. For example, the chemotherapeutic afatinib targets cysteines in epidermal growth factor receptor and has been proven to be effective for treating specific forms of lung cancer.[129] The binding of ΔFOSB to its AP1 response element in DNA is modulated by oxidation of a cysteine residue, and targeting this site could become a key strategy for finding compounds that modulate ΔFOSB function but avoid some of the potential side effects. Specifically, the ΔFOSB bZIP domain must undergo a large conformational rearrangement that is controlled by a "redox switch" at C172 when converting from an oxidized to a reduced state in order to adopt a DNA-binding compatible form[111] (Figure 2B), and studies with purified proteins suggest that a ΔFOSB/JUND dimer undergoes this structural transition and can no longer bind to an AP1 DNA sequence when it is oxidized and the disulfide bond is present, suggesting that the ΔFOSB function is sensitive to cellular redox homeostasis.[111] This is consistent with reports that AP1 complexes of FOS and JUN are also oxidized at conserved cysteine residues, which prevents DNA binding,[130] suggesting that such disulfide bonds may be a conserved mechanism for controlling ΔFOSB transactivation in response to the cellular redox state. It is possible to conceive of compounds that allow modulation of the specific transcriptional effects of ΔFOSB downstream of oxidation for the treatment of diseases associated with increased oxidative stress. For instance, it is well-known that many neurodegenerative diseases cause oxidative stress in affected brain regions, and it is likely that this contributes to neurodegeneration,[131] although antioxidant therapies have been largely unsuccessful.[132,133] It is possible that some of the deleterious effects of oxidative stress driving memory impairments, aberrant behavior, or even neurodegeneration occur via long-term changes in gene expression through altered ΔFOSB expression[28,29] and also perhaps redox-regulated function. Thus, compounds targeting the ΔFOSB redox switch could prevent or reverse changes in gene expression in specifically affected brain regions but might have fewer "off-target" effects on ΔFOSB in brain regions where oxidative stress is lower or in bone or immune cells, where neurodegenerative diseases may have no effect on redox state at all. Of course, many other syndromes in which ΔFOSB plays a central or potential role, like cocaine addiction or epilepsy, also involve alterations in redox state,[134,135] and thus compounds targeting the ΔFOSB redox switch may prove to have multiple therapeutic but safe uses by only affecting tissues where ΔFOSB accumulates concomitant with oxidative stress.

Excitingly, collaborations involving our groups, structural biologists, and medicinal chemists have uncovered compounds targeting ΔFOSB,[115] and multiple classes of compounds targeting ΔFOSB/DNA interactions are rapidly coming to light.[136] We are employing a strategy informed by protein structural data, taking advantage of the findings from our groups and others demonstrating novel ΔFOSB conformations, oligomerization partners (e.g., heterodimers vs homodimers and potential multimers), and post-translational modifications like oxidation or phosphorylation. We are using cell-free, cell-based, and mouse model assays to screen existing compound libraries to find compound scaffolds that can then be further modified by medicinal chemistry to refine and improve specificity, efficacy, and bioavailability in an iterative process. We are using this approach with the goal of uncovering both ΔFOSB antagonists and potentiators, as inhibiting ΔFOSB as

it accumulates in one cell type in NAc could prove useful for reducing the rewarding effects of abused drugs and decreasing relapse to addiction, for instance, while potentiating the function of ΔFOSB as it accumulates in the hippocampus after seizures could reduce neuronal excitability and prevent recurrence of seizure activity.

The challenge, of course, will be to modulate the function of ΔFOSB in cells or tissues requiring treatment while minimizing effects on ΔFOSB underlying normal cell functions and physiological or behavioral outputs, like memory formation or bone growth. The very nature of ΔFOSB accumulation may provide some traction in this regard. Because ΔFOSB accumulates due to chronic cell activity, its function is by nature exaggerated in the cells and ensembles associated with the stimuli causing ΔFOSB production. For instance, epileptiform activity induces ΔFOSB in the regions that are initial foci of the seizure, like the hippocampus, for example.[28,29,55,137] In contrast, ethanol exposure causes a greater accumulation of ΔFOSB in the nucleus accumbens than in the hippocampus.[40] Thus, while ΔFOSB has many functions throughout the brain in behaviors unrelated to each particular disease state, systemically administered compounds that modulate ΔFOSB function may have the greatest effects on the cells that have ΔFOSB accumulation, and those cells may drive the physiological and behavioral outcomes specifically associated with the disease, such as seizures or alcohol abuse. The key to targeting the cells and systems underlying a disease state with minimal effects on those expressing ΔFOSB as a function of normal physiology may therefore be accurate dosing or potency of ΔFOSB-targeting compounds. This idea is not without precedent, as low doses of acetylsalicylic acid (aspirin, 75 to 81 mg/day) are sufficient to irreversibly acetylate serine 530 of cyclooxygenase (COX)-1 and produce antithrombotic effects, whereas higher doses (650 mg to 4 g/day) inhibit COX-1 and COX-2, blocking prostaglandin (PG) production and having analgesic and antipyretic effects.[138]

As mentioned above, it is possible that specificity could also be partially achieved by small molecules targeting the redox switch or a specific arrangement of ΔFOSB oligomerization. However, it is also conceivable that systemically administered viral vectors that cross the blood–brain barrier could drive expression or inhibition of ΔFOSB with cell type-specific promoters to selectively target the affected cell populations. Indeed, in mouse brain, we have used viral vectors in combination with CRISPR technology to achieve knockdown of ΔFOSB expression in specific circuits,[31] and we have used viral vector epigenetic remodeling of the *Fosb* promoter to knock down ΔFOSB in specific cell types.[57,127] The transition of such technology from injections into mouse brain to safe and systemic treatments in the clinic will be an enormous challenge, but there is reason to expect that viral gene therapy for the treatment of neurological and psychiatric disorders will become a reality in the coming decades.[139–142]

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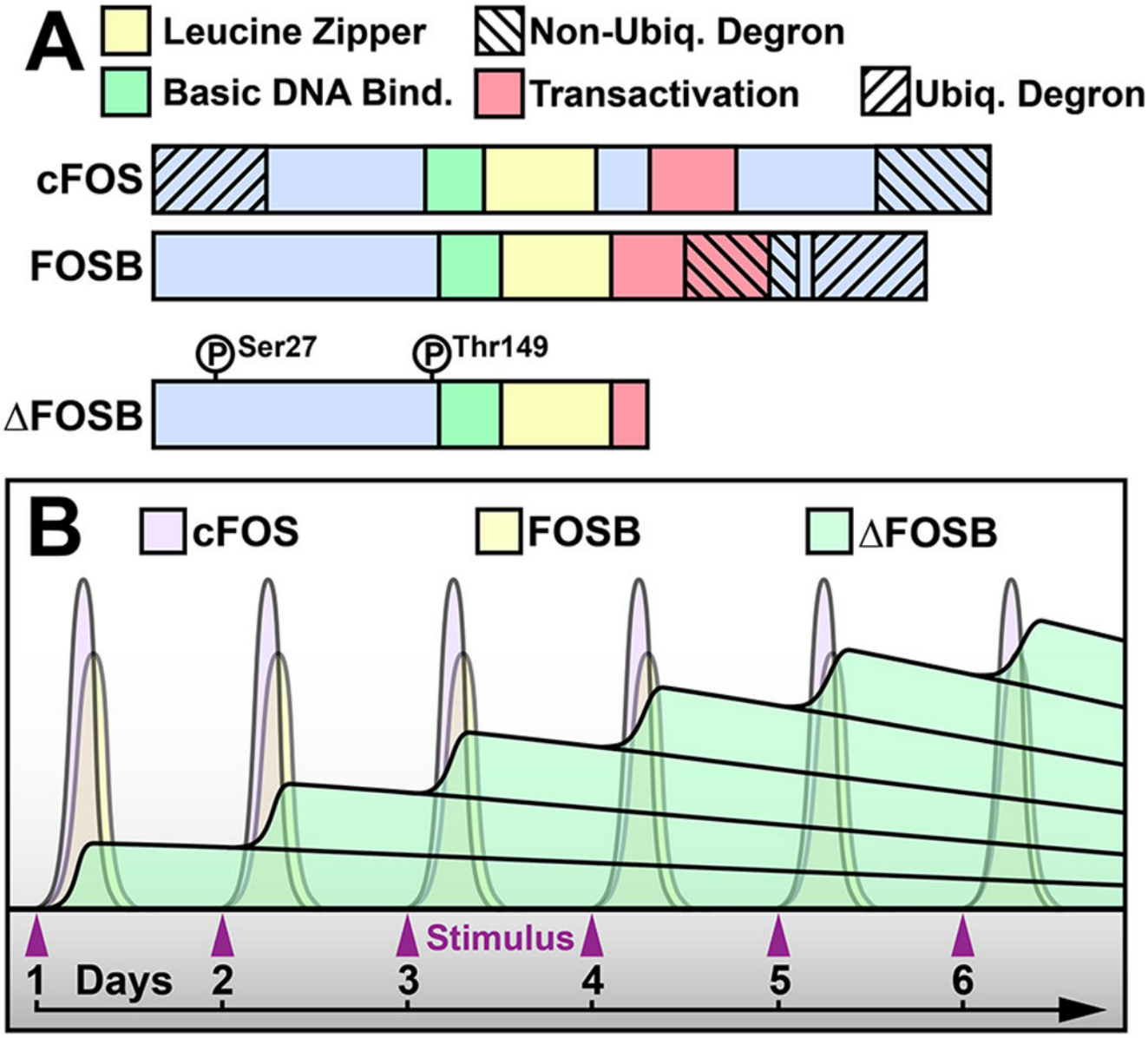

Figure 1.

ΔFOSB's stability allows it to accumulate with chronic stimuli. (A) FOS family protein domain structures. ΔFOSB lacks both ubiquitin-dependent and ubiquitin-independent degron domains present in other FOS family members' C-terminal regions, reducing ΔFOSB's proteolytic degradation. Phosphorylation at Ser27 also contributes to ΔFOSB stability. (B) While other FOS family members are strongly but transiently induced by daily stimuli, ΔFOSB is initially induced at lower levels but accumulates over many days of chronic activation.

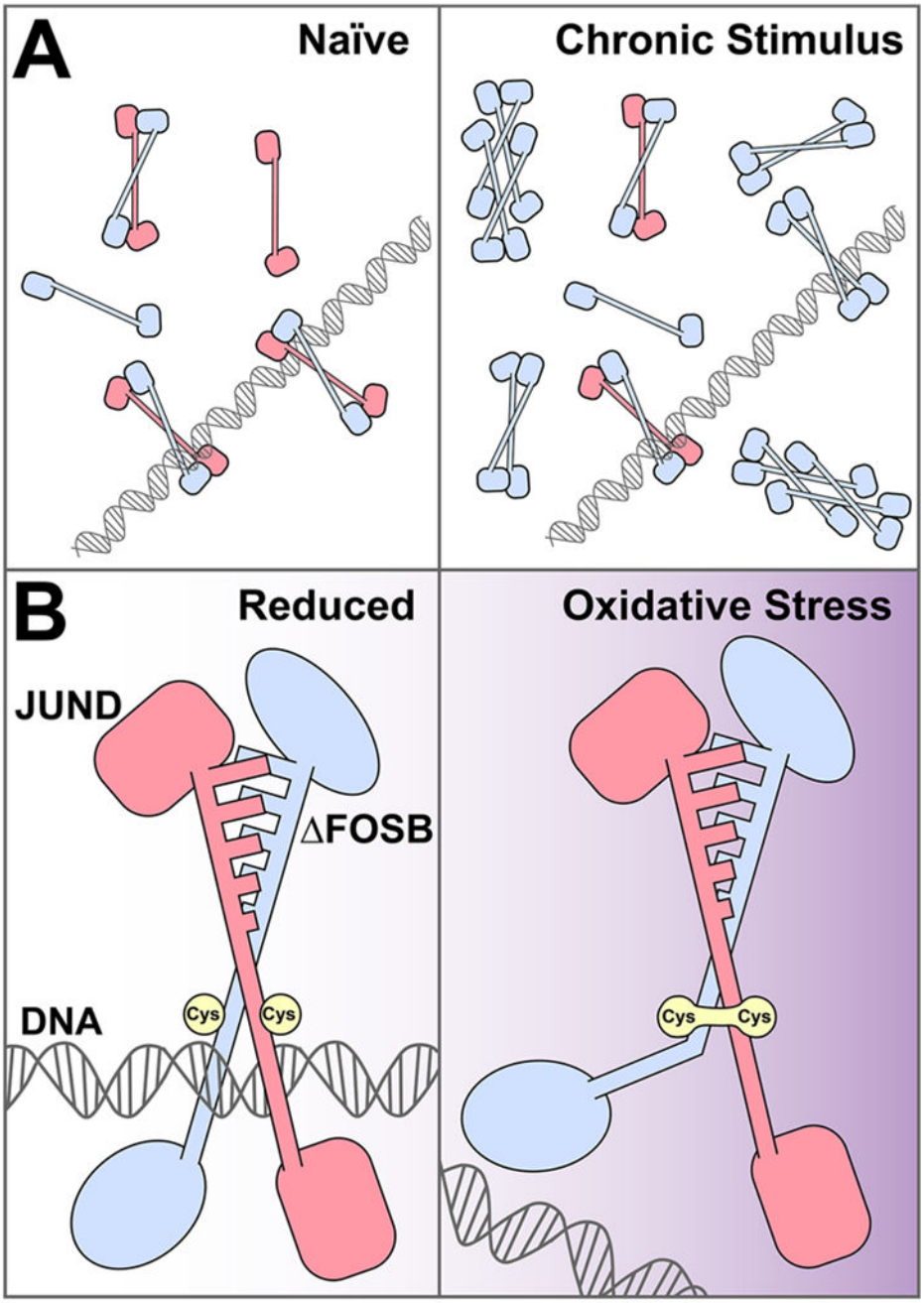

Figure 2.

ΔFOSB structure and function are dynamic. (A) Under naive conditions, ΔFOSB predominantly forms high-affinity heterodimers with JUND. Upon accumulation in response to chronic stimuli, ΔFOSB forms homodimers or larger oligomers that may have different DNA binding affinity or target sites. (B) ΔFOSB and JUND heterodimerize via a leucine zipper motif, allowing DNA binding and bringing cysteines 172 and 285 into close proximity. Upon oxidative stress, a disulfide bond forms between the two cysteines, causing a kink in the ΔFOSB helical structure and preventing the complex from binding DNA.

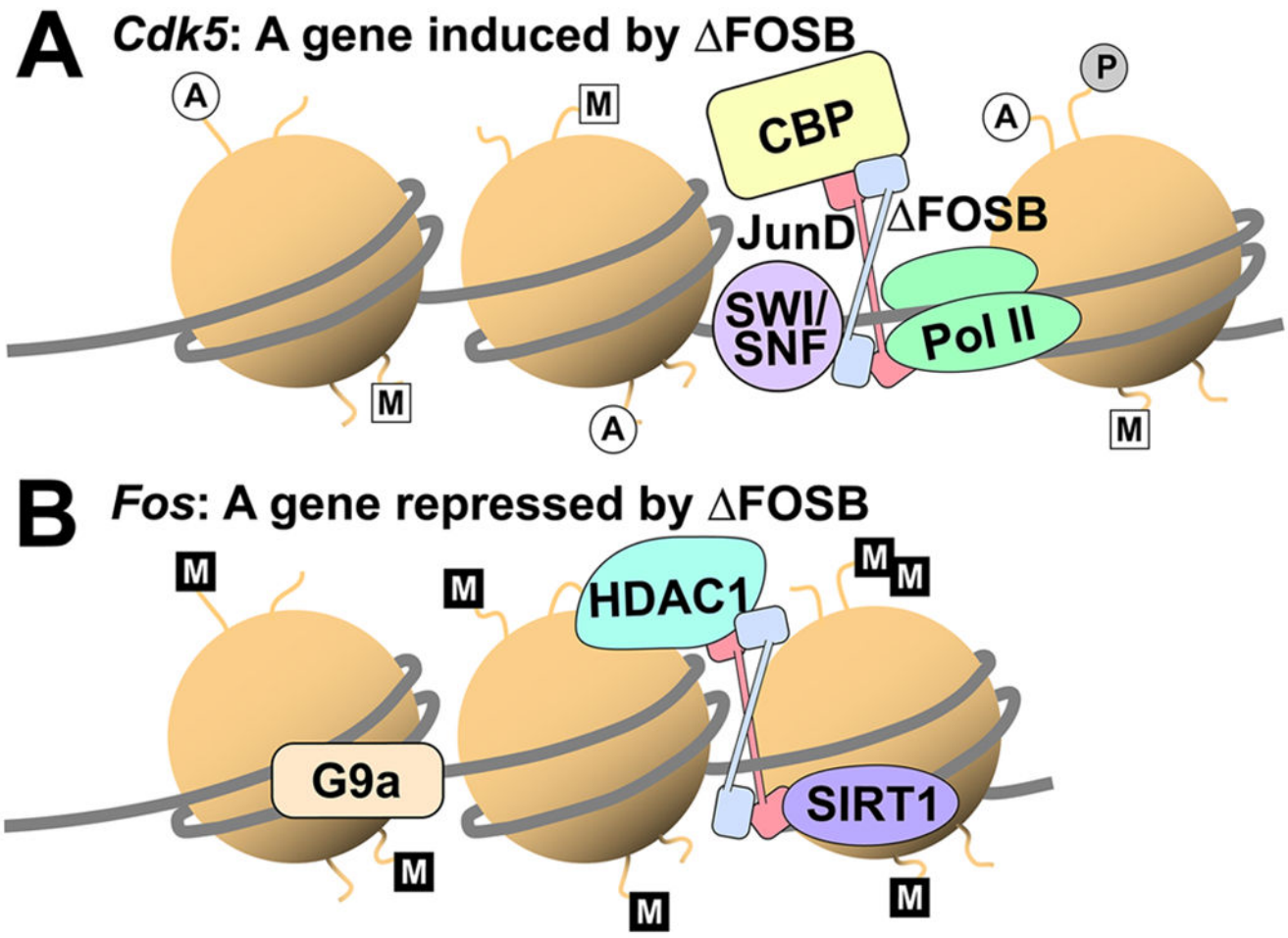

Figure 3.

ΔFOSB as a transcriptional activator and repressor. (A) At some genes, like *Cdk5*, ΔFOSB/JUND (blue and pink) acts to recruit histone acetyltransferases like CREB binding protein (CBP), promoting histone acetylation (white circles) and binding of the SWI/SNF chromatin remodeling complex, which allows greater separation of nucleosomes. The resulting permissive chromatin conformation, including the activating trimethylation of H3 at lysine 4 (white squares) and histone phosphorylation (gray circle), allows binding of RNA polymerase (Pol II) and the basal transcription complex with subsequent gene expression. (B) At other genes, such as *Fos*, ΔFOSB/JUND recruits histone deacetylases like HDAC1 and sirtuin-1 (SIRT1), resulting in reduced histone acetylation and allowing histone methyltransferases like G9a to dimethylate H3 at lysine 9 (black squares). This results in a repressive chromatin state in which the gene is not readily expressed.