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Mechanisms that communicate features of neuronal activity to the genome

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Stimulus-driven gene expression is a ubiquitous feature of biological systems, allowing cells and organisms to adapt their function in a stimulus-driven manner. Neurons exhibit complex and heterogeneous activity-dependent gene expression, but many of the canonical mechanisms that transduce electrical activity into gene regulation are promiscuous and convergent. We discuss literature that describes mechanisms that drive activity-dependent gene expression with a focus on those that allow the nucleus to decode complex stimulus-features into appropriate transcriptional programs.

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Introduction

Stimulus-dependent gene regulation is a core feature of every cell, in every organism, and at every stage of life. An intricate web of molecular signaling pathways links the stimulus to the genomic response driving relevant changes in function. *Escherichia coli* that have access to glucose will produce the transporters and enzymes necessary for its uptake and metabolism. Starve it of glucose, but give it lactose, and the Lac operon is engaged, revamping the cell's metabolic capabilities in favor of the available energy source. This 'and-gate' is elegant in its execution: a transcriptional repressor is inhibited by an early lactose metabolite), and a transcriptional activator kicks in when the glucose concentration is low [1]. The conjunction of these two events allows for the expression of the operon, and so *E. coli* adapts its function in the particular manner that allows its survival. The precise coupling between input and output is a ubiquitous theme in biological systems, with transcriptional regulation closely aligned to fluctuations in functionally relevant stimuli.

In neurons, the relationship between stimuli and gene regulation remains mesmerizingly inscrutable. In the mid 80's, several groups made the observation that extracellular stimuli could trigger the expression of proto-oncogenes including *c-Fos* and *c-Myc* (also called *Fos* and *Myc*) in a variety of cell types [2–6]. Soon, several groups demonstrated that seizures and sensory stimuli induced *Fos* expression in the brain [7–9] and the field of activity-dependent gene regulation in neurons was born.

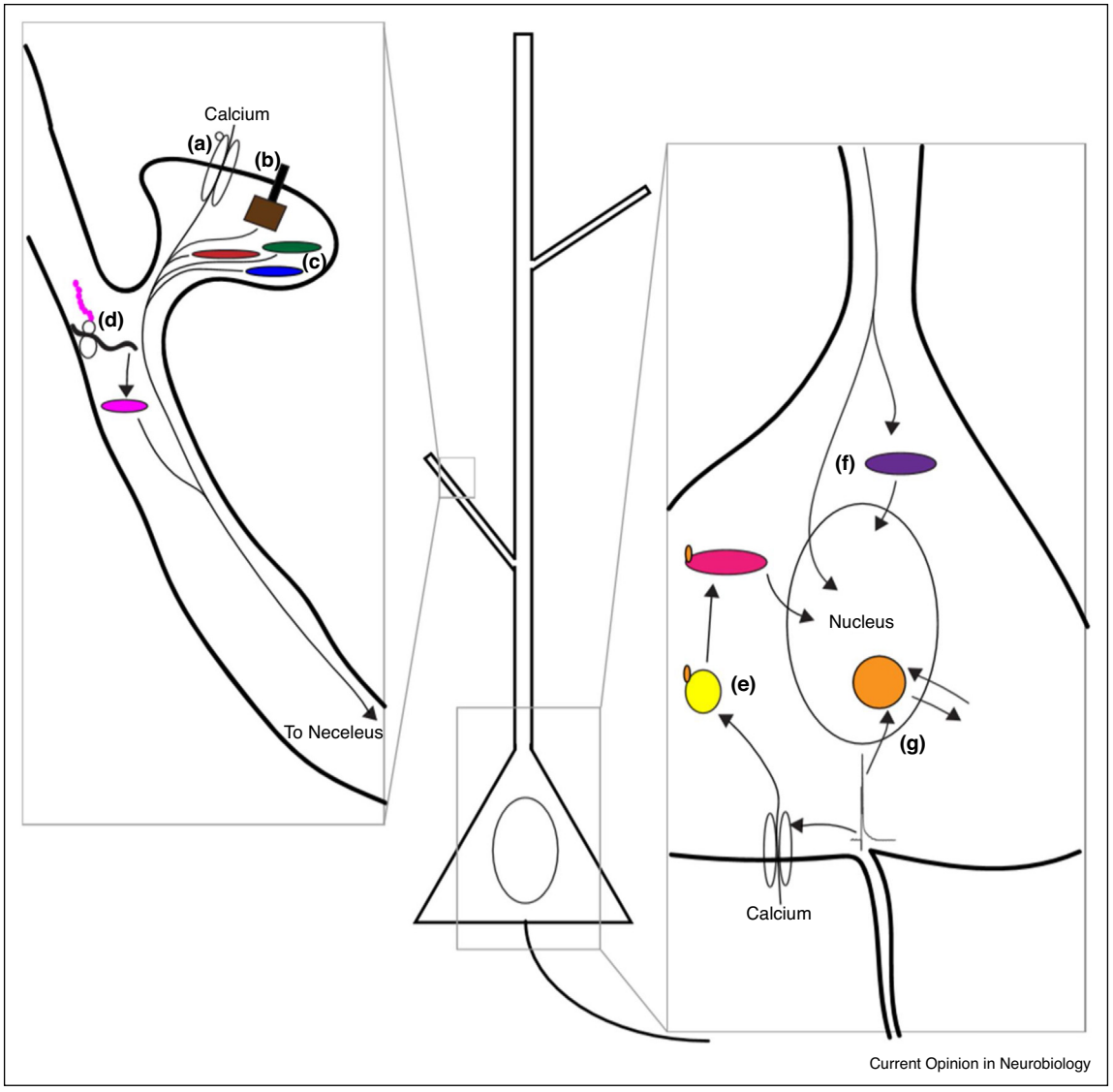
Many of the stimuli critical to a neuron's function arise from synaptic activity and action potentials. How do neurons, with their extraordinary morphologies and signaling repertoires, tailor their transcriptional programs to match these molecularly, spatially, and temporally complex stimuli? We have made significant progress in the past 30 years in understanding how signaling pathways link global depolarization to gene regulation. Depolarization leads to calcium (Ca) influx through NMDA receptors and L-type voltage-gated Ca channels (L-VGCCs). These Ca signals engage a fleet of kinases, notably of the ERK and CaMK families, that subsequently activate a small number of phosphorylation-dependent transcription factors (TFs), for example CREB, SRF, and MEF2 which regulate gene expression ([10–14], reviewed by Ref. [15]). At face value, this represents a highly convergent program of activity-dependent gene regulation. However, such convergence lacks the dexterity necessary to drive programs of gene expression that reflect the complexity of the neuronal stimulus space.

However, many examples of clear stimulus-specific genomic regulation exist. *In vivo*, many experiences and pharmacological manipulations transiently, and heterogeneously, change the transcriptome of neurons [16–19]. Remarkably, positive and negative experiences as well as those with hedonic value or addictive properties generate transcriptional signatures that are distinct enough that the original experience can be inferred from the expression levels of a few genes [20••]. This indicates that there are mechanisms that push back against convergence of signaling pathways within a cell, and support the articulation of stimulus-selective and experience-selective transcriptional responses. Here we discuss some of the recent work that is beginning to reveal the layers of refinement in these mechanisms (Figure 1).

Specificity that emerges from transcriptional repressors

A first order mechanism that can contribute to the customization of stimulus-specific gene regulation is the

Figure 1



Mechanisms for communicating synaptic and neuronal activity to the nucleus. **(a)** Synaptic activity produces Ca signals via NMDA receptors and/or L-VGCCs that drive signaling cascades that propagate to the soma. **(b)** Stimulus-dependent proteolysis of synaptic proteins, such as LRP8, produces peptides that signal to the nucleus and interact with the genome. **(c)** Synaptically localized proteins, including Importins, transcriptional repressors, and TF co-regulators, translocate to the nucleus in response to activity. **(d)** Synaptic activity induces local translation of TFs, for example NPAS4 and ARNT1, which translocate to the nucleus. **(e)** Depolarization-induced Ca influx through L-VGCCs leads to activation of kinases that phosphorylate transcription factors such as SRF, CREB, and MEF2. **(f)** Synaptic Ca signals (a) lead to translocation of kinases, such as ERK, and TFs, such as NFAT, into the nucleus. **(g)** Depolarization leads to dynamic regulation of transcriptional repression.

induction of stimulus-selective transcription factors. Most inducible TFs are somewhat promiscuous, sensitive to a wide variety of stimuli when bath applied *in vitro* [12,21–24]. The transcription factor NPAS4, however, is thus far a notable and illustrative exception. NPAS4 is induced robustly by depolarization [25], yet is largely insensitive to neurotrophins, growth factors, or cAMP. Thus, NPAS4 is poised to execute depolarization-selective gene regulation. Currently, little is known about how the transcription of *Npas4* itself is regulated, but it is clear that SRF binds the *Npas4* gene and is necessary for its full induction [26]. At face value, this presents a paradox, as *Npas4* induction exhibits more selectivity than SRF or other mediators of stimulus-dependent transcription, suggesting additional mechanisms contribute to the stimulus-specificity.

A dynamic landscape of repression might shape the activity-dependent transcriptional response in a way that directs the convergent activity-dependent pathways

towards stimulus-selective transcriptional programs. This possibility carries weight as it was recently demonstrated that NCoR2, in association with ARNT2, suppresses the expression of depolarization-induced genes in the absence of depolarization. This suppression is decoupled following depolarization, permitting transcription of the NCoR2 bound genes [27•]. An additional mechanism for dynamic repression of activity-regulated genes is observed with the Class II HDACs which translocate to the nucleus in response to stimuli and repress depolarization induced genes, including *Npas4* [28,29]. The interaction between repressors and activators is by definition a competition; the absolute number of activating and repressing proteins in the nucleus can sway the outcome of this competition. Moreover, from an experimental standpoint, it is easier to demonstrate induction rather than repression of transcription. It will be essential moving forward to assess these interactions in concert using naturalistic stimuli that more accurately capture the dynamic range of activity-dependent gene expression.

Specificity that emerges from temporal dynamics

The specificity of a stimulus-dependent transcriptional response also emerges from the duration and temporal pattern of depolarization. Stimulus-dependent gene regulation has long been described as having early and late phases that are translation independent and dependent, respectively (reviewed by Ref. [30]), with only the early response genes (ERGs) being the direct consequence of the stimulus. Recently, it has been discovered that in cortical neurons the early response elicited by direct depolarization, disinhibition, or sensory experience can be mechanistically subdivided into two stimulus duration-dependent components [31••]. The first requires ERK signaling; the second is independent of ERK but associated with open chromatin state. The mechanisms driving this second stage may prove to be highly stimulus selective, although this has yet to be determined.

Duration is not the only temporal feature that influences gene regulation. In dissociated dorsal root ganglion neurons, bursts of the same number of electrical stimuli lead to different patterns of transcriptional regulation and TF binding depending on the frequency and inter-burst interval of the stimulus trains [32,33]. This demonstrates that even within the same cell type, different patterns of activity can be interpreted into different genomic responses.

Specificity that emerges from the synapse

As telling as these results are, they are unable to distinguish between gene regulation that is triggered by synaptic activity or action potentials. Indeed, distinct mechanisms that communicate synaptic activity to the nucleus have been described, several of which are sensitive to the location and distribution of the active synapses. For example, P-ERK and NFAT are detected in the nucleus in response to the activity of small numbers of synapses in CA1 pyramidal neurons from organotypic cultures. In the case of ERK, glutamate uncaging over as few as six spines, when distributed over as many dendrites, produces an NMDA receptor-mediated signal that leads to P-ERK in the nucleus [34•]. For NFAT, uncaging over spines, preferentially distributed throughout the distal dendrites, triggers L-VGCC-mediated Ca spikes that propagate to the soma and lead to translocation of NFAT from the soma into the nucleus [35••]. Interestingly, in this latter example, even though the synapses that are activated are further from the soma, the signaling to the nucleus occurs more rapidly, likely due to the use of voltage-gated ion channels. Synaptically induced P-ERK accumulation is much slower, requiring tens of minutes and a delay that scales with the distance of the activated synapses from the soma, suggesting the need for translocation of signaling molecules from the dendrites to the soma and nucleus.

While clusters of synapses can collectively produce signals that are conveyed to the nucleus, even individual synapses may have this capability by virtue of the complement of molecules contained at and near synapses. Transformative work out of the Martin lab has described a number of synaptic molecules which undergo activity-dependent nuclear translocation and which have the potential to shape gene expression, including Importins, transcriptional co-activators, and transcriptional repressors [36–38]. This opens the possibility that the activity of single synapses can tune gene regulation in a synapse-specific manner

An intriguing example of this is seen with the dendritically localized protein Jacob. Global NMDA receptor activation in cultured neurons leads to Jacob translocation to the nucleus where it triggers the sustained dephosphorylation of CREB, synaptic pruning and cell death [39]. In contrast, activation of synaptic NMDA receptors, via disinhibition of cultures, leads to ERK-dependent phosphorylation of dendritic Jacob, P-CREB and the regulation of a plasticity-associated gene program ([40•]). Thus, building off the work of the Bading lab [41], Jacob conveys information to the nucleus about the activity of synaptic and extrasynaptic NMDA receptors and elicits different programs of gene regulation accordingly.

Synaptic activity can also lead to the proteolysis of synaptic intramembrane proteins, liberating peptides that signal to the nucleus (reviewed by Ref. [42]). This has been shown to be the case with the low-density lipoprotein receptor-related protein 8 (LRP8). LRP8 is a component of a multiprotein complex at excitatory synapses that contains the NMDA receptor [43]. Coincident NMDA receptor activation and Reelin binding leads to LRP8 cleavage and translocation of the intracellular

domain to the nucleus where it binds enhancers and facilitates the transcription of many ERGs [44••]. For Jacob, LRP8, and all molecules that signal synaptic activity to the nucleus, it remains unknown how many synapses need to be active to affect an impactful change on gene regulation. To get to this point, additional improvements in single-cell sequencing techniques that can be used in combination with synapse-specific stimulation paradigms and the tracking of small numbers of molecules are needed.

Specificity that emerges from dendritic translation

Through the work of many labs dendritic translation has been shown to have stimulus, synapse, and transcript specificity in a variety of systems ([23,45,46], reviewed by Ref. [47]). However, relatively few have pointed to activity-dependent dendritic translation as an additional mechanism for signaling to the nucleus [48••,49,50]. Recent surveys of the 'dendritic transcriptome' have identified many mRNAs, the overwhelming majority of which encode proteins with a local function [51,52]. Transcriptome analysis excels at detecting mRNAs that are abundant; the least numerous mRNAs, however, are often not counted as 'significantly enriched.' As relatively few nuclear signaling molecules are required to drive a cellular response, these mRNAs are likely to be low abundance, possibly accounting for their absence in these datasets.

We have recently discovered an interesting example of how dendritic translation can communicate information about the activity of a spatially restricted population of synapses to the nucleus. NPAS4 is induced by depolarization [25] but it had been unclear if it was reporting action potentials or synaptic activity to the nucleus. In CA1 pyramidal neurons in acute slices, delivering a brief train of action potentials leads to the transcription of NPAS4 through conventional ERG pathways. NPAS4 induced through this mechanism heterodimerizes with ARNT2, as has been previously described [53]. However, synaptic activity *also* induces NPAS4, but through an unconventional mechanism that is engaged by a spatially restricted population of synapses. We have identified a small pool of *Npas4* mRNAs, which are distinctive in that they have a long 5' untranslated region (5' UTR), that are trafficked to a specific region of the dendrites. When synapses in this region are active, the mRNAs are translated and NPAS4 protein is produced locally. Remarkably, a different NPAS4 binding partner, ARNT1, also has mRNA in the dendrites; these mRNAs have a similar localization to *Npas4*, are translated in response to the same stimulus, and the two proteins heterodimerize before being translocated to the nucleus. Critically, the NPAS4-ARNT1 and NPAS4-ARNT2 heterodimers exhibit distinct patterns of DNA binding, likely influencing distinct aspects of one or more transcriptional programs [48••].

Dendritic translation of *Npas4* and *Arnt1* mRNA enables NPAS4 to convey information originating from a select population of synapses to the nucleus. While NPAS4 is the first clear example of this, it is unlikely to be unique. There are many other transcription factors with alternative 5' UTRs that could be localized to the dendrites, perhaps even with non-overlapping distributions and translational dependencies. Stimulus-specific dendritic translation of TF mRNAs may be able to serve as labeled lines of communication with the nucleus.

Aspirations for the future

Neurons receive and send a constant stream of depolarizing signals which lead to gene regulation. A significant challenge for the future is to understand how naturalistic, and ultimately behaviorally driven, fluctuations of these signals are communicated to the nucleus and decoded into relevant changes in gene expression. This is particularly important since artificial levels of activity can lead to preternaturally high levels of second messengers, activated kinases, and inducible transcription factors that obscure our ability to accurately assess the relationship between stimuli and gene regulation. We are entering an exciting era. As methods advance for delivering refined stimuli that are informed by neuronal connectivity and circuit architecture, we will continue to discover new mechanisms that allow neurons to use stimulus-dependent transcription to update their function.

Conflict of interest statement

Nothing declared.

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