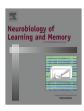
ELSEVIER

Contents lists available at ScienceDirect

## Neurobiology of Learning and Memory

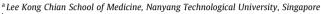
journal homepage: www.elsevier.com/locate/ynlme



CrossMark

## Activity-dependent synapse to nucleus signaling

Agnes Fang Yi Lim<sup>b,1</sup>, Wei Lee Lim<sup>a,1</sup>, Toh Hean Ch'ng<sup>a,b,\*</sup>



<sup>&</sup>lt;sup>b</sup> School of Biological Sciences, Nanyang Technological University, Singapore

## ARTICLE INFO

Article history: Received 14 May 2016 Revised 20 July 2016 Accepted 23 July 2016 Available online 26 July 2016

Keywords:
Synapse-to-nucleus
Long-term plasticity
Nucleus
Importin
Transcription-dependent plasticity
Retrograde transport
Nuclear import

#### ABSTRACT

The unique polarity of neurons requires that synaptic inputs are relayed to the nucleus to trigger changes in gene expression. This long distance signaling process is crucial for the function and survival of neuronal circuits. To that end, neurons have developed multiple modes of signal transmission from the synapse to the nucleus. In this review, we summarize the latest research on activity-dependent movement and nuclear import of postsynaptic proteins that modulate neuronal plasticity. We also focus on the mechanism of active transport as well as the role of importins in mediating nuclear import of the postsynaptic proteins. Finally, we briefly discuss the role of synapse to nucleus signaling in the context of transcription-dependent plasticity and conclude by describing future challenges in this field of research.

#### 1. Introduction

Neurons receive a range of stimuli and respond to them by making changes to their cellular structure and function in order to grow, function and survive. While some of these stimuli may trigger local short-term adaptations, others can result in longlasting structural and functional modifications. Many of these long-lasting changes require cells to initiate signal transduction cascades to trigger transcription in the nucleus. In the brain, synapses are intercellular sites of communication between neurons where a variety of biochemical signals are both received and transmitted. In order to initiate transcription, synaptic inputs must be relayed to the nucleus. However, unlike in other cell types, signal transduction in neurons poses a far greater challenge due to their unique polarity where axons and dendrites can span long distances from the cell body. To bridge the distance between synapse and nucleus, neurons have evolved multiple modes of longdistance signal transduction in both axons and dendrites.

One example of rapid communication between the synapse and the nucleus is through calcium signaling. Here, the activation of synapses and subsequent depolarization of the postsynaptic membranes will trigger neurons to fire action potentials. Repeated action potentials result in a rapid rise of intracellular calcium concentrations at the soma and nucleus which in turn triggers calcium-dependent signaling cascades that change gene expression (Bengtson & Bading, 2012; Hagenston & Bading, 2011). Apart from direct calcium influx at the soma, calcium signals can also be transmitted from activated postsynaptic compartments to the nucleus through the propagation of regenerative calcium waves released from internal calcium stores in the endoplasmic reticulum (ER). The propagation of this calcium wave is possible because the ER surrounds the nucleus and also extends into axons and dendrites (Ross, 2012).

Several comprehensive reviews have already described calcium and other mechanisms of long-distance signaling in neurons, either from presynaptic (Howe & Mobley, 2004; Marlin & Li, 2015) or postsynaptic (Bengtson & Bading, 2012; Ch'ng and Martin, 2011; Jordan & Kreutz, 2009; Kaushik, Grochowska, Butnaru, & Kreutz, 2014; Wiegert, Bengtson, & Bading, 2007) compartments to the nucleus. Hence, in this review, we will instead focus on recent advances in our understanding of the activity-dependent transport of soluble signals from the postsynaptic compartment in dendrites to the nucleus. Following an up-to-date overview of postsynaptic proteins that undergo long-distance translocation and subsequent regulated nuclear import, we will discuss synapse to nucleus signaling in the context of transcription-dependent synaptic plasticity as well as future challenges in the field.

<sup>\*</sup> Corresponding author at: Lee Kong Chian School of Medicine, Nanyang Technological University, 61 Biopolis Drive, #04-10B, Proteos Building, Biopolis, Singapore 138673, Singapore.

E-mail address: thchng@ntu.edu.sg (T.H. Ch'ng).

<sup>&</sup>lt;sup>1</sup> Equal contribution as co-authors.

## 2. Activity-dependent translocation of synaptic proteins to the nucleus

In this first part, we will provide a detailed overview of the latest research on synaptic proteins that undergo activity-dependent nuclear translocation with special focus on the mechanism of active translocation and regulated nuclear entry. All the discussed proteins are localized at dendritic spines or associated with the postsynaptic density and thus, their translocation has been studied mainly from the postsynaptic compartment to the nucleus. Table 1 summarizes the list of proteins described below.

#### 2.1. Jacob

In a series of studies, Jacob, a myristoylated synapto-nuclear protein messenger was reported to undergo long-distance synapse to nucleus translocation in response to NMDA receptor activation in rodent hippocampal neurons (Dieterich et al., 2008). At the synapse, Jacob associates with Caldendrin (a neuronal calcium sensor protein) which competes with importin  $\alpha$  for access to the bipartite nuclear localization signal (NLS) in Jacob (Dieterich et al., 2008). Upon NMDA receptor activation leading to local calcium influx at the postsynaptic compartment, Caldendrin dissociates from Jacob, allowing the nuclear adaptor protein importin  $\alpha$ to bind to the exposed NLS. Once in the nucleus, the ability of Jacob to activate different transcription programs largely depends on its phosphorylation state at Ser180. In case of Ser180 phosphorylation by ERK1/2 at the synapse, Jacob will undergo nuclear entry to enhance CREB (cAMP response element-binding protein) activation and transcription associated with synaptic plasticity. Conversely, if Jacob enters the nucleus with dephosphorylated, CREB will be shut-off and the cell death pathway activated. The long-distance nuclear translocation of phospho-Jacob is dynein-mediated and dephosphorylation during the nuclear transit, Jacob interacts with α-internexin, an intermediate filament present at dendrites (Karpova et al., 2013). Of note, Jacob has been shown to accumulate in the nucleus of CA1 neurons during long-term potentiation (LTP) at the Schaffer-collateral pathway (Behnisch et al., 2011). In agreement with latter observation, Jacob knockout mice are affected by reduced LTP at CA1 synapses and impaired hippocampusdependent learning (Spilker et al., 2016).

#### 2.2. CRTC1

CREB Regulated Transcriptional Coactivator 1 (CRTC1) undergoes activity-dependent synapse to nucleus signaling to activate CREB-mediated transcription in neurons. We and others have shown that CRTC1 is required for selective upregulation of CREBmediated transcription which is independent of CREB phosphorylation at Ser133 (Ch'ng et al., 2012; Nonaka et al., 2014). Upregulation of CRTC1 in rodent hippocampal neurons has been reported to enhance LTP, long-term memory consolidation and reconsolidation. In contrast, siRNA knockdown of CRTC1 in the amygdala results in memory deficits during contextual fear condition (Nonaka et al., 2014; Sekeres et al., 2012; Wu, Zhou, & Xiong, 2007). When neurons are quiescent, CRTC1 is extensively phosphorylated and sequestered at the cytoplasm by the cytoplasmic anchoring protein 14-3-3ε. Subsequent glutamatergic receptordependent synaptic activation leads to dephosphorylation of CRTC1 by calcineurin and nuclear translocation of the protein from dendritic and synaptic sites (Ching et al., 2012). Live imaging of photo-activated fluorescent protein Dendra2-tagged CRTC1 at dendritic spines after local uncaging of glutamate reveals a preferential movement of the protein toward the nucleus which is mediated by

microtubules and the motor protein dynein (Ch'ng et al., 2015). Importantly, experiments using membrane-permeable calcium chelators with different  $Ca^{2+}$  buffering capacities (i.e. BAPTA and EGTA) suggest that rapid calcium influx at the synapse (and not a general rise of intracellular calcium) is responsible for the nuclear translocation of CRTC1. While an arginine-rich NLS has been functionally characterized in CRTC1, knockdown of importin  $\beta$ 1 expression or blocking with NLS peptides did not prevent nuclear entry, suggesting that CRTC1 may enter the nucleus via a non-canonical import pathway (Ch'ng et al., 2012, 2015).

#### 2.3. CREB2

CREB2 (also known as ATF4) is a member of the CREB family of transcription factors and is a transcriptional repressor that regulates long-term plasticity and memory in both sea slugs (Aplysia) and mice. In rodents, knockdown of CREB2 impairs both LTP and long-term depression (LTD) in CA3-CA1 hippocampal neurons whereas in Aplysia, CREB2 represses long term facilitation (LTF) (Bartsch et al., 1995; Chen et al., 2003). Lai et al. demonstrated the presence of CREB2 in rodent hippocampal synapses and in distal neurites of Aplysia sensory-motor neuron cultures. When exposed to a stimulus associated with LTD, CREB2 undergoes retrograde nuclear transport from dendrites by associating with importin  $\alpha 1$  and  $\alpha 6$  in rodent neurons or importin  $\alpha 3$  in *Aplysia* cultures (Lai, Zhao, Ch'ng, & Martin, 2008). As with other NLS-bearing cargo proteins, nuclear entry of CREB2 can be disrupted in the presence of saturating NLS peptides which prevents cargo binding by the classical nuclear import pathway (Lai, Zhao, Ch'ng, & Martin, 2008). Apart from retrograde movement from the postsynaptic compartment to the nucleus, recent reports indicate CREB2 also undergoes local synthesis in axons and growth cones in the presence of A<sub>β</sub>1-42 oligomers (refer to separate section below for CREB2 function in axons).

#### 2.4. AIDA-1

Amyloid precursor protein intracellular domain associated-1 protein (AIDA-1) was initially identified via mass spectroscopy as a postsynaptic density (PSD) protein in rodent brains (Jordan et al., 2004). Subsequent studies indicate that AIDA-1d, an AIDA-1 splice variant, is enriched at the PSD and undergoes activitydependent proteolytic cleavage and nuclear accumulation during activation of NMDA receptors (Jordan, Fernholz, Khatri, & Ziff, 2007). Interestingly, even though AIDA-1 has been shown to exit the PSD during excitatory stimulation, nuclear accumulation of AIDA-1 does not depend on local calcium influx, evident by the inability of calcium chelators, like BAPTA or EGTA, to block nuclear AIDA-1 entry. In the nucleus, AIDA-1 is found highly enriched at p80coilin-positive Cajal bodies (Jordan et al., 2007). These circular structures have been suggested to regulate ribosomal transcription and assembly. More recently, the AIDA-1 conditional knockout in mouse forebrain neurons showed an imbalance in the composition of NMDA receptor subunit expression at the synapse, leading to deficit in LTP and LTD at CA1 hippocampal neurons during Schaffer-collateral stimulation (Tindi et al., 2015). Like Jacob and CREB2, AIDA-1 encodes a functional NLS. However, direct interaction of the NLS with specific members of the classical nuclear import pathway has not been examined (Jordan et al., 2007).

#### 2.5. Abi1

Abelson-interacting protein 1 (Abi1) is found in axons and growth cones during development and at enriched concentrations in the PSD of mature neurons. Abi1 knockdown in neurons affects both dendrite formation and synaptogenesis, suggesting that Abi1

### Download English Version:

# https://daneshyari.com/en/article/5043322

Download Persian Version:

https://daneshyari.com/article/5043322

<u>Daneshyari.com</u>