

## FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

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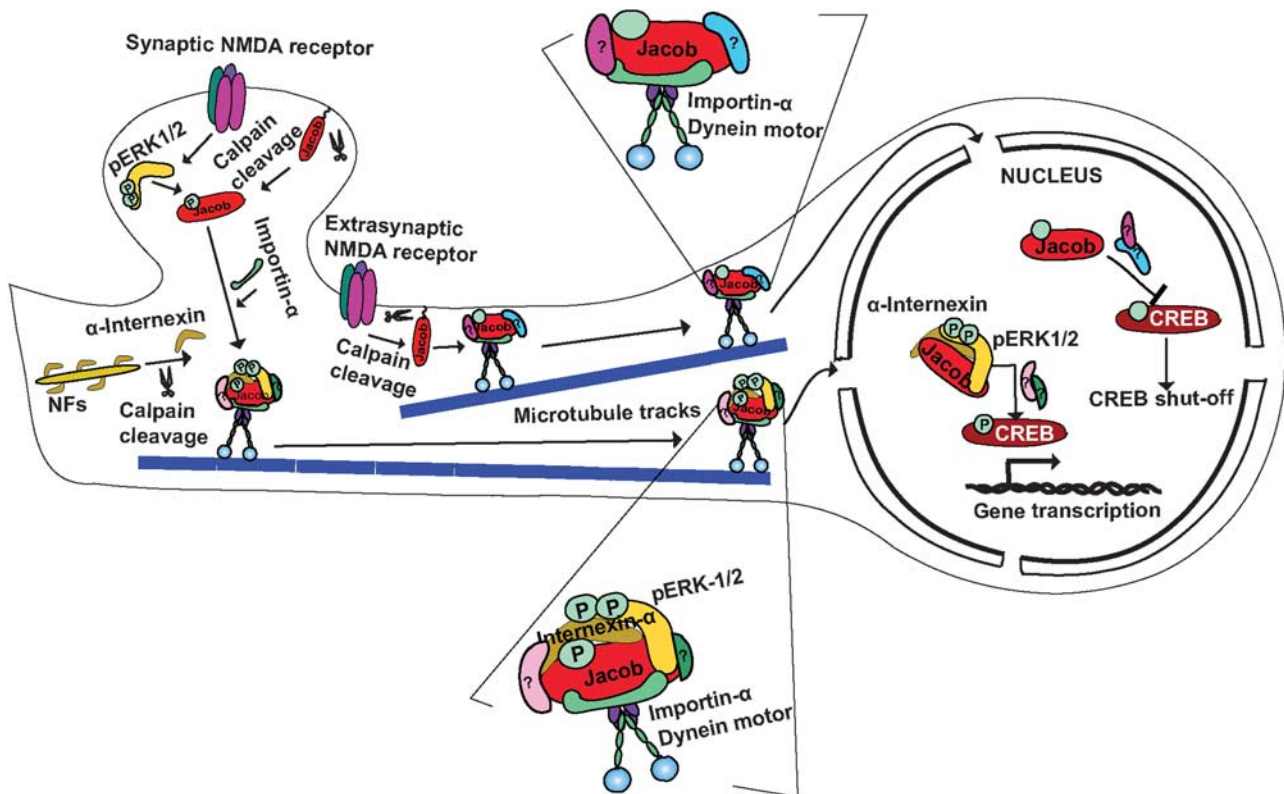
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*Neuropsychopharmacology Reviews* (2014) **39**, 244–245; doi:10.1038/npp.2013.203

## When Synaptic Proteins Meet the Genome: Transcriptional Regulation in Cell Death and Plasticity by the Synapto–Nuclear Messenger Jacob

Neurons express more genes than any other cell type and it is therefore unlikely that synapto–nuclear  $Ca^{2+}$  signaling alone can explain the specific genomic response to the plethora of extracellular stimuli that control gene expression. Possible candidates for encoding of signals at the origin and later decoding at a nuclear destination are synapto–nuclear protein messenger. These proteins translocate to the

nucleus in a stimulus-dependent manner, where they can regulate via their nuclear target interactions very specific aspects of gene expression (Jordan and Kreutz, 2009). However, this type of signaling is challenged by space and time constraints. Synapses are localized far away from the nucleus and synaptic signals are very labile and rapidly degraded. On top the minute quantities of signaling molecules that can be released from synaptic sites are greatly diluted in relation to the entire volume of the dendritic arborization or nucleus. A precise machinery is therefore required to deliver the signal to nuclear target sites, but unfortunately very little is known on just how protein messenger can translocate several hundred micrometers, avoid degradation, retain signal and do this in a reliable manner.



**Figure 1.** Schematic illustrating the encoding of the origin of synaptic and extrasynaptic NMDAR signals by Jacob. Neuronal activity leads to Calpain-mediated cleavage of  $\alpha$ -internexin and the myristoylated N terminus of Jacob. High but not low frequency stimulation of synaptic NMDAR results in ERK activation, ERK binding, and phosphorylation of the serine180 in Jacob. This is then followed by recruitment of C-terminal fragments of  $\alpha$ -internexin or a tighter assembly of an already preformed complex, which is then efficiently protected against phosphatase activity analogous to a mechanism demonstrated by Perlson *et al* (2005) for the retrograde transport of pERK after axon injury. In the nucleus, this complex can dock to CREB and potentially other sites and will enhance plasticity and cell survival promoting gene expression. Following the extrasynaptic NMDAR activation, ERK is not activated and remains outside of the nucleus, while non-phosphorylated Jacob will dock yet unknown protein components to CREB that eventually induce CREB shut-off and cell death.

N-methyl-D-aspartate receptors (NMDAR) make an essential contribution to activity-dependent gene expression in learning and memory. However, NMDAR are present at both synaptic and extrasynaptic sites, and the subcellular localization of each receptor profoundly and differentially affects the nuclear response to its activation. Activation of synaptic NMDAR induces the expression of cell survival and plasticity genes, while their extrasynaptic counterparts primarily drive the expression of cell death genes, linking the pathway to disease (Hardingham and Bading, 2010). An unresolved issue is how can the distant nucleus discriminate between synaptic and extrasynaptic NMDAR-induced signals?

Jacob is a synapto-nuclear messenger, and previous work has shown that extrasynaptic NMDAR activation induces nuclear translocation of Jacob, which results in sustained dephosphorylation and transcriptional inactivation of the transcription factor CREB, a loss of synaptic contacts, a retraction of dendrites and eventually cell death (Dieterich *et al*, 2008). However, Jacob also transits to the nucleus of CA1 neurons, following induction of Schaffer collateral-dependent long-term potentiation (LTP) but not long-term depression (LTD), and hence acts as a messenger for both synaptic and extrasynaptic NMDAR pathways (Behnisch *et al*, 2011). How does the protein get to the nucleus and what is the molecular basis for these different functions after nuclear import of Jacob? Neuronal importins are present in axons, dendrites, and synapses and they can associate with a dynein motor for active retrograde transport along microtubuli to the nucleus. Jacob utilizes this transport system after activation of both type of receptors and in a recent study we found that Jacob, following its nuclear import, can encode the synaptic and extrasynaptic origin of NMDAR signals (Karpova *et al*, 2013). ERK1/2-kinase binding and ERK-dependent phosphorylation of the serine180 residue in Jacob encodes synaptic but not extrasynaptic NMDAR activation.

A stable trimeric complex with proteolytically cleaved fragments of the neurofilament  $\alpha$ -internexin is formed, which protects Jacob and active ERK against phosphatase activity during retrograde transport. In the nucleus, this signalosome-like complex enhances 'plasticity-related' and 'CREB-dependent' gene expression as well as synaptic strength. It appears that Jacob operates as a mobile hub that docks NMDA receptor-derived signalosomes to nuclear target sites and it will be interesting to clarify the molecular identity of these complexes, because they are attractive targets for pharmacological interventions in activity-dependent gene transcription.

#### ACKNOWLEDGEMENTS

This study was supported by the DFG (SFB 779/TPB8), DIP grant, CBBS Magdeburg, MC-ITN NPlast, and the Leibniz Foundation (Pakt für Forschung).

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#### FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

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*Neuropsychopharmacology Reviews* (2014) **39**, 245–246; doi:10.1038/npp.2013.204

## Maintaining and Modifying Connections: Roles for Axon Guidance Cues in the Mature Nervous System

Upon reaching its target, an axon differentiates to form synaptic connections. Remarkably, recent studies have revealed that proteins initially identified as axon guidance cues are re-emerging as regulators of synaptic plasticity in the adult brain. Canonical axon guidance proteins such as semaphorins, ephrins, and slits, and the prototypical myelin-associated inhibitors of axon regeneration, MAG, Nogo, and OMgp, have been found to influence circuit remodeling and synaptic plasticity in the mature nervous system (Mironova and Giger, 2013). Following a study by Horn *et al* (2013), the netrin receptor DCC now joins this list.

Mechanisms that direct neural development have long been suggested to regulate plasticity in the mature brain. Cajal's (1911) proposal that chemotropism might direct axon extension in the embryo included a hypothesized attractant for commissural axons secreted by floor plate cells in the embryonic spinal cord. In a stunning act of prescience, Cajal (1911) suggested that his putative chemoattractant might also influence synaptic plasticity and learning and memory: 'The ability of neurons to grow in an adult and their power to create new associations can explain learning.' He speculated that 'the mechanisms are probably chemotactile like the ones we observed during histogenesis of the spinal cord'.

Netrins were the first identified floor plate-derived axonal chemoattractants (Lai Wing Sun *et al*, 2011). Although shown to regulate synaptogenesis during development in *Caenorhabditis elegans* and *Drosophila melanogaster*, a role for netrins at synapses in the mature vertebrate CNS had not been investigated. Horn *et al*