Transcriptional Regulation by NPAS4

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

30/10/2022
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 82

This document contains 3 pathways (see Table of Contents)

https://reactome.org
NPAS4 (Neuronal PAS domain containing protein 4) is a calcium dependent transcription factor predominantly expressed in neurons that regulates activation of genes involved in neuronal circuit formation, function, and plasticity (Ooe et al. 2004; Lin et al. 2008; Ramamoorthi et al. 2011; Maya-Vetencourt 2013; Sun and Lin 2016; Weng et al. 2018). NPAS4 possesses a conserved basic helix loop helix (bHLH) motif and a PAS domain (Fahim et al. 2018). NPAS4 is among the most rapidly induced immediate early genes (IEGs), which are activated after sensory and behavioral experience and thought to be crucial for formation of long term memory (Ramamoorthi et al. 2011; Sun et al. 2016; Heslin and Coutellier 2018; Weng et al. 2018). NPAS4 is activated within minutes of neuronal stimulation to regulate the formation of inhibitory synapses (Lin et al. 2008). NPAS4 enables gene regulation to be tailored to the type of depolarizing activity along the somato dendritic axis of a neuron (Brigidi et al. 2019). Transcriptional targets of NPAS4 include transcription factors and proteins involved in signal transduction and protein trafficking (Lin et al. 2008, Brigidi et al. 2019). NPAS4 regulates development of glutamatergic and GABAergic synapses essential for information processing and memory formation (Lin et al. 2008, Weng et al. 2018). NPAS4 induced gene expression programs differ between excitatory and inhibitory neurons (Spiegel et al. 2014), leading to a circuit wide homeostatic response. Besides directly regulating function of neurons, NPAS4 may be involved in the regulation of neuroinflammation and neuronal apoptosis (Zhang et al. 2009; Choy et al. 2015; Fan et al. 2016; Zhang et al. 2021). NPAS4 is expressed in the pancreatic beta cells and regulates their function under stress conditions (Sabatini et al. 2018). For review, please refer to Sun and Lin 2016, and Fu et al. 2020.

**Literature references**


**Editions**

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NPAS4 is predominantly expressed in neuronal cells. In neurons, expression of NPAS4 is regulated by 
Ca2+, which ties NPAS4 level to neuronal activity (Lin et al. 2008; Zhang et al. 2009; Kim et al. 2010; Mell-

NPAS4 expression is regulated by signaling pathways activated downstream of the N-methyl-D-aspartate
(NMDA) receptor and L-type Ca2+ channel (Coba et al. 2008; Lin et al. 2008; Horvath et al. 2021).

In vivo, NPAS4 expression is activated by visual stimulation (Lin et al. 2008), contextual learning
(Ramamoorthi et al. 2011), as well as pharmacologically induced generalized seizure (Flood et al. 2004).
Chronic stress induces downregulation of NPAS4 gene expression in the hippocampus (Furukawa-Hibi et
al. 2015), so does social isolation (Ibi et al. 2008). Adult female mice who were exposed to early maternal
separation (early life stress) show upregulation of NPAS4 in the prefrontal cortex later in life (Ryabushk-
ina et al. 2020). NPAS4 is thought to have a neuroprotective effect and is downregulated during neurode-
generation (Ooe et al. 2009; Zhang et al. 2009; Louis Sam Titus et al 2019). NPAS4 level is reduced in the
hippocampus of aged, memory-impaired mice (Qiu et al. 2016). Studies in mice indicate that NPAS4 af-
fected synaptic connections in excitatory and inhibitory neurons, neural circuit plasticity, and memory
formation (reviewed by Sun and Lin 2016). NPAS4 may be involved in the functioning of the circadian
system (Unfried et al. 2010; West et al. 2013; Xu et al. 2021).

Npas4 mRNA levels are downregulated upon infection with Zika virus through an unknown mechanism

Besides neuronal cells, NPAS4 is also expressed in pancreatic beta cells, where its levels are regulated by
intracellular calcium, as in the nervous system (Speckmann et al. 2016).

Literature references
Costa, VV., Campolina-Silva, GH., Teixeira, MM., Marim, FM., Saliba, J., Gatignol, A. et al. (2021). Profound down-
regulation of neural transcription factor Npas4 and Nr4a family in fetal mice neurons infected with Zika virus.


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NPAS4 regulates expression of target genes

**Location:** Transcriptional Regulation by NPAS4

**Stable identifier:** R-HSA-9768919

**Compartments:** nucleoplasm

NPAS4 is a basic helix loop helix (bHLH) transcription factor that needs to dimerize with another bHLH protein, either ARNT, ARNT2 or ARNTL, in order to be able to bind to target DNA (Ooe et al. 2004; Ooe et al. 2009; Brigidi et al. 2019).

NPAS4 is implicated as a transcriptional regulator of genes involved in neuronal development such as CDK5 (Yun et al. 2013), CDK5R1 (Yun et al. 2013), RBFOX3 (NeuN) (Yun et al. 2013), BDNF (Pruunsild et al. 2011) and RET (Sribudiani et al. 2011), genes involved in synaptogenesis and synaptic transmission such as NPTX2 (Lin et al. 2008), MDM2 (Yoshihara et al. 2014; Lv et al. 2021), FOS (Ramamoorthi et al. 2011), IQSEC3 (Kim et al. 2021), PLK2 (Weng et al. 2018) and possibly other genes (Lin et al. 2008; Shan et al. 2018), circadian rhythm-related genes such as NAMPT (West et al. 2013), and genes involved in neuroprotection upon injury such as GEM (Takahashi et al. 2021), SYT10 (Woitecki et al. 2016) and possibly other genes (Qiu et al. 2013). In pancreatic beta-cell, NPAS4 is implicated as a regulator of insulin synthesis under stress conditions (Sabatini et al. 2013).

The circadian clock regulated gene CRY1 was identified as NPAS4 target gene in sheep brain (West et al. 2013), but this finding was not reproduced in the high throughput identification of NPAS4 targets in rat primary neurons (Brigidi et al. 2019). The DBNL gene, encoding Drebrin, a dendritic cytoskeleton modulator, was initially identified as a gene directly upregulated by Npas4 (Ooe et al. 2004), but a high throughput study of NPAS4 targets showed DBNL gene expression to be repressed by NPAS4, although not significantly (Brigidi et al. 2019).

NPAS4 is expressed in endothelial cells and may play a role in angiogenesis (Esser et al. 2017).

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