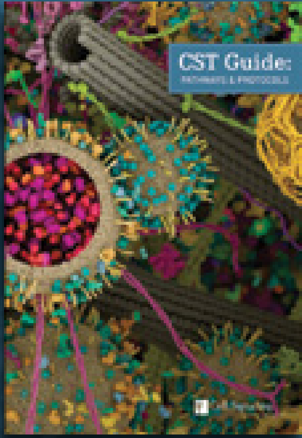
Neuroscience

An excerpt from the first edition of the
CST Guide: Pathways & Protocols

Cell Signaling
TECHNOLOGY®

First Edition

CST Guide



GUIDE COVER PHOTO:

Cellular Landscape:

Vesicle Trafficking
Multiple levels shown of key pathways and structures involved in ER and Golgi-mediated trafficking and protein processing, including post-translational modifications.

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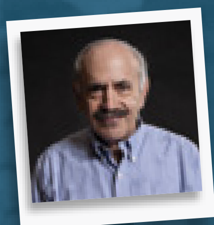

"...the time has come for us... to puzzle out, one protein at a time, how signals are really processed inside cells to create the marvelously functioning apparatus – the eukaryotic cell."

Dr. Robert A. Weinberg
Daniel K. Ludwig Professor for Cancer Research, MIT

Diagram & Table Keys

Pathway Diagram Key

The pathway diagrams found in this guide and on our website have been assembled by CST scientists and outside experts to provide succinct and current overviews of selected signaling pathways.

Direct Stimulatory Modification	Deacetylase
Direct Inhibitory Modification	Ribosomal subunit
Multistep Stimulatory Modification	TIM-3
Multistep Inhibitory Modification	Galectin-9
Tentative Stimulatory Modification	B7-H3
Tentative Inhibitory Modification	B7-H4
Separation of Subunits	CTLA-4
Joining of Subunits	CD80, 86
Translocation	PD-1
Transcriptional Stimulatory	PD-L1
Transcriptional Inhibitory	TCR
Kinase	MHC
Phosphatase	ICOS
Transcription Factor	ICOSL
Caspase	OX40
Receptor	OX40L
Enzyme	CD40
pro-apoptotic	CD40L
pro-survival	CD27
GAP/GEF	CD70
GTPase	CD137
G-protein	CD137L
Acetylase	CD28

Applications Key

While all of our antibodies are rigorously tested in a number of relevant applications, some products are more suitable for a specific application. This information is summarized in various lists and tables found throughout this guide.

WB	Western Blotting	**ChIP**	Chromatin Immunoprecipitation
IP	Immunoprecipitation	**-IC**	Immunocytochemistry
IHC	Immunohistochemistry	**-P**	Paraffin
IF	Immunofluorescence	**-F**	Frozen
F	Flow Cytometry	**E-P**	Peptide ELISA

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CST Guide: Pathways & Protocols

08

Neuroscience

Neuroscience is a broad scientific area consisting of cellular and molecular biology, anatomy, physiology, and development of neurons and the nervous system. The field also includes cognitive neuroscience and behavioral research.

Neuronal Development

Development of the peripheral and central nervous systems begins early in embryogenesis and can be tracked throughout its different stages using lineage markers specific to each stage of neuronal development. Neural stem cells are derived from the ectoderm and differentiate into neural crest cells, glial progenitor cells, and neuronal progenitor cells. Markers for neural stem cells include Sox1 and Sox2. The neural crest further differentiates into a diverse array of cell types including neurons, glia, craniofacial cartilage, and connective tissue, and is sometimes referred to as the fourth primary germ layer. Neural crest markers include FoxD3 and Notch1. Glial progenitor cells develop into astrocytes, which provide structural support and help form the blood-brain barrier, and oligodendrocytes, which form the insulating myelin sheaths that surround axons. Neuronal progenitor cells, which can be identified using the markers Nestin and Musashi-1, give rise to mature neurons.

Neuronal Development Markers

Neural progenitor: Nestin, Musashi-1

Astroglial precursor: Notch1

Oligodendrocyte progenitor: A2B5, PDGFRα

Neuronal differentiation: CEND1

Neuronal stem cell marker: Sox1, Sox2

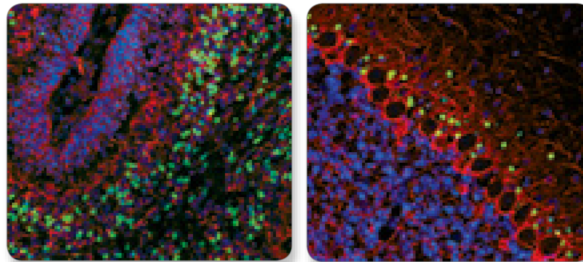
Neuron: Neurofilament L, Neurofilament M, Neurofilament H, β3-tubulin, MAP2, Tau

Oligodendrocytes: CNPase, MAG, MBP

Schwann: Vimentin

Astroglia: GFAP

Sox1, a marker for neuronal stem cells, is expressed in 1-day old rat brain but not adult rat brain.

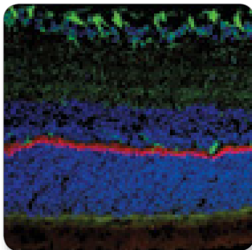


Sox1 Antibody #4194: Confocal IF analysis of postnatal day 1 (left) and adult (right) rat brain using #4194 (green) and Neurofilament-L (DA2) Mouse mAb #2835 (red). Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye).

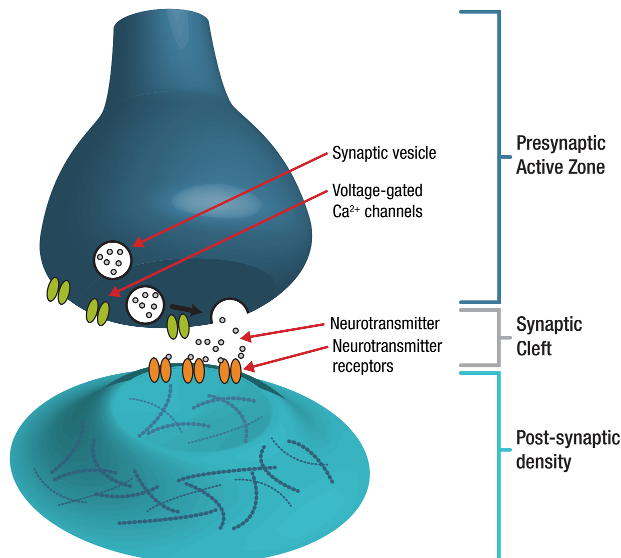
Synaptic Signaling

Neurons are the building blocks of extensive neural networks. Transfer of information between neurons occurs at the synapse, where the neuronal information is converted from electrical action potentials into neurochemical signals. The synapse comprises a presynaptic active zone, the synaptic cleft, and the postsynaptic density.

PSD95, a scaffolding protein within the postsynaptic density, is expressed in rat retina.



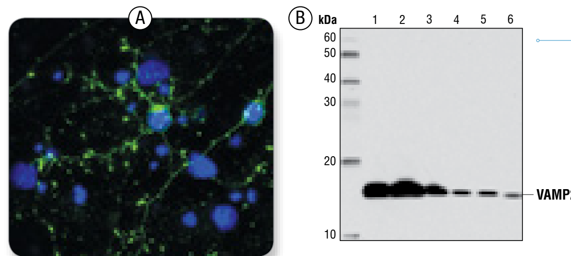
PSD95 (D27E11) XP® Rabbit mAb #3450: Confocal IF analysis of rat retina using #3450 (red) and Neurofilament-L (DA2) Mouse mAb #2835 (green). Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye).



 See inside front cover for Pathway Diagrams and Application keys.

Synaptic signaling occurs when the signal from one neuron is transmitted across the synaptic cleft to another neuron through the action of neurotransmitters (NTs). These NTs, such as dopamine, glutamate, and GABA (γ-aminobutyric acid), are stored in synaptic vesicles in the presynaptic neuron. Upon receiving an action potential, vesicles containing NT dock, prime, and fuse to the presynaptic membrane in a highly regulated mechanism through the action of SNARE family (VAMP, syntaxin-1, SNAP25), chaperone (complexin), and calcium binding proteins (synaptotagmin). Vesicle fusion results in NT release into the synaptic cleft, where it binds one of several receptors on the postsynaptic membrane. Receptor families such as the dopamine receptor, which is a GPCR, can signal through adenylate cyclase to activate PKA and other signaling intermediates to regulate gene expression through the actions of CREB and other transcription factors. Other NTs bind ion channels such as NMDAR or AMPAR that regulate flux of Ca^{2+} and Na^{+}, thereby perpetuating the action potential through the postsynaptic neuron. Continual NT release into a synapse and clustering of postsynaptic receptors can strengthen synaptic signaling over time. Synaptic plasticity, or the ability to modulate the number of NT receptors at the synapse, is a mechanism involved in many adaptative processes such as stress, addiction, and learning and memory.

VAMP2, a SNARE protein expressed in brain tissue, cell lines, and primary neurons, facilitates the docking, priming, and fusion of NT-containing vesicles to the presynaptic membrane.



VAMP2 (D601A) Rabbit mAb #13508: Confocal IF analysis of primary rat cortical neurons grown for 21 days **(A)** using #13508 (green). Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye). WB analysis of extracts from various cell lines and tissues **(B)** using #13508.

Lanes

1. mouse brain
2. rat brain
3. human cerebellum
4. OVCAR8
5. SK-N-SH
6. Neuro-2a

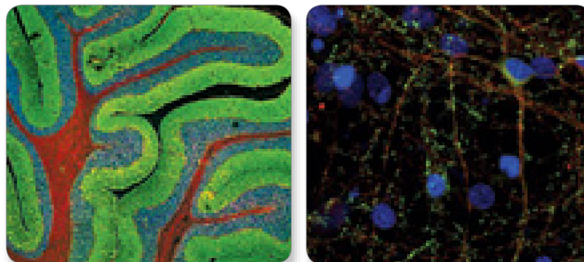
Neuronal Markers

Markers are proteins with a very specific and well-defined localization that are used to identify or localize a subset of neurons (i.e. glutamatergic or GABAergic) or cellular compartment (i.e. presynaptic or postsynaptic compartment).

Neuronal Type
Glutamatergic: EAAT1, EAAT2, EAAT3, VGluT1, VGluT2
Dopaminergic: Tyrosine hydroxylase, Parkin
GABAergic: GAD1, GAD2, DARPP-32

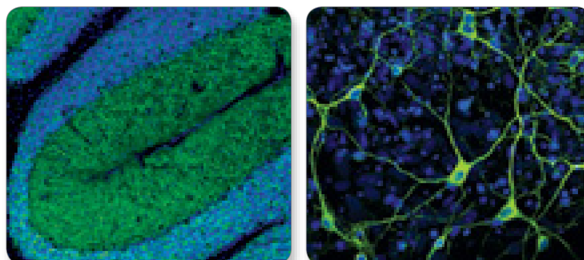
Subcellular Compartment
Presynaptic: Synapsin-1, Synaptophysin, SYT1, NSF
Postsynaptic: PSD95, SHANK2
Dendrite: MAP2
Axon: β3-tubulin, Tau

Synapsin-1 (D12G5) XP® Rabbit mAb #5297: Confocal IF analysis of mouse brain (left) or primary rat cortical neurons grown for 21 days (right) using #5297 (green) and β3-Tubulin (TU-20) Mouse mAb #4466 (red). Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye).



Synapsin-1, a presynaptic marker, is expressed in mouse brain and primary neurons.

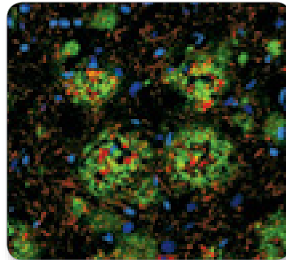
MAP2 (D5G1) XP® Rabbit mAb #8707: Confocal IF analysis of frozen rat cerebellum (left) or primary rat cortical neurons grown for 21 days (right) using #8707 (green). Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye).



MAP2, a marker for dendrites, is expressed in rat cerebellum and primary neurons.

Neurodegeneration

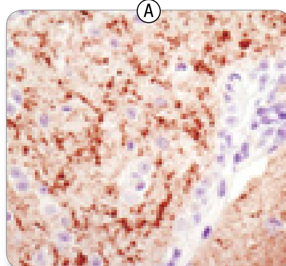
Devastating diseases arise from loss of neuron structure or function and are generally known as neurodegenerative diseases. One of the most common neurodegenerative diseases worldwide is Alzheimer's disease (AD). This condition is characterized by the presence of extracellular amyloid plaques that form through abnormal APP (amyloid β precursor protein) processing and aggregation of β-amyloid peptides. AD is also characterized by the formation of neurofibrillary tangles that result from hyperphosphoryation of the tau protein. Parkinson's disease, another neurodegenerative disorder, occurs when genetic mutation or environmental toxins result in misfolded α-synuclein protein that aggregates to form Lewy bodies. These aggregates alter dopamine signaling, particularly in the nigrostriatal pathway, ultimately leading to neuronal dysfunction and cell death.

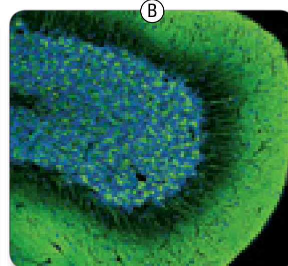


β-amyloid fragments aggregate to form the amyloid plaques characteristic of Alzheimer's disease.

β-Amyloid (D54D2) XP® Rabbit mAb #8243: Confocal IF analysis of paraffin-embedded human Alzheimer's brain using #8243 (green) and Tau (Tau46) Mouse mAb #4019 (red). Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye).

α-Synuclein is the main component of pathogenic Lewy bodies and Lewy neurites characteristic of Parkinson's disease.



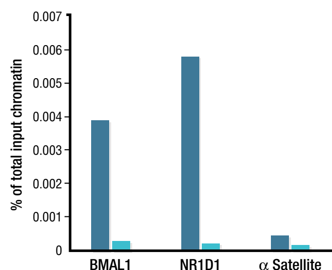


α-Synuclein (D37A6) XP® Rabbit mAb #4179: IHC analysis of paraffin-embedded mouse brain **(A)** using #4179. Confocal IF analysis of normal rat cerebellum using #4179 (green) **(B)**. Blue pseudocolor = DRAQ5® #4084 (fluorescent DNA dye).

Circadian Rhythms

Circadian rhythms govern many key physiological processes that fluctuate with a period of approximately 24 hours. These processes include the sleep-wake cycle, glucose, lipid and drug metabolism, heart rate, hormone secretion, renal blood flow, and body temperature, as well as basic cellular processes such as DNA repair and the timing of the cell division cycle. The mammalian circadian system consists of many individual tissue-specific clocks (peripheral clocks) that are controlled by a master circadian pacemaker residing in the suprachiasmatic nuclei (SCN) of the brain. The periodic circadian rhythm is prominently manifested by the light-dark cycle, which is sensed by the visual system and processed by the SCN. The cellular circadian clockwork consists of interwoven positive and negative regulatory loops, or limbs. The positive limb includes the CLOCK and BMAL1 proteins, two transcription factors that bind E box enhancer elements and activate transcription of their target genes. The negative limb is formed by CRY and PER proteins, which inhibit CLOCK/BMAL1-mediated transcriptional activation. In tissues, roughly six to eight percent of all genes exhibit a circadian expression pattern. For example, expression of the nuclear receptor Rev-Erbα oscillates with circadian rhythm in liver cells. Rev-Erbα regulates expression of several key regulators of circadian rhythm, including BMAL1, ApoA-I, and ApoC-III.

Rev-Erbα regulates expression of several genes, including circadian regulator protein BMAL1.



Rev-Erbα (E1Y6D) Rabbit mAb #13418: Chromatin IPs were performed with cross-linked chromatin from 4 x 10^6 Hep G2 cells and either 10 µl of #13418 or 2 µl of Normal Rabbit IgG #2729 using SimpleChIP® Enzymatic Chromatin IP Kit (Magnetic Beads) #9003. The enriched DNA was quantified by real-time PCR using human BMAL1 promoter primers, SimpleChIP® Human NR1D1 Promoter Primers #13413, and SimpleChIP® Human α Satellite Repeat Primers #4486. The amount of immunoprecipitated DNA in each sample is represented as a percent of the total input chromatin.

Rev-Erbα (E1Y6D) Rabbit mAb #13418
Normal Rabbit IgG #2729

 See inside front cover for Pathway Diagrams and Application keys.

Select Reviews

Dzamko, N., Zhou, J., Huang, Y., and Halliday, G.M. (2014) *Front. Mol. Neurosci.* 7, 57. • Florio, M. and Huttner, W.B. (2014) *Development* 141, 2182–2194. • Franco, S.J. and Müller, U. (2013) *Neuron* 77, 19–34. • Kalsbeek, A., la Fleur, S., and Fliers, E. (2014) *Mol. Metab.* 3, 372–383. • Kojetin, D.J. and Burris, T.P. (2014) *Nat. Rev. Drug Discov.* 13, 197–216. • Spires-Jones, T.L. and Hyman, B.T. (2014) *Neuron* 82, 756–771. • Südhof, T.C. (2013) *Neuron* 80, 675–690. • Südhof, T.C. (2013) *Nat. Med.* 19, 1227–1231. • Tenreiro, S., Eckermann, K., and Outeiro, T.F. (2014) *Front. Mol. Neurosci.* 7, 42.

Commonly Studied Neuroscience Targets

Target	M	P
A2B5	●	
AMPA Receptor (GluR 1)	●	
Phospho-AMPA Receptor (GluR 1) (Ser845)	●	
AMPA Receptor (GluR 2/3/4)		●
AMPA Receptor (GluR 2)	●	
Phospho-AMPA Receptor (GluR 2) (Tyr869/873/876)		●
Phospho-AMPA Receptor (GluR 2) (Tyr876)		●
AMPA Receptor (GluR 3)	●	●
AMPA Receptor (GluR 4) (Arg860)	●	●
APBA2		●
ApoE	●	
ApoE4	●	
APP		●
Phospho-APP (Thr668)	●	●
APP/β-Amyloid	●	
β-Amyloid	●	●
Arrestin 1/S-Arrestin		●
Ataxin-1		●
BACE	●	
β-Amyloid (pE3 Peptide)		●
β-Amyloid (1-37 Specific)	●	
β-Amyloid (1-39 Specific)	●	
β-Amyloid (1-40 Specific)	●	
β-Amyloid (1-42 Specific)	●	
BMAL1	●	
Brn2/POU3F2	●	
BRSK1	●	
BRSK2	●	
Bassoon	●	
Calbindin	●	
CaMKI-δ		●
CaMKII-α	●	●
CaMKII (pan)	●	●
Phospho-CaMKII (Tyr231)		●
Phospho-CaMKII (Thr286)	●	●
CaMKIV		●
Phospho-CAMKK2 (Ser511)		●
CASK	●	●
Caspr2		●
Cathepsin B		●
CD13/APN	●	
CDK5	●	●
CEND1	●	●
CIRBP		●
CK1δ		●
CK1ε		●
CLCN3	●	

Target	M	P
CNPase	●	●
Complexin-1		●
Complexin-1/2		●
CREB	●	
Phospho-CREB (Ser133)	●	
CRMP-2		●
Phospho-CRMP-2 (Thr514)		●
Dab1		●
Phospho-Dab1 (Tyr220)		●
Phospho-Dab1 (Tyr232)		●
DAG Lipase α	●	
DARPP-32	●	●
Phospho-DARPP-32 (Thr34)	●	
Phospho-DARPP-32 (Thr75)		●
Phospho-DARPP-32 (Ser97)	●	
DCBLD2		●
DDC		●
Delta FosB		●
DJ-1	●	
Dopamine β-Hydroxylase (DBH)		●
Doublecortin		●
Phospho-Doublecortin (Ser297)		●
Phospho-Doublecortin (Ser334)		●
Drebrin		●
Drebrin A		●
DYRK1A	●	●
DYRK1B	●	●
Dysbindin		●
EAAT1	●	●
EAAT2		●
EAAT3		●
EGR1	●	
EGR3		●
FABP7	●	
FE65		●
GABA(B)R1		●
GABA(B)R2	●	●
GAD1		●
GAD2	●	●
GAP43	●	●
GFAP	●	
GGA3	●	●
Cleaved GGA3 (Asp313)	●	
GKAP		●
Glutamate Dehydrogenase 1/2	●	
GNB3		●
GPR50	●	●

Target	M	P
GRAF1		●
GRK2		●
GSTP1	●	
Homer1		●
5-HTR1A		●
5-HTR4	●	
Huntingtin	●	●
KISS1R	●	
LIS1		●
LRRK2	●	●
MAG	●	●
MAP2	●	●
Phospho-MAP2 (Ser136)		●
Phospho-MAP2 (Thr1620/1623)		●
MELK		●
Mena	●	●
Merlin	●	
Phospho-Merlin (Ser518)	●	●
mGluR1	●	
mGluR2		●
Munc18-1	●	
Musashi	●	●
Myelin Basic Protein	●	
STOP	●	
Na Channel β1 Subunit	●	
NCS1	●	
Nestin	●	
NeuN	●	
NeuroD	●	●
Neurofilament-H	●	
Neurofilament-L	●	
Neurofilament-M	●	
Neurogenin 2	●	
Neuropeptide Y	●	
Neuropilin-1	●	
Neuropilin-2	●	
NG2		●
NGF		●
NHERF1	●	●
NHERF2	●	
Nicastrin	●	●
NKCC1	●	●
NMDAR1	●	
Phospho-NMDAR1 (Ser890)		●
Phospho-NMDAR1 (Ser896)		●
Phospho-NMDAR1 (Ser897)		●
NMDAR2A		●
Phospho-NMDAR2A (Tyr1246)		●
NMDAR2B	●	●

These protein targets represent key nodes within neuroscience pathways and are commonly studied in neuroscience research. Primary antibodies, antibody conjugates, and antibody sampler kits containing these targets are available from CST.

Listing as of September 2014. See our website for current product information.

M **Monoclonal Antibody**
P **Polyclonal Antibody**

Target	M	P
Phospho-NMDAR2B (Tyr1070)		●
Phospho-NMDAR2B (Ser1284)		●
Phospho-NMDAR2B (Tyr1472)		●
Nna1		●
nNOS	●	●
Nogo-A		●
NT5E/CD73	●	
Oligophrenin-1		●
Phospho-μ-Opioid Receptor (Ser375)		●
p35/25	●	
p39		●
p75NTR	●	●
PARK9		●
Parkin	●	●
PC1/3		●
PC2	●	
PEN2	●	●
PINK1	●	
Plexin A1		●
Plexin A2	●	●
Plexin A3	●	
Plexin A4	●	
Presenilin-1	●	●
Presenilin-2	●	●
PSD93		●
Phospho-PSD93 (Tyr340)		●
PSD95	●	●
Phospho-PSD95 (Tyr236/ Tyr240)		●

Target	M	P
Ras-GRF1		●
Phospho-Ras-GRF1 (Ser916)		●
RGS4		●
Rhodopsin		●
SAP102		●
Secretagogin	●	
Semaphorin 3B	●	
Phospho-Semaphorin 4B (Ser825)		●
SHANK2		●
Shootin1		●
SLC1A4		●
SNAP25	●	●
SOD1	●	●
Spinophilin	●	●
SSTR1		●
Stargazin	●	●
STEP	●	●
Non-phospho-STEP (Ser221)	●	
Synapsin	●	●
Phospho-Synapsin (Ser9)		●
Synaptophysin	●	●
SynGAP	●	●
Syntaxin 1A		●
α-Synuclein	●	●
α/β-Synuclein	●	
Synaptotagmin	●	●
Tau	●	
Phospho-Tau (Thr181)	●	
Phospho-Tau (Ser202)		●
Phospho-Tau (Ser396)	●	

Target	M	P
Phospho-Tau (Ser400/ Thr403/Ser404)		●
TDP43		●
Tenascin C	●	
TFAM	●	●
Thy1		●
TMP21		●
Torsin A	●	
TPH-1	●	
Trk (pan)	●	
TrkA	●	●
Phospho-TrkA (Tyr490)		●
Phospho-TrkA (Tyr490) /TrkB (Tyr516)	●	
Phospho-TrkA (Tyr674/675) /TrkB (Tyr706/707)	●	
Phospho-TrkA (Tyr785) /TrkB (Tyr816)	●	
TrkB	●	●
TrkC	●	
β3-Tubulin	●	
Tyrosine Hydroxylase		●
Phospho-Tyrosine Hydroxylase (Ser31)	●	●
Phospho-Tyrosine Hydroxylase (Ser40)		●
UNC5B	●	
VAMP2	●	
VAMP3		●
VGLUT1		●
VGLUT2	●	●
Vti1a		●

75

2012–2014 CITATIONS

CST antibodies for Phospho-CREB (Ser133) have been cited over 75 times in high-impact, peer-reviewed publications from the global research community.

Select Citations:

Madiraju, A.K. et al. (2014) Metformin suppresses gluco-neogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. *Nature* 510, 542–546.

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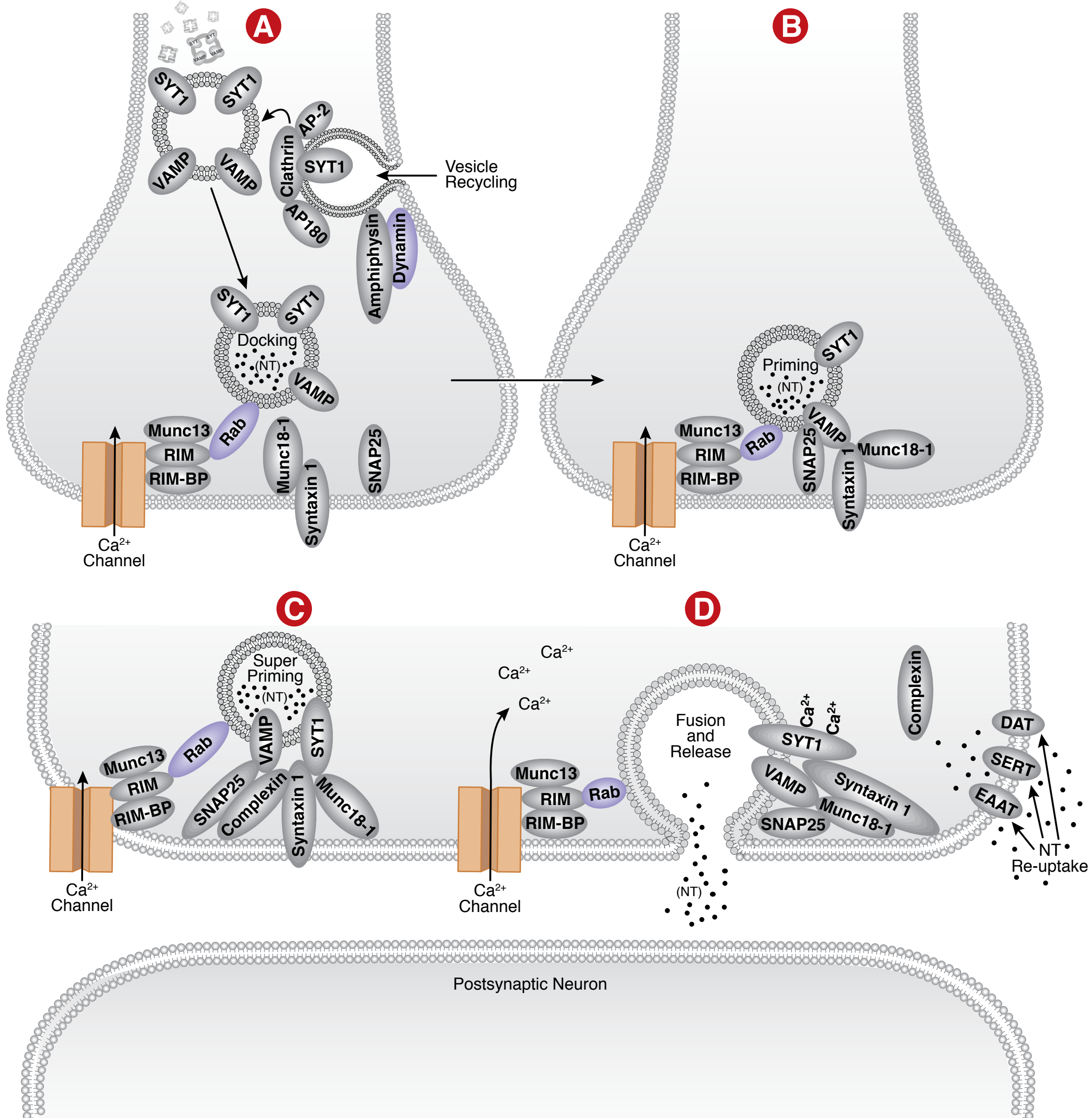
Antibody Validation Principles

Please visit our website to learn more about what Antibody Validation means at Cell Signaling Technology.
www.cellsignal.com/cstvalidation

Vesicle Trafficking in Presynaptic Neurons: Synchronous Release



Neuronal communication is a very connective process. Transfer of information between neurons occurs at the synapse, where the neuronal information is converted from electrical action potentials into neurochemical signals. The synapse comprises a presynaptic active zone (a clustering of vesicle fusion sites and calcium channels on the presynaptic cell membrane), the synaptic cleft, and the postsynaptic density, an electron-dense domain of the postsynaptic neuron specializing in the reception and integration of synaptic signals. Intracellular vesicles containing neurotransmitter (NT) rapidly fuse to the presynaptic membrane and release their contents into the synaptic cleft upon arrival of an action potential—a type of neurotransmission termed synchronous release. The docking, priming, and fusion of these vesicles is carried out by SNARE family and other chaperone proteins located on both the vesicle and presynaptic cell membrane. Synaptic vesicles dock to predetermined sites in the active zone through the interaction of vesicle-associated Rab3 (or Rab27) with RIM, which can bind to calcium channels directly and via RIM-BP **(A)**. SNARE proteins might also play a role in docking based on studies of non-neuronal cells, but there is no conclusive evidence for such a role in mammalian neurons. The vesicle SNARE protein, VAMP (also called synaptobrevin), binds to SNARE proteins on the cell membrane, syntaxin 1 and SNAP25, priming the vesicle for fusion **(B)**. Munc18-1 binds to monomeric syntaxin 1 as well the SNARE complex and assists with complex assembly. The co-chaperone protein complexin and the calcium-binding protein synaptotagmin 1 (SYT1) associate with SNARE proteins to form tight complexes, bringing the lipid membranes together **(C)**. When an action potential in the presynaptic neuron opens voltage-gated calcium channels, calcium binds to SYT1 and allows SYT1 to interact with the SNARE complex as well as the plasma membrane resulting in membrane fusion and release of NT into the synaptic cleft **(D)**. The fast response to an action potential is due in part to the proteins RIM, RIM-BP, and Munc13, which form physical interactions between the vesicle, the cell membrane, and calcium channels, bringing the three necessary elements into close proximity. Released NT can be recycled through specific transporters such as EAATs (reuptake of glutamate) or a monoamine transporter, such as SERT (reuptake of serotonin) or DAT (reuptake of dopamine) back into the cytoplasm of the neuron.

Select Reviews:

Blakely, R.D. and Edwards, R.H. (2012) *Cold Spring Harb. Perspect. Biol.* 4, a005595. • Jahn, R. and Fasshauer, D. (2012) *Nature* 490, 201–207. • Saheki, Y. and De Camilli, P. (2012) *Cold Spring Harb. Perspect. Biol.* 4, a005645. • Südhof, T.C. (2013) *Neuron* 80, 675–690. • Südhof, T.C. (2013) *Nat. Med.* 19, 1227–1231. • Südhof, T.C. (2012) *Neuron* 75, 11–25.

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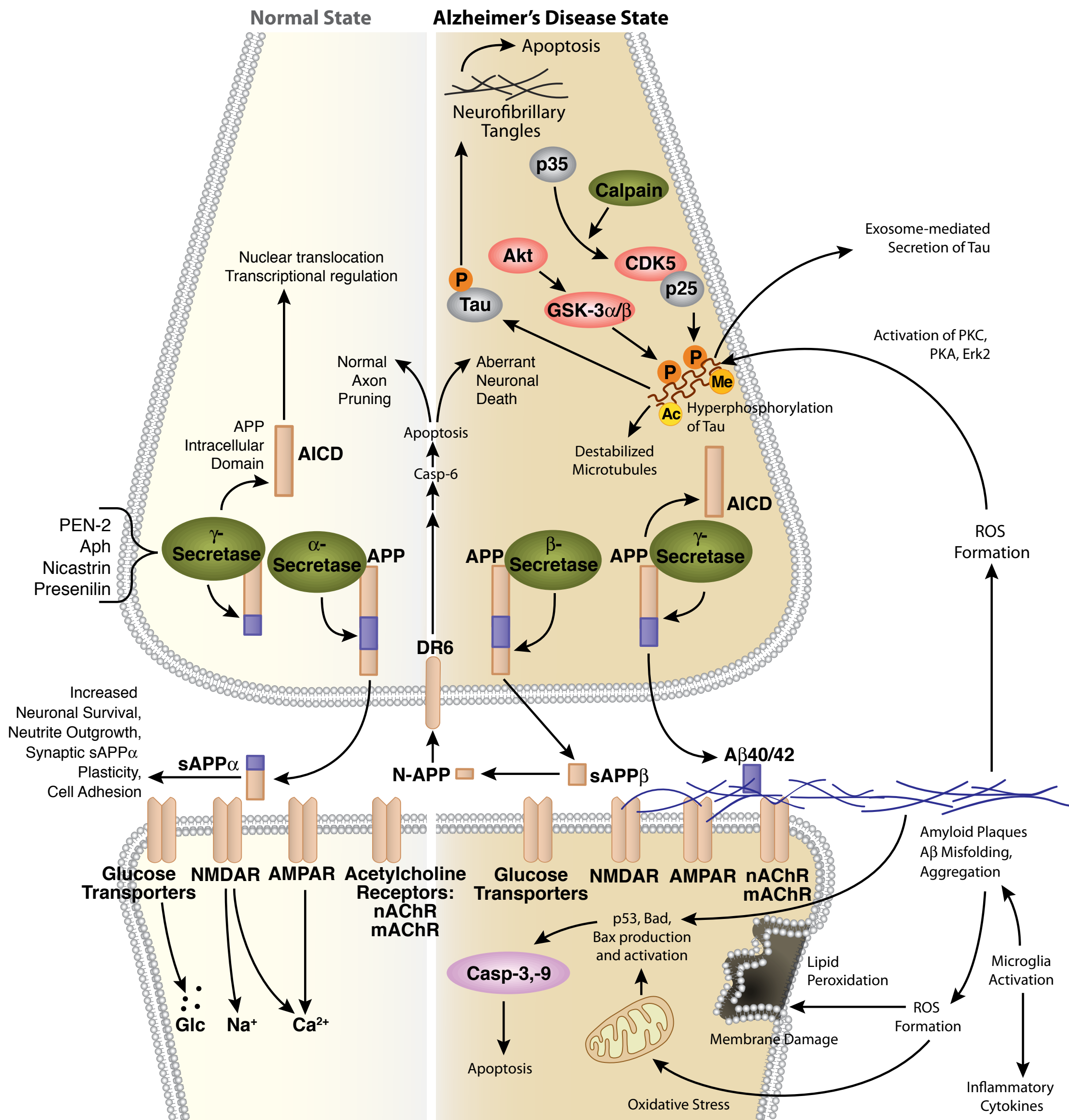
Amyloid Plaque and Neurofibrillary Tangle Formation in Alzheimer's Disease



Alzheimer's disease is one of the most common neurodegenerative diseases worldwide. Clinically, it is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles, resulting in neuronal dysfunction and cell death. Central to this disease is the differential processing of the integral membrane protein APP (Amyloid β Precursor Protein) in the normal versus disease state. In the normal state, APP is initially cleaved by β-secretase to generate sAPPα and a C83 carboxy-terminal fragment. The presence of sAPPα is associated with normal synaptic signaling and results in synaptic plasticity, learning and memory, emotional behaviors, and neuronal survival. In the disease state, APP is cleaved sequentially by β-secretase and γ-secretase to release an extracellular fragment called Aβ40/42. This neurotoxic fragment frequently aggregates and results in Aβ40/42 oligomerization and plaque formation. Aβ40/42 aggregation results in blocked ion channels, disruption of calcium homeostasis, mitochondrial oxidative stress, impaired energy metabolism and abnormal glucose regulation, and ultimately neuronal cell death. Alzheimer's disease is also characterized by the presence of neurofibrillary tangles. These tangles are the result of hyperphosphorylation of the microtubule-associated protein Tau. GSK-3β and CDK5 are the kinases primarily responsible for phosphorylation of Tau, although other kinases such as PKC, PKA, and Erk2 are also involved. Hyperphosphorylation of Tau results in the dissociation of Tau from the microtubule, leading to microtubule destabilization and oligomerization of the Tau protein within the cell. Neurofibrillary tangles form as a result of Tau oligomerization and lead to apoptosis of the neuron.

Select Reviews:

Bossy-Wetzel, E., Schwarzenbacher, R., and Lipton, S.A. (2004) *Nat. Med.* 10, 2–9. • Chen, J.X. and Yan, S.S. (2010) *J. Alzheimers Dis.* 2, S569–S578. • Claeysen, S., Cochet, M., Donneger, R., Dumuis, A., Bockaert, J., and Giannoni, P. (2012) *Cell. Signal.* 24, 1831–1840. • Marcus, J.N. and Schachter, J. (2011) *J. Neurogenet.* 25, 127–133. • Müller, W.E., Eckert, A., Kurz, C., Eckert, G.P., and Leuner, K. (2010) *Mol. Neurobiol.* 41, 159–171. • Nizzari, M., Thellung, S., Corsaro, A., Villa, V., Pagano, A., Porcile, C., Russo, C., and Florio T. (2012) *J. Toxicol.* 2012, 187297. • Thinakaran, G. and Koo, E.H. (2008) *J. Biol. Chem.* 283, 29615–29619.

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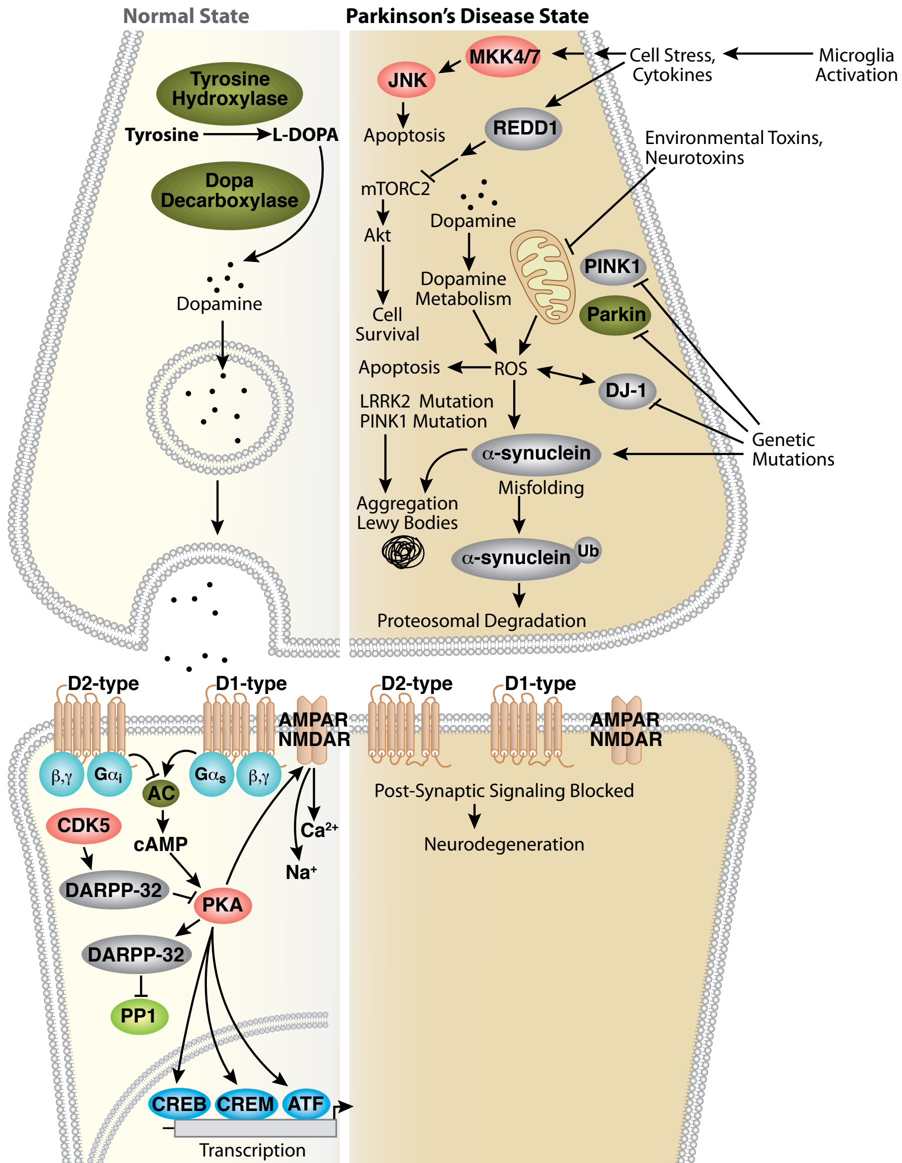
Dopamine Signaling in Parkinson's Disease



Parkinson's disease is the second most prevalent neurodegenerative disorder. Clinically, this disease is characterized by bradykinesia, resting tremors, and rigidity due to loss of dopaminergic neurons within the substania nigra section of the ventral midbrain. In the normal state, release of the neurotransmitter dopamine in the presynaptic neuron results in signaling in the postsynaptic neuron through D1- and D2-type dopamine receptors. D1 receptors signal through G proteins to activate adenylate cyclase, causing cAMP formation and activation of PKA. D2-type receptors block this signaling by inhibiting adenylate cyclase. Parkinson's disease can occur through both genetic mutation (familial) and exposure to environmental and neurotoxins (sporadic). Recessively inherited loss-of-function mutations in parkin, DJ-1, and PINK1 cause mitochondrial dysfunction and accumulation of reactive oxidative species (ROS), whereas dominantly inherited missense mutations in α-synuclein and LRRK2 may affect protein degradation pathways, leading to protein aggregation and accumulation of Lewy bodies. Mitochondrial dysfunction and protein aggregation in dopaminergic neurons may be responsible for their premature degeneration. Another common feature of the mutations in α-synuclein, Parkin, DJ-1, PINK1, and LRRK2 is the impairment in dopamine release and dopaminergic neurotransmission, which may be an early pathogenic precursor prior to death of dopaminergic neurons. Exposure to environmental and neurotoxins can also cause mitochondrial functional impairment and release of ROS, leading to a number of cellular responses including apoptosis and disruption of protein degradation pathways. There is also an inflammatory component to this disease, resulting from activation of microglia that cause the release of inflammatory cytokines and cell stress. This microglia activation causes apoptosis via the JNK pathway and by blocking the Akt signaling pathway via REDD1.

Select Reviews:

Dauer, W. and Przedborski, S. (2003) *Neuron* 39, 889–909. • Girault, J.A. and Greengard, P. (2004) *Arch. Neurol.* 61, 641–644. • Patten, D.A., Germain, M., Kelly, M.A., and Slack, R.S. (2010) *J. Alzheimers Dis.* 20, 357–367. • Imai, Y. and Lu, B. (2011) *Curr. Opin. Neurobiol.* 21, 935–941. • Springer, W. and Kahle, P.J. (2011) *Autophagy* 7, 266–278.

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