Understanding Axonal mRNA Transport in Various Organisms

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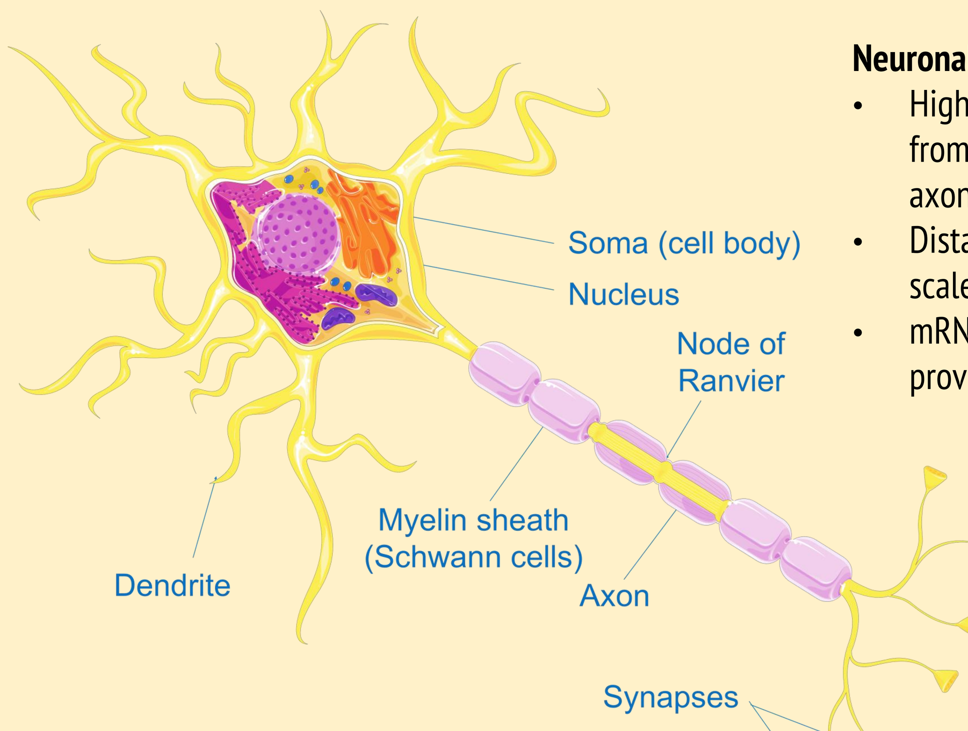
Abstract

The localization and translation of mRNAs within subcellular domains of neurons such as axons is crucial to supply proteins in the right time at the right place. These proteins have various functions ranging from axonal growth, regeneration, maintenance, repair as well as a platform for retrograde signaling. In this Review, we elucidate the mRNA genes, which are found in the axonal compartment of different organisms. We also summarize the improved methodologies, such as physical isolation of axons from the cell body, RNA detection methods and imaging techniques that uncover the complexity of axon transcriptome and how it is regulated. Furthermore, we matched the listed genes with its respective homologs in C. elegans. This will provide useful information for the future development of approaches to visualize axonal mRNA transport in live animals. Such a tool will be useful to reveal novel roles of locally synthesized proteins in injury responses and neurological diseases.

Introduction



Neuronal Morphology:

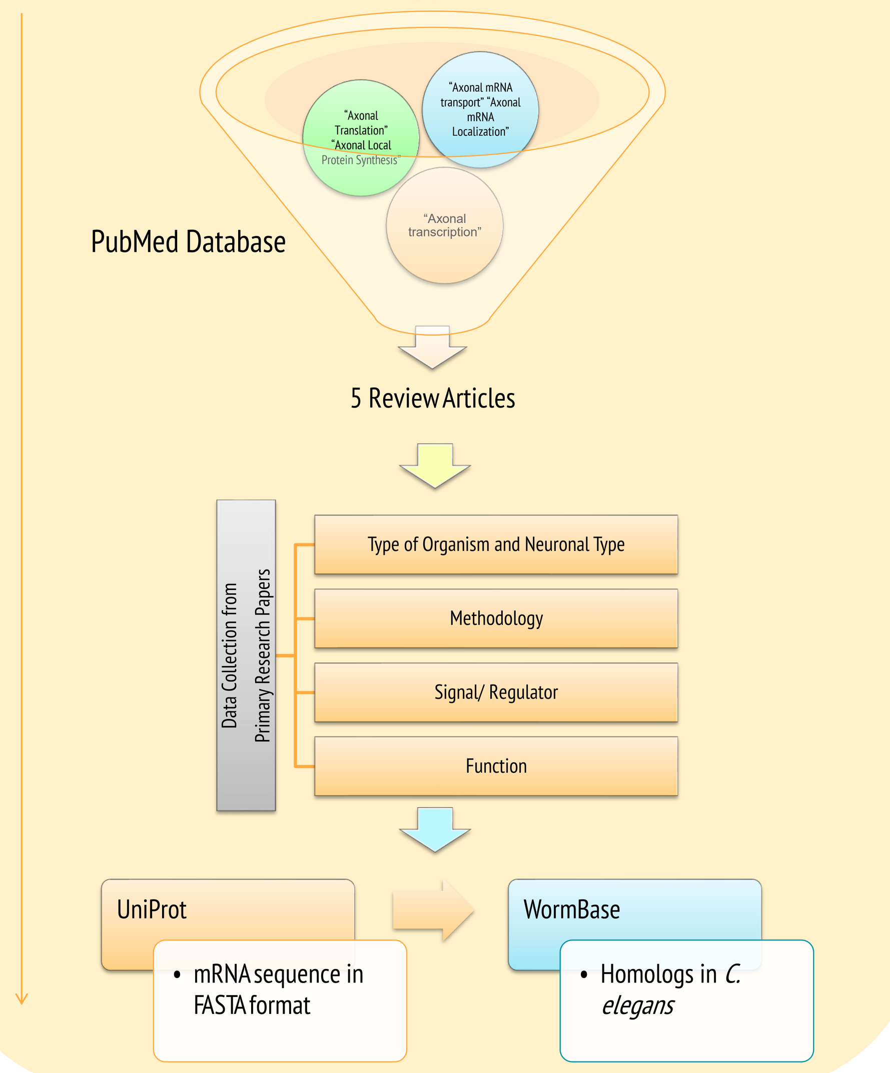
- Highly polarized cells, composed of a cell body from which cytoplasm emanate to form a single axon and multiple dendrites.
- Distal axon must respond to stimuli at short time scales to fulfill demands for new proteins.
- mRNA localization and on-site protein synthesis to provide subcellular functions.

Functions of Axonally Transported Genes
Axonal growth
Axonal survival/ maintenance
Axonal path finding
Retrograde Signalling

Objective:

1) List the axonally transported and translated mRNA genes
2) Illustrate recent experimental advances used to visualize the mRNA localization
3) Highlight the functions of the axonally transported mRNA genes, the mechanisms and signals for regulation of mRNA transport and translation.
4) Match these genes with their respective homologs in *Caenorhabditis elegans.c*

Materials & Methodology



Results and Discussion

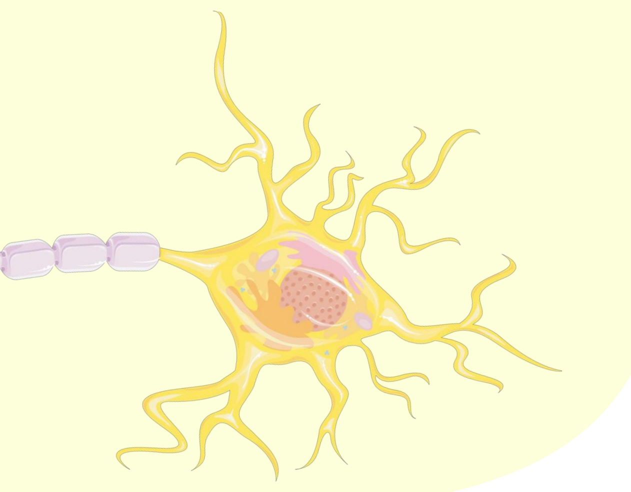
Table 1. Preview of mRNA genes localized and expressed in axons, their functions and *C. elegans* homologs.

mRNA	Protein Encoded	Organism	Neuronal Type	Methodology (detection/ visualisation/validation)	Signal/Cue/ Treatment	Signal effect	Regulator	Function	Reference	Homologs in *C. elegans*
ADF	Actin depolymerizing factor	Chicken	Sympathetic	*in situ* hybridization, immunoprecipitation, ^{35}S metabolic labeling, fluorography, autoradiography	Nerve growth factor	Increase axonal protein synthesis	Unknown	Axon guidance*	(Lee & Hollenbeck, 2003)	*gsnl-1* [K06A4.3]
Annexin A2	Annexin A2; SMN associated mRNA	Human (ALS patients)	Motor neurons	Immunohistochemistry; Alkaline phosphatase anti-alkaline phosphatase (APAAP) method	formalin-fixed, paraffin embedded post-mortem central nervous system tissues	-	Unknown	Disruption may lead to selective vulnerability of motor neurons	(Probst-Cousin, Bergmann, Maihofner, Neundorfer, & Heuss, 2004)	*>nex2* [T07C4.9]; *>nex-1* [ZC155.1]; *>nex-3* [C28A5.3]
Arp2	Actin related protein 2	Chicken	DRG	Quantitative immunocytochemical methods, live imaging fluorescence recovery from photobleach (FRAP); compartmentalized chambers to obtain purified axonal preparations; PCR-based amplification and detection of individual mRNA species.	Nerve growth factor	Increase axonal protein synthesis	WAVE1 (activation of Arp2/3 complex); cortactin (stabilization of Arp2/3-mediated branch actin filaments)	Branching	(Spillane et al., 2012)	*arx-2* [K07C5.1]
Atf4	Activating Transcription Factor; Cyclic AMP-dependent transcription factor ATF-4	Mouse; human	Hippocampal	Comparative analysis of the RNA-seq data sets and quantitative RT-PCR; Axonal Atf4 mRNA levels determined by quantitative fluorescence in situ hybridization (FISH)	Aβ1-42	Increase axonal protein synthesis	Unknown	Axon survival	(Baleriola et al., 2014)	N/A
Atp5g1	ATP synthase F(0) complex subunit C1, mitochondrial	Rat	SCG	In-situ hybridization, RT-PCR	Transfection of miR-338	Decrease mitochondrial activity	Unknown	Surviving	(Aschrafi et al., 2008)	[Y82E9BR.3]
		Rat	SCG	Transfection, GFP, qt-PCR, axonal staining with MitoTracker Red , FISH, Western Blot analysis & fluorescent microscopy	Silencing local COX IV	Attenuation of axon elongation	Unknown	Surviving	(Aschrafi et al., 2010)	
		Mouse	SCG	qRT-PCR, immunofluorescence, CellTiter-Glo Luminescent Cell Viability Assay, Image-iT Live Green Reactive Oxygen Species Detection, MitoSOX Red	Overexpression of COXIV zipcode	Decrease in endogeneous COXIV mRNA levels	Unknown	maintain mitochondrial ATP production	(Kar et al., 2014)	
Atp5g2	ATP synthase F(0) complex subunit C2, mitochondrial	Mouse or rat	SCG	FISH, qRT-PCR, Western analysis, Click-iT AHA	Nerve growth factor	Increase axonal protein synthesis	miR-338	Axon maintenance	(Natera-Naranjo et al., 2012)	
Atp5g3	ATP synthase F(0) complex subunit C3, mitochondrial	Rat	Sympathetic	FISH, qRT-PCR, Western analysis, Click-iT AHA	Silencing local ATP5G1	Production of ROS, attenuation of elongation of axons	Unknown	Surviving	(Natera-Naranjo et al., 2012)	
bclw	aka (*Bcl212*)	Rat	DRG	Compartmentalized axon cultures, FISH, qRT-PCR, Western blotting, 4-thiouridine labelling	Neurotrophin simulation	Transcription, transport to axon, and translation of bclw mRNA	Unknown	Surviving	(Cosker, Pazyra-Murphy, Fenstermacher, & Segal, 2013)	N/A
Calreticulin	Calreticulin	Mouse or rat	DRG, CTX	FISH, immunofluorescence staining, FRAP, RT-PCR	Neurotrophin 5	Increase axonal protein synthesis	Unknown	Axon guidance	(Vuppalanchi et al., 2010)	*crt-1* [Y38A10A.5]
		Mouse or rat	DRG, CTX	FISH, immunofluorescence staining, FRAP, RT-PCR	Myelin-associated glycoprotein	Increase axonal protein synthesis	Unknown	Axon guidance*	(Vuppalanchi et al., 2010)	
		Mouse or rat	DRG	q-PCR, FISH, cDNA array	Semaphorin 3A	Increase axonal protein synthesis	Unknown	Axon regeneration	(Willis et al., 2007)	
		Rat	DRG	RT-qPCR, immunofluorescence, immunoblotting, FRAP	Lysophospatidic acid (LPA); injury	Increase axonal protein synthesis	Unknown	ER Chaperone protein	(Vuppalanchi et al., 2012)	
		Mouse or rat	DRG	RT-PCR, SDS PAGE, immunofluorescence, MALDI TOF/TOF MS, MS/MS sequencing	Neurotrophin 3	Increase axonal protein synthesis	Unknown	Axon regeneration	(Willis, Li et al., 2005)	
Catenin receptor	-							Necessary for proper neuronal localization and turning once	(Costa & Willis, 2018)	*hmp-2* [K05C4.6a, 6b]
CEBP-1	CAAT enhancer binding protein 1	*C. elegans*	Touch neurons	qRT-PCR, fluorescent reporters (GFP::NLS::MS2 fluorescence), laser axotomy	Unknown	Increase axonal protein synthesis	MAPK	Axon regeneration	(Yan, Wu, Chisholm, & Jin, 2009)	CEBP-1
cfl1	Cofilin	*Xenopus laevis*	RGC	RT-PCR, immunoprecipitation	Slit2 (repulsive)	Increase axonal protein synthesis	Unknown (perhaps Vg1RBP1)	Growth Cone collapse, Axon path finding	(Piper et al., 2006)	[F53E2.2]
Cortactin (CTTN1)	Cortactin; Src substrate protein p85	Chicken	DRG	Quantitative immunocytochemical methods, live imaging fluorescence recovery from photobleach (FRAP); compartmentalized chambers to obtain purified axonal preparations; PCR-based amplification and detection of individual mRNA species.	Nerve growth factor	Attractive	Unknown	Axon pathfinding	(Spillane et al., 2012)	[F42H10.3]; *dbn-1*
COX IV	Cytochrome c oxidase subunit 4 isoform 1, mitochondrial	Rat	SCG	In-situ hybridization, RT-PCR	Transfection of miR-338	Decrease mitochondrial activity	Unknown	Surviving	(Aschrafi et al., 2008)	*cox-4* [W09C5.8]
		Rat	SCG	Transfection, GFP, qt-PCR, axonal staining with MitoTracker Red , FISH, Western Blot analysis & fluorescent microscopy	Silencing local COX IV	Attenuation of axon elongation	Unknown	Surviving	(Aschrafi et al., 2010)	
		Mouse or rat	SCG	FISH, qRT-PCR, Western analysis, Click-iT AHA	Nerve growth factor	Increase axonal protein synthesis	miR-338	Axon maintenance	(Natera-Naranjo et al., 2012)	
		Mouse	SCG	qRT-PCR, immunofluorescence, CellTiter-Glo Luminescent Cell Viability Assay, Image-iT Live Green Reactive Oxygen Species Detection, MitoSOX Red	Overexpression of COXIV zipcode	Decrease in endogeneous COXIV mRNA levels; reduction in local ATP levels	Unknown	Maintain mitochondrial ATP production	(Kar et al., 2014)	
		Mouse or rat	Midbrain dopaminergic	Immunohistochemistry, Western blot assay (densitrometric quantification)	Engrailed 1 and 2	Increase axonal protein synthesis	Unknown	Cell survival	(Alvarez-Fischer et al., 2011)	
CPG15	Neuritin (aka NRN1)	Mouse or rat	Spinal Motor Neuron	Mass spectrometry, colocalization analysis, FRAP, qRT-PCR	Nerve growth factor, Brain-derived neurotrophic factor	Increase axonal protein synthesis	SMN protein and HUD	Axon maintenance; promote motor axon branching and	(Akten et al., 2011)	*dys-1* [F15D3.1j]
CPR-2 receptor	G-protein coupled receptor	*Lymnaea stagnalis*	Visceral ganglia	non-radioactive *in situ* hybridization, immunocytochemistry and electrophysiology, electron microscopy	Isolated axons (in absence of soma) were injected with mRNA encoding G-protein coupled conopressin receptor	-	Unknown	Axonal survival, regeneration, synaptogenesis, synaptic plasticity, learning and memory	(Spencer, Syed et al., 2000)	*lrp-1* [F29D11.1];
CREB	Cyclic AMP responsive element-binding protein	Mouse or rat	DRG	Boyden chamber, FISH, qRT-PCR, Western blot	Nerve growth factor	Increase axonal protein synthesis	Unknown	Cell survival	(Cox, Hengst, Gurskaya, Lukyanov, & Jaffrey, 2008)	*crh-1* [Y41C4A.4c]
DAP5	death-associated protein 5 (also named p97 and NAT1); Arylamine N-acetyltransferase 1	Mouse	Hippocampal neuron culture	Puro-PLA, immunocytochemistry, dual-luciferase reporter assay, immunoblotting, qRT-PCR, FISH	BDNF	Upregulated	Unknown	Axonal outgrowth	(Seo et al., 2019)	N/A
Dctn1	p150^{Glued}; Dynactin subunit 1	Rat	DRG	Quantitative FISH, quantitative immunofluorescence, immunoblot, RNA immunoprecipitation, RT-PCR, puromycylation assay\	Nerve growth factor	Smaller signalling endosomes require both Lis1 and p150Glued	Unknown	Surviving	(Villarin, McCurdy, Martinez, & Hengst, 2016)	*dnc-1* [ZK593.5e]
DSCR1.4	Down syndrome critical region 1-4; Calcipressin-1 [Rcan1]	Mouse	Hippocampal neuron culture	Puro-PLA, immunocytochemistry, dual-luciferase reporter assay, immunoblotting, qRT-PCR, FISH	BDNF	Upregulated	DAP5 (bind at 5' UTR)	Regulates axtin filament formation in axon	(Seo et al., 2019)	*rcan-1* [F54E7.7]
eEF1A	Eukaryotic elongation factor 1α	*Aplysia*	Sensory	*In situ* hybridization, Western blot	5-hydroxytryptamine (serotonin)	Increase axonal protein synthesis	Unknown	Long-term facilitation	(Giustetto et al., 2003)	*eef-1A.2* [R03G5.1]; *eef-1A.1* [F31E3.5]
elF2B2	Translation initiation factor eIF-2B subunit beta	Rat	Sympathetic, SCG	FISH, metabolic labelling (Click-iT)	Knockdown with miR16	Inhibition of local protein synthesis and axon growth	miR-16	Surviving, axon growth	(Kar, MacGibeny, Gervasi, Gioio, & Kaplan, 2013)	eif-2Bbeta [Y47H9C.7]
elF4G2	Eukaryotic translation initiation factor 4, gamma 2	Rat	Sympathetic, SCG	FISH, metabolic labelling (Click-iT)	Nerve growth factor	Inhibition of local protein synthesis and axon growth	miR-16	Surviving, axon growth	(Kar, MacGibeny, Gervasi, Gioio, & Kaplan, 2013)	*ifg-1* [M110.4e]
EphA2 receptors	Eph receptor A2;Receptor protein-tyrosine kinase	Chicken	Retinal axons	RNA encoding GFP reporter, fluorescence micrscopy, RT-PCR, Western Blot, Fluorescent Timer	Conserved 3' UTR RNA sequence attached to reporter and electroporated into embryonic spinal cord	Upregulate protein expression to the distal segment of commissural axons	3' UTR RNA	Appropriate navigation of spinal cord commissural axons to their targets; axon growth	(Brittis, Lu et al., 2002)	*vab-1* [M03A1.1]
Erp29	Endoplasmic reticulum resident protein 29	Mouse or rat	DRG	RT-PCR, SDS PAGE, immunofluorescence, MALDI TOF/TOF MS, MS/MS sequencing	Injury	Increase axonal protein synthesis	Unknown	Axon growth	(Willis, Li et al., 2005)	N/A
GAP43	Growth associated protein43; Neuromodulin	Rat	PC12	Immunoblot, light microscopic immunocytochemistry, FISH	Nerve growth factor	Increase axonal protein synthesis	HUD	Axon guidance*; expressed at high levels in neuronal growth cones during development and axonal regeneration, and it is	(Smith et al., 2004; Sahoo, Smith, Perrone-Bizzozero, & Twiss, 2018)	N/A
		Rat	DRG	RT-qPCR, immunofluorescence, immunoblotting, FRAP	Lysophospatidic acid (LPA); injury	No significant changes	Unknown		(Vuppalanchi et al., 2012)	

*Indicates that the finding was not directly addressed in the study.

References retrieved from:
(Jung, Yoon, & Holt, 2012)
(Farias et al., 2019)
(Sahoo, Smith, Perrone-Bizzozero, & Twiss, 2018)
(Costa & Willis, 2018)
(Holt, Martin, & Schuman, 2019)

- 70 mRNA genes found to be transported to the axon.
- Organisms: Majority on mouse or rat models, post-mortem central nervous system tissues from amyotrophic lateral sclerosis (ALS) patients (Homo sapiens) [6], chicken[7-9], *Xenopus laevis* [10-13] and *Aplysia* [14], *Lymnaea stagnalis* [15], and *C. elegans* [16].
- Neuronal Type: Retinal ganglion, dorsal root ganglion, hippocampal neurons, and touch neurons.
- Methodologies: microfluidic chambers or Campenot culture, Reverse Transcriptase-quantitative Polymerase Chain Reaction (RT-qPCR), Western Blotting analysis, fluorescence *in situ* hybridization (FISH), immunoprecipitation, Fluorescence Recovery After Photobleaching (FRAP), metabolic labeling method such as Click-iT L-azidohomoalanine (AHA)[17, 18] , RNA-Sequencing, Axon-Translating Ribosome Affinity Purification (Axon-TRAP) and Puromycylation-Proximity Ligation Assay (Puro-PLA) [3].
- 3' untranslated regions (UTR) of the mRNAs[14, 19-21], 5' UTR-localization motifs [22, 23], RNA binding proteins (e.g. ZBP1 binds to β-actin mRNA[24]), and microRNA (microRNA-338 regulates the COX IV mRNA levels) [25] Treatments: nerve growth factors, netrin, brain-derived neurotrophic factor and neurotrophin-3 stimulate axonal protein synthesis [7, 8, 17, 21, 26-32].
- Function of axonally transported mRNA: Axonal growth [15, 22, 26, 30, 31, 33-39], axonal regeneration[15, 16, 26, 27, 40-48], axonal guidance and pathfinding [7, 8, 10, 13, 14, 23, 49-53] as well as branching [8, 28, 54, 55], to support survival and maintenance by promoting mitochondrial functions [9, 11, 12, 15, 17, 18, 20, 21, 25, 29, 32, 45, 56-60], a platform for retrograde signaling [32, 61], result in analgesia [62, 63] or hyperalgesia [64, 65], mutations (loss or gain of function) result in neurological diseases [6, 66] (e.g. Annexin A2[6] and SOD1 genes are implicated in patients with ALS, while SP22 and Uch-L1 genes are linked to Parkinson's Disease [26]).



Conclusion

Axonally synthesized proteins are crucial for temporally-sensitive events in development, such as axonal growth, survival, plasticity and injury response, to name a few. The transport of mRNA to the axons is cost and time effective, providing a local renewable source of proteins. Just as one would not assemble the furniture and transport the bulky, completed piece cross country, so too does neuron prefer to produce proteins locally in axons when required.

Future studies could incorporate both omics strategies with gene-specific approaches to further identify axonally transported genes. New tools to image the mRNA transport in live animals along with enhanced spatial and temporal resolution will be useful to advance our understanding in intra-axonal protein synthesis.

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