



# Neuronal Mitochondrion Trafficking

*BCH441 Project: Defining a System*

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The source code, notebook, and data pipeline can be found at [github.com/thejmazz/biologicalsystem](https://github.com/thejmazz/biologicalsystem).  
Cover image (mitochondrion in Purkinje neuron) by *Atlas of Ultrastructural Neurocytology*<sup>1</sup>

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<sup>1</sup>[synapses.clm.utexas.edu/atlas/1\\_1\\_2\\_8.stm](http://synapses.clm.utexas.edu/atlas/1_1_2_8.stm)

# Contents

<b>1</b>	<b>Introduction</b>	<b>2</b>
<b>2</b>	<b>The System</b>	<b>3</b>
2.1	Systems Role Ontology . . . . .	4
<b>3</b>	<b>Gene Collection</b>	<b>5</b>
3.1	Signal Integration . . . . .	5
3.1.1	RHOT1 <i>Mitochondrial Rho GTPase 1</i> . . . . .	5
3.1.2	RHOT2 <i>Mitochondrial Rho GTPase 2</i> . . . . .	6
3.1.3	TIAM2 <i>T-lymphoma invasion and metastasis-inducing protein 2</i> . . . . .	6
3.2	Set . . . . .	6
3.2.1	CLUH <i>Clustered mitochondria protein homolog</i> . . . . .	6
3.2.2	MAP1B <i>Microtubule-associated protein 1B</i> . . . . .	6
3.2.3	MAPT <i>Microtubule-associated protein tau</i> . . . . .	6
3.2.4	MTM1 <i>Myotubularin</i> . . . . .	6
3.2.5	SYBU <i>Syntabulin</i> . . . . .	6
3.3	Transmit . . . . .	6
3.3.1	BHLHA15 <i>Class A basic helix-loop-helix protein 15</i> . . . . .	6
3.3.2	GABA <i>Gamma-amino-N-butyrate transaminase</i> . . . . .	6
3.3.3	TRAK1 <i>Trafficking kinesin-binding protein 1</i> . . . . .	6
3.3.4	TRAK2 <i>Trafficking kinesin-binding protein 2</i> . . . . .	6
3.4	Transform . . . . .	6
3.4.1	GAN <i>Gigaxonin</i> . . . . .	6
3.4.2	TTL <i>Tubulin-tyrosine ligase</i> . . . . .	6
3.5	Regulate . . . . .	6
3.5.1	ATCAY <i>Caytaxin</i> . . . . .	6
3.5.2	MGARP <i>Mitochondria-localized glutamic acid-rich protein</i> . . . . .	6
3.5.3	MSTO1 <i>Protein misato homolog 1</i> . . . . .	6
3.5.4	SNPH <i>Syntaphilin</i> . . . . .	6
3.6	Output . . . . .	6
3.6.1	KIF1B <i>Kinesin-like protein KIF1B</i> . . . . .	6
3.6.2	KIF5B <i>Kinesin-1 heavy chain</i> . . . . .	6
3.6.3	KLC1 <i>Kinesin light chain 1</i> . . . . .	6

## 1 Introduction

The “powerhouse of the cell” as it is so commonly called, the mitochondria is one of the most vital organelles in eukaryotes. This structure is thought to have developed through a symbiotic relationship among engulfed prokaryotic cells and their hosts. As such, it is rooted quite deeply evolutionarily, and one might expect its proper functioning to be absolutely vital, that is, knock-out mutants will not survive. This is true - but as we will see, it is not just the performance of this organelle which is centrally important, but where it is localized within the cell as well.

Images of isolated mitochondria were first observed in 1979 by Johnson et al.:

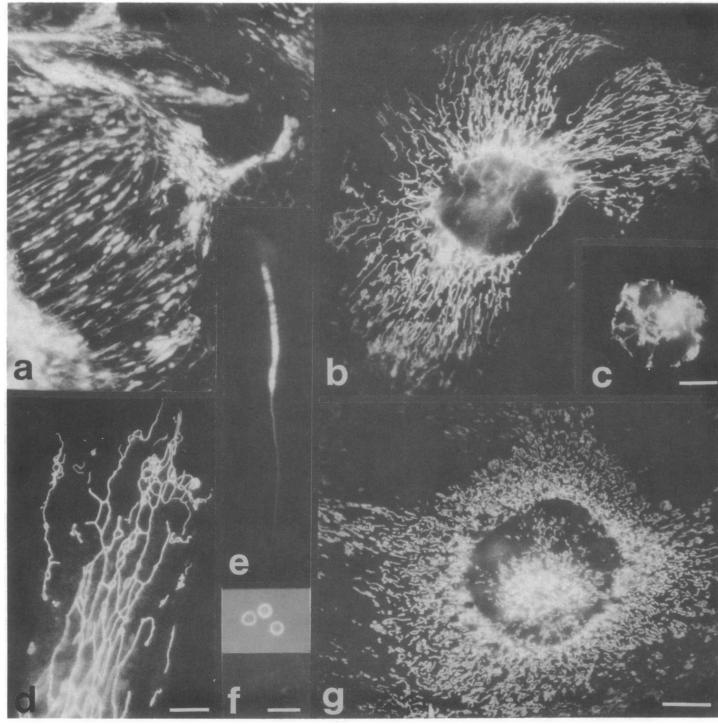


FIG. 5. Living cells stained with rhodamine 123: (a) rat cardiac muscle; (b) Pt KI marsupial kidney; (c) mouse B lymphocyte; (d) mouse 3T3; (e) mouse sperm; (f) human erythrocytes (phase-contrast above and rhodamine 123-treated but unstained below); (g) rat embryo fibroblast. Bar represents: 15  $\mu\text{m}$  in a, b, e, and g; 10  $\mu\text{m}$  in c; 8  $\mu\text{m}$  in d; 10  $\mu\text{m}$  in f.

The variety of mitochondrion shape and size is clear, ranging from globular to filamentous to networked structures. As well, the authors observed movement during 15-30 sec intervals, between fluorescent and phase-contrast photographs.

The primary role of a mitochondrion is to supply energy to the cell in the form of ATP units, through the electron transport chain among the cristae. Where is that energy needed? Consider highly polar and elongated cells such as neurons. The cell body of a neuron is distant from its synaptic endings, where as it happens, large amounts of energy are required for neurotransmitter release and absorption. Following, we will investigate the **system** whose **functional role** is the **localization of mitochondrion within neurons**.

## 2 The System

<i>Name</i>	Localization/Trafficking of mitochondrion within neurons
<i>Description</i>	The collective of functional units represented by genes which process signals, transduce these events, initiate, and maintain the actions necessary to transport mitochondrion to distal points along the axon of a neuron.
<i>Associated GO Terms</i>	<a href="#">GO:0051646</a> (mitochondrion localization) <ul style="list-style-type: none"> <li>• <a href="#">GO:0051659</a> (maintenance of mitochondrion localization)               <ul style="list-style-type: none"> <li>– <a href="#">GO:1990456</a> (mitochondrion-ER tethering)</li> </ul> </li> <li>• <a href="#">GO:0034643</a> (establishment of mitochondrial localization, microtubule mediated)               <ul style="list-style-type: none"> <li>– <a href="#">GO:0034642</a> (mitochondrial migration along actin filament)</li> <li>– <a href="#">GO:0034643</a> (establishment of mitochondrial localization, microtubule mediated)                   <ul style="list-style-type: none"> <li>* <a href="#">GO:0034640</a> (establishment of mitochondrion localization by microtubule attachment)</li> <li>* <a href="#">GO:0047497</a> (mitochondrion transport along microtubule)</li> </ul> </li> <li>– <a href="#">GO:0090146</a> (establishment of mitochondrial localization involved in mitochondrial fission)</li> </ul> </li> </ul>

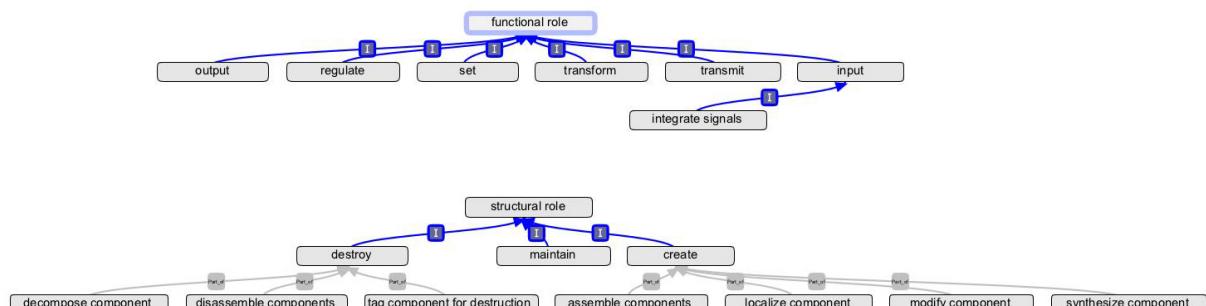
- \* [GO:0090147](#) (regulation of establishment of mitochondrion localization involved in mitochondrial fission)
- [GO:0048311](#) (mitochondrion distribution)
  - [GO:0048312](#) (intracellular distribution of mitochondria)
  - [GO:0000001](#) (mitochondrion inheritance)

Why this system? Originally I was looking into “mitochondrial localization.” Amongst the genes returned by the ontology, there appeared those related to mitochondrial localization during cellular reproduction, transport, microtubules, tethers, mRNA-binding, and various “popular” genes such as ubiquitins, serum albumin, leucine-rich repeat serine/threonine-protein kinase, basic helix-loop-helix protein. There was a fair amount of variety. In order to gather together a structured list of genes I would need to filter these out, and to filter these out I would need a functional goal. I decided to choose the neuronal process because it is one of the most extreme cases of mitochondrial movement in all cell types, there was a decent amount of related literature available, some elements of its processes had been recently elucidated, and it has important neurophysiological consequences. A review by Reis et al. (2009) explored the atypical Miro GTPases and their role in transporting mitochondria in neurons. The authors note that abnormal mitochondrial dynamics can contribute to Amyotrophic Lateral Sclerosis (ALS), Huntington’s, Parkinson’s, and Alzheimer’s diseases. A more recent experiment by Loss and Stephenson (2015) examines the role of TRAK1 and TRAK2 kinesin adaptor proteins which link mitochondria to kinesin motor proteins. Furthermore, Miro proteins are expressed in a large variety of cell types, potentially extending this current analysis to new domains (Reis et al., 2009).

## 2.1 Systems Role Ontology

To define this system in a structured manner, I considered its functionality in the context of the Systems Roles Ontology, which can be found at [github.com/hyginn/SyRO](https://github.com/hyginn/SyRO):

SyRO – Systems Role Ontology (2015-10-27)



Name	ID	Context Within Neuronal Mitochondrion Localization
<b>input</b>	16	compounds or signals prompting the directed movement of mitochondrion
<b>integrate signals</b>	22	machinery which directs input signals/compounds to the system
<b>output</b>	21	mitochondrion transport towards synaptic endings
<b>regulate</b>	20	components which ensure regular mitochondrial motility
<b>set</b>	19	preparing the functional units, “setting the stage” as it were
<b>transform</b>	18	altering the system status so that it may be reversed, stopped, reinstated
<b>transmit</b>	17	the physical machinery to move mitochondria

These functions collaborate to produce the **functional role** of localizing mitochondria **for the proper functioning of neural communication**. I will define the bounds of this system as any genes which can be annotated with the functional role annotations above. Structural role annotations will be considered second to function, and will be used largely to describe how that component physically determines its function. With this goal in mind, I fetched and filtered data from the Gene Ontology Consortium, QuickGO, UNIPROT, IntAct, and STRING. Those genes which did not make the cut can be seen through the *Summary of first pool* in my [notebook](#).

### 3 Gene Collection

Gene	Accession	Name	SyRO
ATCAY	Q86WG3	Caytaxin	regulate
BHLHA15	Q7RTS1	Class A basic helix-loop-helix protein 15	transmit
CLUH	I3L2B0	Clustered mitochondria protein homolog	set
GABA	P80404	Gamma-amino-N-butyrate transaminase	transmit
GAN	Q9H2C0	Gigaxonin	transform
KIF1B	O60333	Kinesin-like protein KIF1B	output
KIF5B	P33176	Kinesin-1 heavy chain	output
KLCA1	Q07866	Kinesin light chain 1	output
MAPT	P10636	Microtubule-associated protein tau	set
MAP1B	P46821	Microtubule-associated protein 1B	set
MGARP	Q8TDB4	Mitochondria-localized glutamic acid-rich protein	regulate
MTM1	Q13496	Myotubularin	set
MSTO1	Q9BUK6	Protein misato homolog 1	regulate
PFDNS	Q99471	Prefoldin subunit 5	regulate, integrate, assemble, localize
RHOT1	Q8IXI2	Mitochondrial Rho GTPase 1	integrate signals
RHOT2	Q8IXI1	Mitochondrial Rho GTPase 2	integrate signals
SNPH	O15079	Syntaphilin	regulate
SYBU	Q9NX95	Syntabulin	set
TIAM2	Q8IVF5	T-lymphoma invasion and metastasis-inducing protein 2	integrate signals
TRAK1	Q9UPV9	Trafficking kinesin-binding protein 1	transmit
TRAK2	Q8IU62	Trafficking kinesin-binding protein 2	transmit
TTL	Q8NG68	Tubulin-tyrosine ligase	transform

#### 3.1 Signal Integration

##### 3.1.1 RHOT1 *Mitochondrial Rho GTPase 1*

Ability to bind to TRAK1 not Ca2+ dep.

- 3.1.2 RHOT2 *Mitochondrial Rho GTPase 2*
- 3.1.3 TIAM2 *T-lymphoma invasion and metastasis-inducing protein 2*

### 3.2 Set

- 3.2.1 CLUH *Clustered mitochondria protein homolog*
- 3.2.2 MAP1B *Microtubule-associated protein 1B*
- 3.2.3 MAPT *Microtubule-associated protein tau*
- 3.2.4 MTM1 *Myotubularin*
- 3.2.5 SYBU *Syntabulin*

### 3.3 Transmit

- 3.3.1 BHLHA15 *Class A basic helix-loop-helix protein 15*
- 3.3.2 GABA *Gamma-amino-N-butyrate transaminase*
- 3.3.3 TRAK1 *Trafficking kinesin-binding protein 1*

Contains coiled-coiled domain.

- 3.3.4 TRAK2 *Trafficking kinesin-binding protein 2*

Interact with GABA-A receptors.

### 3.4 Transform

- 3.4.1 GAN *Gigaxonin*
- 3.4.2 TTL *Tubulin-tyrosine ligase*

### 3.5 Regulate

- 3.5.1 ATCAY *Caytaxin*
- 3.5.2 MGARP *Mitochondria-localized glutamic acid-rich protein*
- 3.5.3 MSTO1 *Protein misato homolog 1*
- 3.5.4 SNPH *Syntaphilin*

### 3.6 Output

- 3.6.1 KIF1B *Kinesin-like protein KIF1B*
- 3.6.2 KIF5B *Kinesin-1 heavy chain*
- 3.6.3 KLC1 *Kinesin light chain 1*

## References

Lincoln V. Johnson, Marcia L. Walsh, and Lan Bo Chen. Localization of mitochondria in living cells with rhodamine 123. *Proc. Natl. Acad. Sci. USA*, 77:990–994, 1979.

Omar Loss and F. Anne Stephenson. Localization of the kinesin adaptor proteins trafficking kinesin proteins 1 and 2 in primary cultures of hippocampal pyramidal and cortical neurons. *Journal of Neuroscience Research*, 93:1056–1066, 2015.

Katarina Reis, Asa Fransson, and Pontus Aspenstrom. The Miro GTPases: At the heart of the mitochondrial transport machinery. *Federation of European Biochemical Societies Letters*, 583:1391–1398, 2009.