



Neuronal Mitochondrion Trafficking

BCH441 Project: Defining a System

Julian Mazzitelli

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

¹synapses.clm.utexas.edu/atlas/1_1_2_8.stm

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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.:

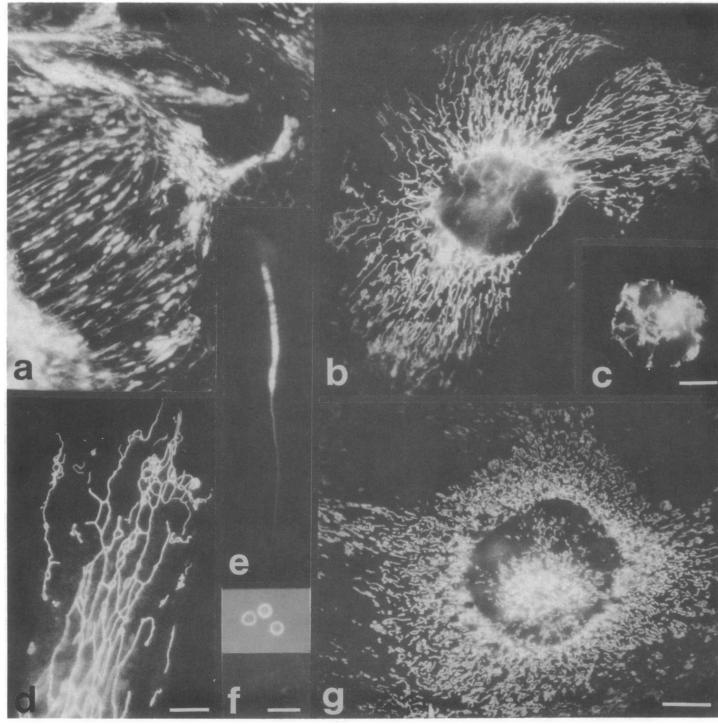


FIG. 5. Living cells stained with rhodamine 123: (a) rat cardiac muscle; (b) Pt KI marsupial kidney; (c) mouse B lymphocyte; (d) mouse 3T3; (e) mouse sperm; (f) human erythrocytes (phase-contrast above and rhodamine 123-treated but unstained below); (g) rat embryo fibroblast. Bar represents: 15 μm in a, b, e, and g; 10 μm in c; 8 μm in d; 10 μm 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>	GO:0051646 (mitochondrion localization)
•	GO:0051659 (maintenance of mitochondrion localization) <ul style="list-style-type: none"> – GO:1990456 (mitochondrion-ER tethering)
•	GO:0034643 (establishment of mitochondrial localization, microtubule mediated) <ul style="list-style-type: none"> – GO:0034642 (mitochondrial migration along actin filament) – GO:0034643 (establishment of mitochondrial localization, microtubule mediated) <ul style="list-style-type: none"> * GO:0034640 (establishment of mitochondrion localization by microtubule attachment) * GO:0047497 (mitochondrion transport along microtubule)
–	GO:0090146 (establishment of mitochondrial localization involved in mitochondrial fission)

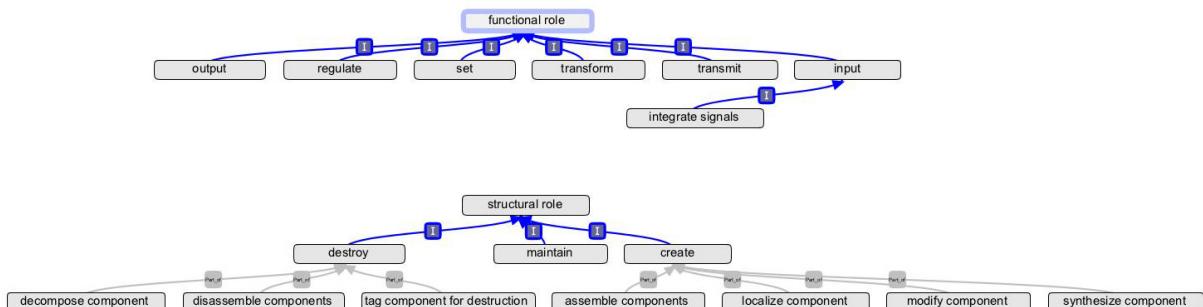
- * GO:0090147 (regulation of establishment of mitochondrion localization involved in mitochondrial fission)
- GO:0048311 (mitochondrion distribution)
 - GO:0048312 (intracellular distribution of mitochondria)
 - GO:0000001 (mitochondrion inheritance)

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:

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



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

<i>Gene</i>	<i>Accession</i>	<i>Name</i>	<i>SyRO</i>
RHOT2	Q8IXI1	Mitochondrial Rho GTPase 2	integrate, assemble
RHOT1	Q8IXI2	Mitochondrial Rho GTPase 1	integrate, assemble
MGARP	Q8TDB4	Mitochondria-localized glutamic acid-rich protein	regulate, localize components
TRAK1	Q9UPV9	Trafficking kinesin-binding protein 1	set
TRAK2	Q8IU62	Trafficking kinesin-binding protein 2	set
MAPT	P10636	Microtubule-associated protein tau	set, localize
MAP1B	P46821	Microtubule-associated protein 1B	set, assemble, integrate signals
TIAM2	Q8IVF5	T-lymphoma invasion and metastasis-inducing protein 2	localize, modify, integrate signals
TTL	Q8NG68	Tubulin-tyrosine ligase	modify, assemble
GAN	Q9H2C0	Gigaxonin	decompose, tag, regulate
KIF1B	O60333	Kinesin-like protein KIF1B	transmit, transform, maintain
AIM21	P40563 (yeast)	Altered inheritance of mitochondria protein 21	assemble, localize, integrate, transmit
MYO19	Q5SV80 (mouse)	Unconventional myosin-XIX	maintain, transform
MDM10	P18409 (yeast)	Mitochondrial distribution and morphology protein 10	regulate, integrate, assemble, localize
PFDNS	Q99471	Prefoldin subunit 5	regulate, integrate, assemble, localize
MDM12	Q92328 (yeast)	Mitochondrial distribution and morphology protein 12	regulate, integrate, assemble, localize
MILT	Q960V3 (fly)	Trafficking kinesin-binding protein milt	assemble, localize, output, set
CLUH	I3L2B0	Clustered mitochondria protein homolog	localize, set
BHLHA15	Q7RTS1	Class A basic helix-loop-helix protein 15	synthesize, assemble, set
MTM1	Q13496	Myotubularin	set, localize, modify
MSTO1	Q9BUK6	Protein misato homolog 1	set, maintain, transform
ATCAY	Q86WG3	Caytaxin	regulate, assemble, transmit
KLCA1	Q07866	Kinesin light chain 1	integrate, assemble

3.1 Signal Integration

3.1.1 RHOT2 *Mitochondrial Rho GTPase 2*

3.1.2 RHOT1 *Mitochondrial Rho GTPase 1*

Ability to bind to TRAK1 not Ca²⁺ dep.

3.1.3 TIAM2 *T-lymphoma invasion and metastasis-inducing protein 2*

3.2 Set

3.2.1 SYBU *Syntabulin*

3.2.2 MAPT *Microtubule-associated protein tau*

3.2.3 MAP1B *Microtubule-associated protein 1B*

3.2.4 CLU1 *Clustered mitochondria protein homolog*

3.2.5 MTM1 *Myotubularin*

3.3 Transmit

3.3.1 TRAK1 *Trafficking kinesin-binding protein 1*

Contains coiled-coiled domain.

3.3.2 TRAK2 *Trafficking kinesin-binding protein 2*

Interact with GABA-A receptors.

3.3.3 BHLHA15 *Class A basic helix-loop-helix protein 15*

3.3.4 GABA *Gamma-amino-N-butyrate transaminase*

3.4 Transform

3.4.1 TTL *Tubulin-tyrosine ligase*

3.4.2 GAN *Gigaxonin*

3.5 Regulate

3.5.1 MGARP *Mitochondria-localized glutamic acid-rich protein*

3.5.2 MSTO1 *Protein misato homolog 1*

3.5.3 ATCAY *Caytaxin*

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.