Identification of terminal selectors and cell-fate Markers in *C. elegans* neurons

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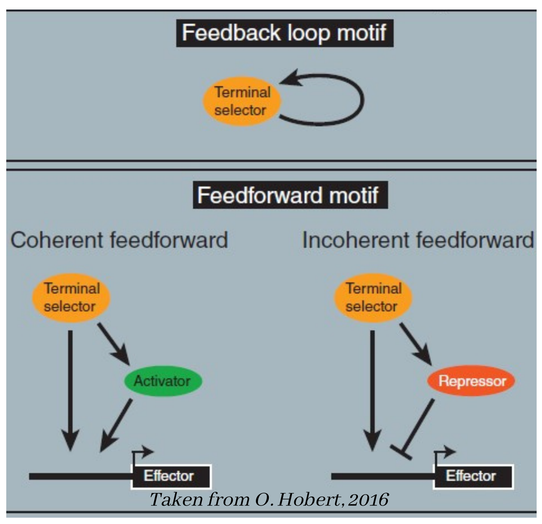
[Physics(Intensive)]

INTRODUCTION

The adult hermaphrodite *Caenorharbditis elegans* worm has **302 neurons divided into 118 neuron classes**. Detailed study of the neuronal system is enabled by means of **cell-fate markers, which are genes and the resulting gene products that only occur in a set of specific neurons**. Identification of highly specific cell fate markers—those which are only expressed in one class of neurons—allows for increased accuracy and efficiency in studying neuronal genetics. Specification of neuronal identity is a complex process involving multiple factors. **Terminal selectors are transcription factors that act cooperatively to biochemically co-regulate the expression of distinct terminal identity features in neurons.**



Taken from O. Hobert, 2016

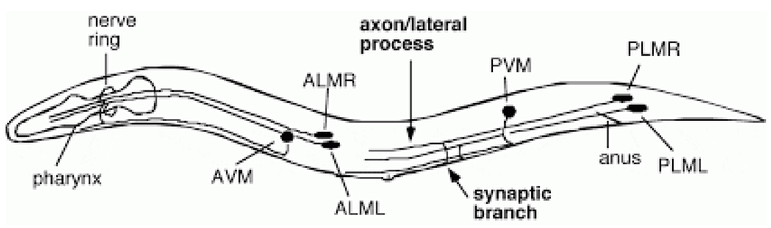
Terminal selectors are necessary to **induce expression of terminally differentiated cell features** such as neurotransmitter identity, morphology, and function by controlling the expression of terminal effector genes. Further, terminal selectors are auto-regulators and are expressed continuously throughout the life of the neuron in order to both induce and maintain its terminally differentiated state. Terminal selectors act via two mechanisms; either by activating effector genes or by inhibiting the expression of cell-fate repressors.

METHOD

The review by O. Hobert published in 2016 compiled all the terminal selectors and cell-fate markers known at the time. Since, there has been a lot of new research done, and my project involved compiling the new findings, to create an up-to-date database of the known terminal selectors and cell-fate markers.

The new database compiled by reading a multitude of papers (some included in the review, but most published after) contains information specific to each neuron class. The table includes terminal selectors (differentiated by mechanism--repression or induction, cell-fate markers --with specificity denoted, interactions of terminal selectors as well as references of the papers from which the information was collected. Data in this database is compiled from between **30 and 40 published papers**. As per the database, there remain about **33 neuron classes for which no cell-fate markers are known as yet**.

A DETAILED EXAMPLE

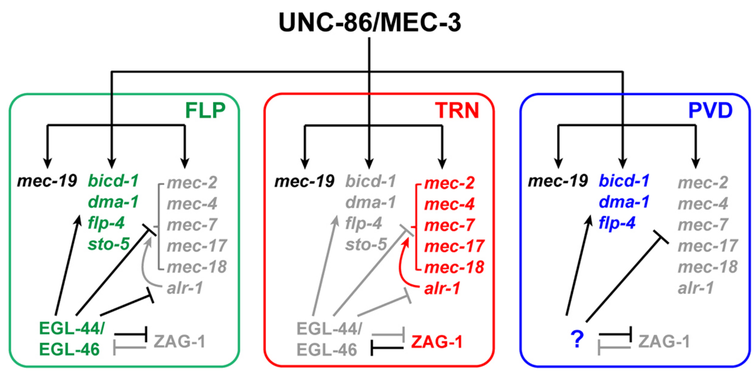


Taken from Nonet Lab, University of Washington School of Medicine in St Louis

The touch receptor neurons (TRNs) –ALM, PLM, AVM and PVM all share three identified terminal selectors: **UNC-86, MEC-3 and ZAG-1**. UNC-86 and MEC-3 activate a set of TRN terminal differentiation genes (such as *mec-4, mec-10, mec-7, mec-12, mec-17* etc) while **ZAG-1 acts as a repressor of the FLP fate.** The transcription factor and zinc-finger protein complex EGL-44/EGL-46 acts as a terminal selector in FLP neurons by supressing TRN fate. In TRNs, ZAG-1 inhibits expression of the EGL-44/EGL-46 complex, and thus promotes TRN fate. Another terminal selector for AVM neurons, **AHR-1**, determines AVM terminal fate by **inhibiting expression of the PVD fate**. The mechanism of inhibition is rather complex, with AHR-1 elevating levels of MEC-3 but blocking the expression of downstream targets of MEC-3 such as HPO-30 (claudlin-like protein). HPO-30 aids in stabilising lateral dendrites in PVD neurons, which are characterized by their highly branched dendritic structure as opposed to AVM neurons which have simple, unbranched morphology.

	Fate inducer	Fate suppressor	Highly specific markers in purple	
Extrapharyngeal Neurons			**Cell fate markers**	**References**
ADA	*unc-86*			*Serrano-Saiz et al., 2018, Current Biology (T1 S)*
ADE	ast-1, ceh-33		*flp-33 (ADE_CEP); dat-1(vtIs1)*	*Lorenzo, 2020, NAR*
ADL	*lin-11, hlh-4*		*hlh-4, T09B9.3, C18H7.6; srb-6(gmIs12); ver-2*	*Masoudi et al., 2018, PLoS Biology ; Li et al., 2012, Nat. Neurosci ; Lorenzo, 2020, NAR*
AFD	ttx-1, ceh-14		*gcy-3; gcy-8(oyIs17)*	*Inada et al., 2006, Genetics*
AIA	ttx-3		*gcy-28*	*Shinkai et al., 2011, J. Neurosci*
AIB	unc-42			
AIM	*unc-86, ceh-14*		*nlp-70; flp-10(otIs92)*	*Lorenzo, 2020, NAR*
AIY	ttx-3, ceh-10		*ttx-3 (mgIs18), sra-11(otIs123), hen-1*	*Wenick et al., 2004, Dev. Cell*
AIZ	unc-86			
ALA	ceh-14, ceh-17			
ALM	unc-86, mec-3	*zag-1*	*mec-4(2dIs5); mec-17(uIs115); mec-18*	*Zheng et al., 2018, Development*
AQR	unc-86, egl-13, ahr-1		*gcy-37(iaIs25); gcy-32(iaIs19); F49H12.4(wdIs51; also PQR)*	
AS	unc-3			
ASE	*che-1, ceh-36, die-1, lim-6*	*cog-1*	*ASEL: gcy-6(otIs162), gcy-7 ; ASER: gcy-4, gcy-5(ntIs1; otIs220)*	*Yu et al., 1997, Proc. Natl Acad Sci U.S.A ; Ortiz et al., 2006, Genetics*
ASG	lin-11, ceh-37		*gcy-15;*	*Ortiz et al., 2006, Genetics*
ASH	unc-42		*gpa-11p2(otEx5336), gpa-13(otEx213), gpa-15(pkIs591), flp-21(ynIs80), sra-6(oyIs14)*	*Baran et al., 1999, Development*
ASI	unc-3	unc-3	*str-3; gpa-4; flp-10(otIs94)*	*Peckol et al., 2001, Proc. Natl Acad. Sci. U.S.A*
ASJ	sptf-1		*sptf-1(gjIs698), ssu-1(vzEx29), trx-1(otEx4), gpa-9(pkIs586)*	*Gonzalez-Barrios et al., 2015, Genetics ; Carrol et al., 2006, J. Biol. Chem.; Miranda-Vizuete et al., 2006, FEBS Lett.*
ASK	ttx-3		*sra-7, sra-9, srb-6(gmIs12), srg-2, srg-8, srbc-64, srbc-66*	*Troemel et al., 1995, Cell ; Kim et al., 2009, Science*
AUA	ceh-6		*flp-8(ynIs2022; ynIs78), flp-10(otIs92), flp-11(ynIs40)*	*Serrano-Saiz et al., 2013, Cell*
AVA	unc-3, unc-42, fax-1		*nmr-1(akIs3); glr-1(nuIs1, nuIs25)*	*Baran et al., 1999, Development*
AVB	unc-3		*sra-11(jEx286; otIs123)*	
AVD	unc-3, unc-42, cfi-1		*nmr-1(akIs3), glr-1(nuIs1, rhIs4)*	*Baran et al., 1999, Development; Shaham et al., 2002, Genes & Dev*
AVE	unc-3, unc-42, fax-1		*nmr-1(akIs3); glr-1(nuIs1, nuIs25)*	*Baran et al., 1999, Development*
AVG	lin-11, ast-1		*nmr-1(akIs3); inx-19(otIs182)*	
AVK	unc-42, fax-1		*flp-1, twk-47*	*Nelson et al., 1998, Science ; Lorenzo, 2020, NAR*
AVL	nhr-67, lim-6		*unc-47(otIs39; oxIs12); unc-25(juIs76) GABAergic neurons*	

Table 1: Part of newly compiled database



Taken from C.Zheng et al., 2018, Development