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Molecular and Cellular Mechanisms of Dopamine Signaling in C. elegans

Khursheed Ahmad Wani, *University of Massachusetts - Amherst*

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First Advisor
Daniel L. Chase

Second Advisor
Rolf O. Karlstrom

Third Advisor
Lawrence M. Schwartz

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Abstract
The main goal of this dissertation has been to identify the molecular and cellular mechanisms that underlie dopamine signaling. To this end, we used genetic, behavioral and molecular approaches available in *C. elegans* , a free-living soil nematode with a simple nervous system comprised of just 302 neurons. Out of these 302 neurons, there are only eight neurons that synthesize and release neurotransmitter dopamine. These features, in combination with an abundance of dopamine-dependent behavioral assays and amenability to forward and reverse

genetic approaches, makes C. elegans an ideal model organism to dissect the molecular and cellular mechanisms that regulate dopamine signaling.

In *C. elegans* , dopamine is released from dopaminergic neurons in response to mechanical stimuli and it binds to G protein-coupled D1- (DOP-1) and D2-like (DOP-3) dopamine receptors to regulate locomotion behavior. This regulation occurs in C. elegans cholinergic and GABAergic ventral cord motor neurons that control locomotion by innervating body wall muscles.

To identify novel signaling components that underlie dopamine signaling, we performed a large-scale RNAi (RNA interference) screen in *C. elegans* . This screen identified *eat-16* and *rsbp-1* , *C. elegans* ,homologs of mammalian R7 family RGS (*r* egulator of *G* protein *s* ignaling) protein and R7BP (*R7* RGS *b* inding *p* rotein), respectively. Since RGS proteins and their binding partners regulate G protein signaling, we characterized the roles of EAT-16 and RSBP-1 in the regulation of G protein-coupled dopamine receptor signaling in C. elegans. To this end, we used a combination of mutant analyses and cell-specific transgenic rescue experiments to investigate the functional interaction between EAT-16 and RSBP-1 within single cell types and to examine their role in the modulation of dopamine receptor signaling. We found that EAT-16 and RSBP-1 function together to specifically regulate DOP-1 and not DOP-3 receptor signaling by acting in cholinergic motor neurons.

All together, my PhD work has shed light on the importance of RGS proteins and their binding partners in the regulation of dopamine receptor signaling and demonstrated that genetic and molecular approaches in *C. elegans* can be used to understand the mechanisms that underlie dopamine signaling.