



# Virus Engineered Immune Circuit Possibly Gates Neuro-Excitability Outcomes in Brains

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## ABSTRACT

Tryptophan derivatives, including serotonin, are the main neurotransmitters that link food cues to neuronal behavior and metabolism, in a wide variety of organisms. In mammalian gut, serotonin is synthesized within populations of enterochromaffin cells and neurons of the enteric nervous system, distributed throughout the gastrointestinal tract and are under direct or indirect control of the microbiota. Dysregulation of the signaling by neurotransmitter dopamine and serotonin can affect mood, appetite and locomotion consequences thereby contributing to several human neurological diseases, including parkinson, schizophrenia, autism and attention deficit hyperactivity disorders. Besides such annotations, remodeling of the intestinal microbial community structure by the gut microbiota could impact the development and/or function of such serotonin-producing cells, but this has yet to be claimed. The gut flora of healthy individuals is composed of a large variety of bacteria and forms an important part of the body's immune system, including being the first line of defense in any fight against pathogen invasion. In most diseases, the gut flora develops a limited diversity compared to that of a healthy individual and its modified interaction with the host can result in abnormalities, such as brain-function impairment. It is also well known that the function and composition of gut flora can be influenced by many external factors, including food and environment contaminants. But the exact mechanisms for how these factors affect the gut flora and result in disease, remain to be elucidated. While serotonin and octopamine have evolutionarily conserved roles over diverse phyla, their roles in nematode model *Caenorhabditis elegans* (*C. elegans*) is similar to that in the model organism *Drosophila*, where it induces behavioral outcomes upon food intake, which facts that this mechanism is evolutionary conserved, although not completely understood. In *C. elegans*, nutritional availability is directly linked to food behavior and can be sensed by the rate-limiting enzyme Tryptophan 2,3-Dioxygenase (TDO in human, TDO-2 in *C. elegans*) in the serotonin-kynurenine pathway that affects serotonin and kynurenic acid levels that results in different excitability states and lifespan extension in response to food cues.

**Keywords:** Tryptophan derivatives; Dysregulation; Serotonin; Octopamine

## INTRODUCTION

The increasing interest to identify the key features of the gut-brain axis signals a striking hypothesis connecting viral infection-change in microbial diversity and behavior outcomes that

plausibly acts through the neurotransmitter modulation. To understand this association in our lab, a proof-of-concept study using the worm-virus model system *C. elegans*. Orsay virus revealed an eye-opening clue to the virus's likely role behind this mechanism in worms. However, the question remains how virus

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reengineers the immune circuit through gut microbiota to bring potential outcomes in brain behavior [1].

The nematode *C. elegans* is a living animal model with a gene complement that is remarkably conserved in vertebrates (38% with human). The worm biology is much less complex than that of higher level vertebrates and the developmental systems, organ types and tissue-specific genes are being studied extensively. Since this organism is optically transparent, molecular candidates can be easily labeled with fluorescence and thus the influence of the viral infection can be directly observed in the body and behavior of the worms [2]. Discovered almost a decade ago, Orsay virus is the only known virus capable of naturally infecting the model organism *C. elegans*.

## DESCRIPTION

Orsay is a bipartite positive-sense single stranded RNA virus related to family *Nodaviridae* that expresses a total of four polypeptides, including an RNA-dependent RNA Polymerase (RdRP), a Capsid Protein-alpha (CP- $\alpha$ ), a non-structural protein delta ( $\delta$ ) and a fusion protein capsid-delta (CP- $\delta/\alpha\delta$ ) produced by ribosomal frameshift [3]. The Orsay virus infection in *C. elegans* initiates a variety of abnormalities, including intestinal damages. While the functions of RdRP in viral transcription and replication, CP- $\alpha$  role during virus maturation, CP- $\delta$  likely function during the virus infection are well recognized; potential characterization of CPs during Orsay infection in the worm remains to be explored [4]. Towards this effort, an approach so-called PROtein FEeding in *C. elegans* (PROFECE), a not yet available experimental system developed in our lab that can deliver any recombinant protein of interest directly to the worm gut through genetically engineered microbiota environment as a food source, allowed us to investigate the undocumented functions if any of viral capsid proteins to host response in worms [5]. However, since *C. elegans* feeds on *Escherichia coli* (*E. coli*) OP50; engineered bacterial lawn expressing recombinant viral proteins were used as a food source to deliver them to the worm gut and survival and behavioral assays by assessing worm mobility were performed. Our approach considers the bacterial lawn of *C. elegans* not only as a food source, but also as a genetically engineered microbiota environment to study host-pathogen interaction in the gut of the nematode. The results show that worm fed with protein  $\alpha\delta$  survived longer while  $\delta$  contributes to worm intestinal defects. Morphological analysis in the gut of the worm suggests that protein  $\alpha$  limits food absorption in the intestine while  $\alpha\delta$  plays a role in food digestion. Moreover, experiments tracking worm mobility showed hyperactive behavior [6]. This indicates that Orsay virus capsid proteins extend life span and causes a hyperactive behavior in *C. elegans* in response to capsid protein ingestion. It offers a convincing and novel finding showing that viral proteins can affect behavior and lifespan through gut interactions and play an important role in virus pathogenicity as virulent factors. Our interpretation is that viral proteins plausibly affect the serotonin level in the worm gut by dysregulating one of the routes of serotonin biosynthesis, which yet requires to be quantified experimentally [7]. Pertinent to this, a study has also shown that virus infection in *C. elegans* shifts the microbiota in

the gut of the nematode. Since Orsay in *C. elegans* alters gut bacterial composition and dysregulation of the kynurenine pathway affects behavior and lifespan in a similar manner as are shown in our study, our future hypothesis it that Orsay virus, possibly through microbiota shift, alters the production of serotonin or kynurenine, which induces behavioral modifications. But there is no information available on how virus governs this behavioral change and are currently under thoroughgoing investigation in our lab. However, in our study, comparative modeling of capsid proteins shows that viral protein delta has a high degree of structural similarity with the rate-limiting enzyme (TDO-2) of the kynurenine pathway. Since TDO-2 controls serotonin production and produces metabolites causing brain excitability, it is also plausible that  $\delta$  mimics and/or interferes with the host TDO-2 activity. Chiming this information may allow us to develop a novel system in *C. elegans* to study the virus-gut-brain axis and further unravel the molecular mechanism by which virus modulates host gut microbiota or target intestinal cells to increase those metabolites products and to assess the contribution of the neurotransmitter serotonin in this change of behavior [8].

## CONCLUSION

Hyperactivity after viral infection has been previously reported to occur in many other virus-human systems, including HIV and Zika, but this is the first time that this behavior is reported in *C. elegans*. Given that *C. elegans* gene repertoire is very similar to humans and since this change of behavior induced by viruses has been observed in other vertebrates and human, it suggests an evolutionarily conserved mechanism to evade the host immune system. With more information is becoming available on the pathogenesis of virus and the associated immune response, significant gaps remain in our understanding of the impact of virus on the nervous system. Impending findings from this continuing work in our lab, would perhaps gate the onset of many neuro-behavioral disorders triggered by an initial viral infection creating neuronal damage being increasingly reported yet with limited knowledge, including the much debated hot research's in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID19, that endorses the neuro-invasive and neuro-inflammatory capacity of virus with devastating consequences of neurological and neuropsychiatric complications in patients.

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