COMMENTARY

# Dual function of a fungal GPCR in activating mitochondrial respiration and initiating prey hunting in fungus-nematode interactions

**Yifan Li,[1,2] Jian Zhang,[1,2] Qirong Shen,[1,2] and Zhenzhong Yu[1,2,*]**

[1]Jiangsu Provincial Key Lab for Organic Solid Waste Utilization, Nanjing Agricultural University, Nanjing 210095, China

[2]Jiangsu Collaborative Innovation Center for Solid Organic Waste Resource Utilization, Nanjing Agricultural University, Nanjing 210095, China

*Correspondence: yuzhenzhong@njau.edu.cn

Received: June 20, 2024; Accepted: August 6, 2024; Published Online: August 28, 2024; https://doi.org/10.59717/j.xinn-life.2024.100087



Citation: Li Y., Zhang J., Shen Q., et al., (2024). Dual function of a fungal GPCR in activating mitochondrial respiration and initiating prey hunting in fungus-nematode interactions. The Innovation Life **2(3)**: 100087.



G protein-coupled receptors (GPCRs) are the largest group of membrane receptors in eukaryotes, which typically transmit extracellular signals through G proteins to regulate different cellular processes. Nematode-trapping fungi (NTF) produce adhesive trapping networks under nutrient-starvation conditions and after sensing nematode-derived pheromones, the ascarosides.[1] Recently, fungal ascaroside-sensing GPCRs were first characterized in two studies published in Nature Microbiology.[2,3] It is shown that GPCRs, homologous to yeast glucose receptors, are implicated in ascaroside-sensing and trap formation in the NTF *Arthrobotrys oligospora* and *Arthrobotrys flagrans*. This suggests that glucose might outcompete ascarosides at the receptor. Only when glucose is absent, ascarosides bind to the GPCRs and initiate the predatory behavior. Additionally, Pth11-like GPCRs are also involved in nematode sensing, but the ligands are not ascarosides, suggesting the presence of other nematode-derived molecules that can be perceived by these fungi. Therefore, NTF appear to use different GPCRs to sense distinct nematode-derived signals.

More interestingly, the study by Hu et al. shows that the GPCR protein GprC of *A. flagrans*, not only localizes at the cytoplasmic membrane for the initiation of a canonical GPCR signaling pathway after sensing ascarosides, but also resides at the outer mitochondrial membrane (mtGprC) to boost respiration.[2] This is the first evidence in a lower eukaryote that a GPCR protein has dual localization and function. In the presence of nematodes, GprC interacted with the G-protein alpha subunit GasA at both, the cytoplasmic membrane and mitochondria, but not in the absence of nematodes. Moreover, the interacting signals of split GFP appeared spatially regulated, namely in hyphal tips at mitochondria and in compartments away from the tip at the cytoplasmic membrane. This might be associated with distinct functions of different compartments of one hypha.

*A. flagrans* produces 6-methyl-salicylic acid (6-MSA) and specific volatile molecules to lure nematodes into the traps. On the other hand, arthrosporols and 6-MSA inhibit trap formation when nematodes are absent. Consistently, the presence of nematodes or ascarosides represses the expression of the polyketide synthase gene, *artA*, which is required for the biosynthesis of arthrosporol and 6-MSA.[2] Using a promoter-reporter assay, the authors confirmed that GprC-GasA signaling is essential for the regulation of *artA* in the fungus-nematode interaction. However, interestingly, they also demonstrated that GprC-GasA signaling is independent of the mitogen-activated protein kinase (MAPK) and cAMP-PKA pathways, which are typically downstream of GPCRs. This suggests an alternative GprC-GasA-dependent signaling mechanism for the regulation of the *artA* cluster.

Besides the canonical function of G-protein signaling, they also found increased reactive oxygen species (ROS) levels at the hyphal tip upon nematode induction in wild type but not in the deletion strains of *gprC* and *gasA*, indicating that the activation of GprC-GasA signaling boosts fungal respiration. This was also confirmed by the measurement of the oxygen consumption rates (OCR). Notably, instead of boosting respiration, the cannabinoid receptor CB1 at mitochondria of mouse neuronal cells decreases the respiration rate.[4] It will be interesting to unravel the relationship between fungal mitochondrial GPCR signaling and the respiratory chain.

The *Caenorhabditis elegans* genome encodes multiple GPCRs, which are involved in pheromone sensing for social communication and dauer stage formation.[5] The ascaroside-sensing receptors SRBC64 and SRBC66 in *C. elegans* sense ascaroside #1 that can strongly induce trap production in *A. oligospora*.[1] By sequence comparison, the authors found that the fungal and nematode receptors share similar ascaroside-binding motifs, which was further confirmed by molecular docking of ascarosides on receptors. Furthermore, hybrids of the last three transmembrane helices of GprC and the receptors SRBC64 and SRBC66 re-complemented the lack of GprC in *A. flagrans*. The functional and structural similarities between fungal GprC and nematode GPCRs suggest convergent evolution.

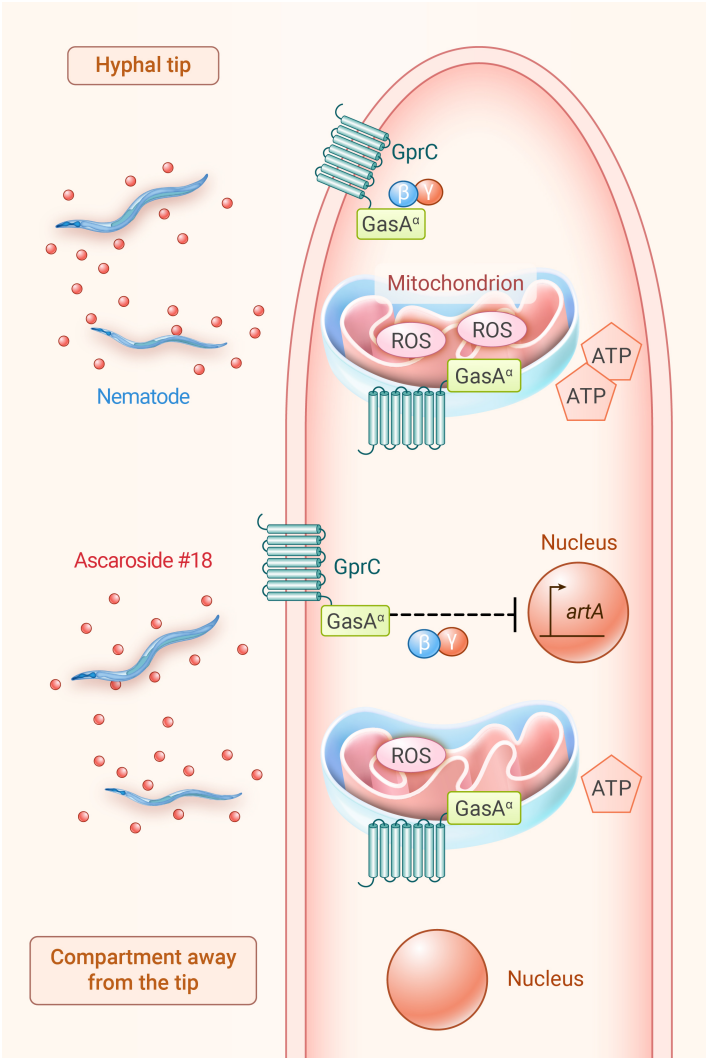


**Figure 1. The schematic model for the dual function of GprC and GasA in the fungus *A. flagrans*.**

Collectively, this study demonstrates that GprC-GasA signaling has dual localization and function in *A. flagrans* for nematode hunting (Figure 1). Bioinformatic analysis of GPCRs of other fungi and nematodes revealed that this property of some GPCRs is a broad phenomenon. How GPCR signaling activates respiration at mitochondria remains to be elucidated in the future.

## REFERENCES


1. Hsueh, Y.P., Mahanti, P., Schroeder, F.C., et al. (2013). Nematode-trapping fungi eavesdrop on nematode pheromones. Curr. Biol. **23**: 83–86. DOI: 10.1016/j.cub.2012.11.035.
2. Hu, X.D., Hoffmann, D.S., Wang, M., et al. (2024). GprC of the nematode-trapping fungus *Arthrobotrys flagrans* activates mitochondria and reprograms fungal cells for nematode hunting. Nat. Microbiol. **9**: 1752–1763. DOI: 10.1038/s41564-024-01731-9.
3. Kuo, C.Y., Tay, R.J., Lin, H.C., et al. (2024). The nematode-trapping fungus *Arthrobotrys oligospora* detects prey pheromones via G protein-coupled receptors. Nat. Microbiol. **9**: 1738–1751. DOI: 10.1038/s41564-024-01679-w.
4. Bénard, G., Massa, F., Puente, N., et al. (2012). Mitochondrial CB1 receptors regulate neuronal energy metabolism. Nat. Neurosci. **15**: 558–564. DOI: 10.1038/nn.3053.
5. Vidal, B., Aghayeva, U., Sun, H., et al. (2018). An atlas of *Caenorhabditis elegans* chemoreceptor expression. PLoS Biol. **16**: e2004218. DOI: 10.1371/journal.pbio.2004218.


## FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (NSFC) (Grant No. 32270053), the Science Fund for Distinguished Young Scholars of Jiangsu Province (Grant No. BK20240091), the Natural Science Foundation of Jiangsu Province (Grant No. BK20241554), the China Postdoctoral Science Foundation (Grant No. 2024M751441) and the Fundamental Research Funds for the Central Universities (Grant No. KYT2024001). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

## AUTHOR CONTRIBUTIONS

Y.L. and Z.Y. conceived of the project. Y. L. and J.Z. drafted the manuscript. Q.S. and Z.Y. reviewed and edited the manuscript.

## DECLARATION OF INTERESTS

The authors declare no competing interests.