OPEN ACCESS

COMMENTARY

MSB2-mediated pheromone pathway is activated by herbicide adjuvant to regulate plasma membrane integrity

Yang Hao,[1,2] Xuguang Yang,[1,2] Mingwen Zhao,[1] and Xiaodi Hu[1,*]

[1]Key Laboratory of Agricultural Environmental Microbiology, Ministry of Agriculture Microbiology Department, College of Life Sciences, Nanjing Agricultural University, Nanjing 210095, China

[2]These authors contributed equally

*Correspondence: huxiaodi@njau.edu.cn

Received: April 27, 2025; Accepted: July 21, 2025; Published Online: July 25, 2025; https://doi.org/10.59717/j.xinn-life.2025.100149

Citation: Hao Y., Yang X., Zhao M., et al. (2025). MSB2-mediated pheromone pathway is activated by herbicide adjuvant to regulate plasma membrane integrity. *The Innovation Life* **3**:100149.

Glyphosate-based herbicides (GBHs) combine glyphosate with adjuvants to enhance efficacy.[1] Despite their agricultural ubiquity, the extensive use of GBHs raises concerns about their ecological impact on non-target soil microbiota. Emerging evidence indicates that while certain fungi metabolize glyphosate, GBH exposure disrupts fungal community dynamics in soils.[2] Notably, commercial GBH formulations exhibit greater fungal toxicity compared to isolated glyphosate,[3,4] suggesting non-active ingredients contribute substantially to these adverse effects. The molecular drivers of this formulation-dependent fungal impairment remain poorly characterized.

In a recent study, Pu et. al uncovered a previously unrecognized mechanism by which the herbicide adjuvant Triton CG-110 exerts its toxicity on *Trichoderma* species.[5] They found that R450 significantly impaired hyphal growth and conidial germination, and further identified Triton CG-110, not glyphosate itself, as the major toxic agent (Figure. 1). Through a series of elegant experiments, they demonstrated that Triton CG-110 disrupts nitrogen uptake by compromising plasma membrane integrity, leading to the induction of the aspartyl protease gene *yps1*. The cleavage of the signaling mucin MSB2 by YPS1 activates the TMK1 pheromone pathway, resulting in the phosphorylation of TMK1 and its interaction with the transcription factor STE12. This, in turn, regulates genes involved in ergosterol biosynthesis, a critical process for maintaining membrane fluidity and stability.

Although glyphosate is traditionally thought to inhibit fungal growth by targeting the EPSPS enzyme, the authors provide evidence that challenges this view. The authors found that glyphosate herbicide toxicity in fungi may depend more on its adjuvants. Interestingly, the adjuvant Triton CG-110 itself promoted glyphosate uptake while restricting nitrogen uptake. Experimental data demonstrated that the addition of Triton CG-110 increased intracellular glyphosate levels in *Trichoderma* mycelium by nearly tenfold compared to glyphosate alone, accompanied by a significant rise in hydrogen peroxide content. Although precise formulation proportions of Triton CG-110 in commercial formulations are not publicly available, this study showed that neither R450 nor glyphosate alone at 0.075% (v/v) inhibited *Trichoderma* hyphal growth while Triton CG-110 alone did, suggesting the concentration threshold of the adjuvant matters for its toxicity.

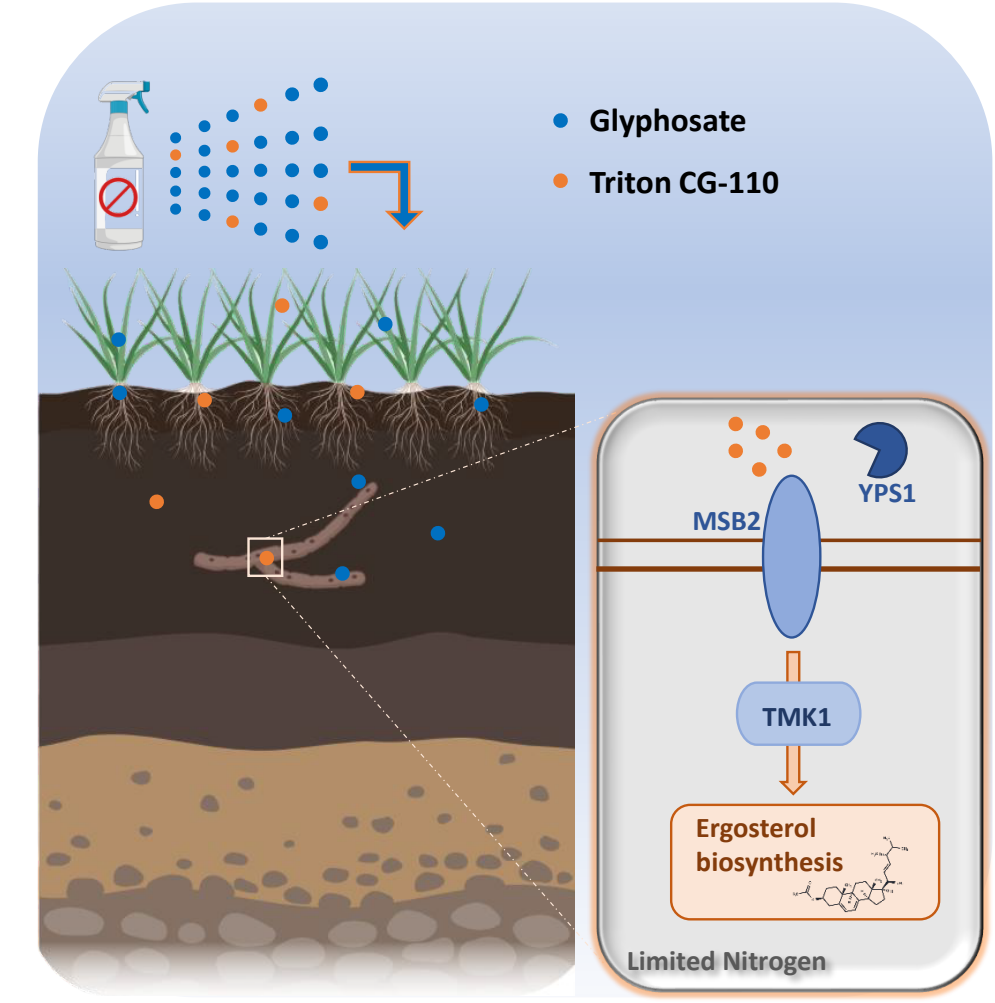

Figure 1. The herbicide adjuvant Triton CG-110 exerts its toxicity on *Trichoderma* species via modulating the MSB2 signaling pathway.

To further elucidate the mechanism by which Triton CG-110 inhibits *Trichoderma* growth, the authors performed transcriptomic analysis and found a significant enrichment of genes related to sterol biosynthesis, which is essential for maintaining membrane fluidity and stability in eukaryotic cells. It was also showed that *erg* genes were activated upon Triton CG-110 treatment in a TMK1- and STE12-dependent manner. These findings reveal a novel mechanism by which membrane stress is counteracted through coordinated transcriptional control of lipid biosynthesis. Importantly, the fungal pheromone signaling pathway contributes to membrane homeostasis. Besides for the enhanced sterol biosynthesis, how Triton CG-110 inhibits fungal growth and damages the cell membrane, needs further elucidation.

The authors clearly outline a signal transduction cascade where MSB2, acting as a receptor of Triton CG-110, initiates the activation of the TMK1 pheromone pathway, eventually promoting the sterol biosynthesis. The shedding of MSB2 extracellular domain was conducted by an Yps1p homolog induced by the changed nitrogen uptake. However, if the nitrogen limitation caused by Triton CG-110 is the ultimate reason to induce the shedding and then the sterol biosynthesis, how the *erg*

genes and fungal growth respond to lack of nitrogen, is yet unknown.

Collectively, this study reveals that Triton CG-110 disrupts fungal membrane integrity and nitrogen metabolism, activating the MSB2-mediated pheromone pathway to drive adaptive ergosterol biosynthesis. This is the first evidence that the pheromone pathway is implicated in ergosterol biosynthesis and plasma membrane integrity. Further investigation into the specific mechanisms by which Triton CG-110 disrupts nitrogen uptake could provide valuable insights into fungal nutrient acquisition. And exploring the potential for other herbicide adjuvants to elicit similar responses in different fungal species could also help in developing more environmentally friendly herbicide formulations. Importantly, understanding the molecular basis of Triton CG-110 toxicity raises the possibility of identifying strategies to mitigate its harmful effects, such as by screening for inhibitors that block its membrane-disrupting activity or by designing safer surfactant alternatives. These findings also highlight the environmental risks of herbicide additives, suggesting the need to reassess their hidden effects on soil microbes.

REFERENCES

1. de Araújo-Ramos A.T., Passoni M.T., Romano M. A. , et al. (2021). Controversies on endocrine and reproductive effects of glyphosate and glyphosate-based herbicides: A mini-review. *Front. Endocrinol.* **12**:627210. DOI:10.3389/fendo.2021.627210
2. Vazquez M.B., Moreno M.V., Amodeo M.R., et al. (2021). Effects of glyphosate on soil fungal communities: A field study. *Rev. Argent. Microbiol.* **4**:349–358. DOI:10.1016/j.ram.2020.10.005
3. Mesnage R., Oestreicher N., Poirier F., et al. (2020). Transcriptome profiling of the fungus *Aspergillus nidulans* exposed to a commercial glyphosate-based herbicide under conditions of apparent herbicide tolerance. *Environ. Res.* **182**:109116. DOI:10.1016/j.envres.2020.109116
4. Nicolas V., Oestreicher N. and Vélot C. (2016). Multiple effects of a commercial Roundup® formulation on the soil filamentous fungus *Aspergillus nidulans* at low doses: evidence of an unexpected impact on energetic metabolism. *Environ. Sci. Pollut. Res.* **23**:14393–14404 . DOI:10.1007/s11356-016-6596-2
5. Pu J.W., Long X.J., Li Y.F., et al. (2025). MSB2-activated pheromone pathway regulates fungal plasma membrane integrity in response to herbicide adjuvant. *Sci. Adv.***11**:eadt8715. DOI:10.1126/sciadv.adt8715

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Fundamental Research Funds for the Central Universities (Grant No. ZJ24195014). The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Y.H. and X.H. conceived of the project. Y.H. and X.Y. drafted the manuscript. M.Z. and X.H. reviewed and edited the manuscript. All authors contributed to the manuscript and approved the final version. All authors contributed equally.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.