OPEN ACCESS

Microbiology COMMENTARY

How ISWI-type chromatin remodelers drive pathogen virulence

Guangfei Tang[1] **and Wende Liu**[1,*]

[1]State Key Laboratory for Biology of Plant Diseases and Insect Pests, Institute of Plant Protection, Chinese Academy of Agricultural Sciences, Beijing 100193, China

*Correspondence: liuwende@caas.cn

Received: October 23, 2025; Accepted: January 4, 2026; Published Online: January 7, 2026; https://doi.org/10.59717/j.xinn-life.2026.100188

Citation: Tang G. and Liu W. (2026). How ISWI-type chromatin remodelers drive pathogen virulence. *The Innovation Life* **4**:100188.

ATP-dependent chromatin remodelers use energy from ATP hydrolysis to reposition nucleosomes, thereby regulating DNA accessibility to transcription factors and RNA polymerase. These chromatin remodeling complexes fall into distinct, well-defined families, including switch/sucrose nonfermentable (SWI/SNF); imitation switch (ISWI); chromodomain, helicase, DNA-binding (CHD); and inositol requiring 80 (INO80).[1] Among these remodelers, the ISWI family has been shown to participate in nucleosome assembly and chromatin organization near promoters, which are critical for transcriptional regulation.[2]

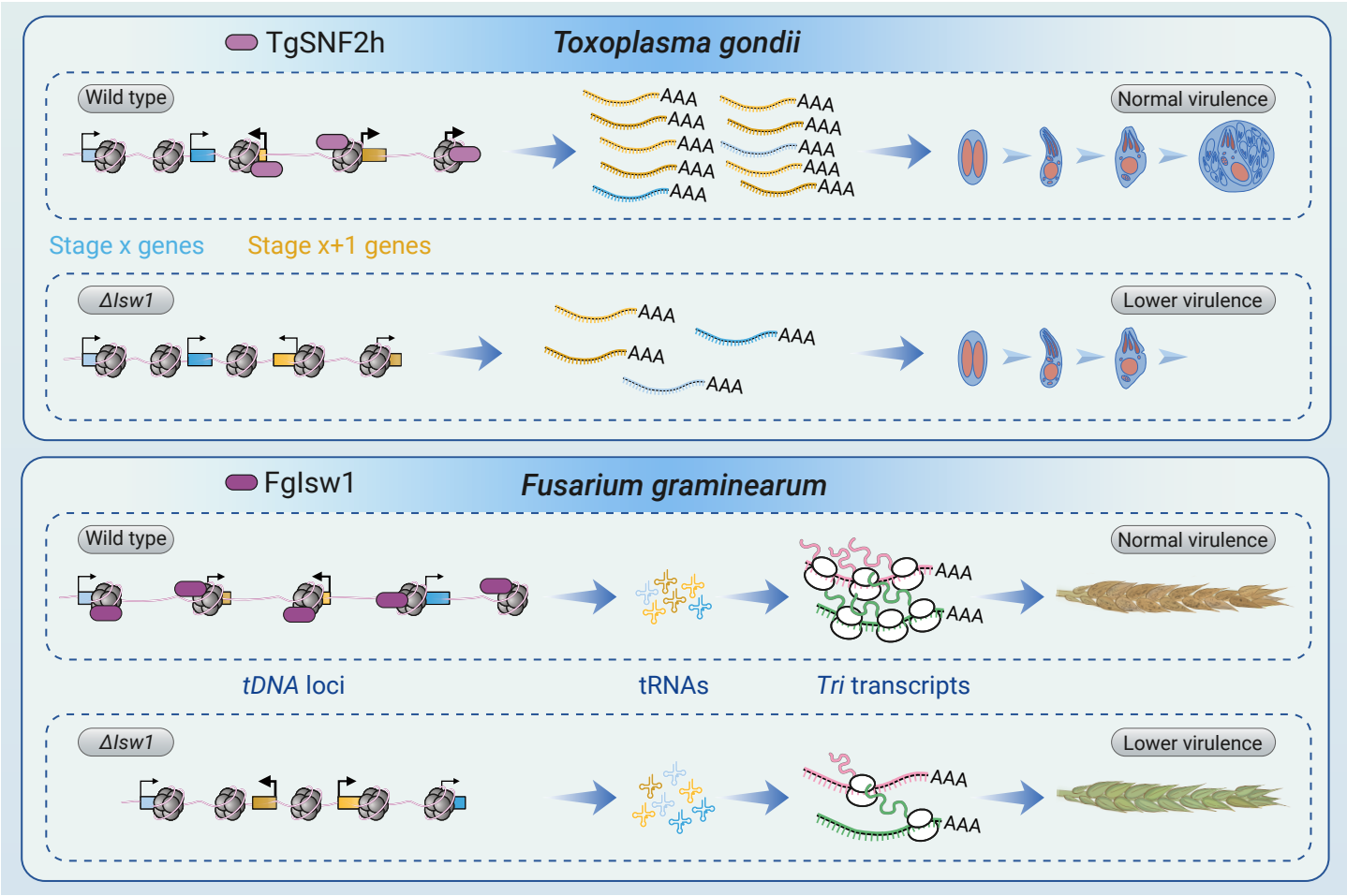

Figure 1. ISWI-Mediated chromatin regulation controls pathogen virulence Diagram illustrating chromatin organization and virulence outcomes in wild-type and ISWI-deficient (Δ*Isw1*) pathogenic strains *Toxoplasma gondii* and *Fusarium graminearum*. In wild-type pathogens, the ISWI-type chromatin remodeler maintains ordered chromatin structure by regulating nucleosome positioning and spacing. By contrast, deletion of *ISWI* (Δ*Isw1*) leads to abnormal chromatin organization, characterized by disrupted nucleosome phasing and spacing. This structural perturbation impairs critical pathways (e.g., transcriptional insulation or translation of virulence factors), resulting in lower pathogen virulence.

ISWI-type chromatin remodelers function in diverse multi-subunit complexes and are evolutionarily conserved from yeast to humans. Within the cell, ISWI homologs interact with a wide range of accessory proteins, which in turn regulate the subcellular localization and functional activity of distinct ISWI-containing complexes.[3] However, the composition and functional roles of ISWI-containing complexes in pathogens remain poorly understood. Recent studies on the animal pathogen *Toxoplasma gondii* [4] and the plant pathogen *Fusarium graminearum* [5] reveal striking mechanistic similarities in how their respective ISWI members support pathogen virulence and adaptability. Despite targeting distinct biological pathways, both ISWI homologs rely on analogous nucleosome regulation mechanism to maintain genome function, highlighting a core mechanism by which ISWI-type remodelers support pathogen success.

A foundational and shared mechanism between the ISWI proteins of *Toxoplasma gondii* and *Fusarium graminearum* is their role as regulators of nucleosome organization through ATP-dependent chromatin remodeling. In *T. gondii*, the ISWI homolog TgSNF2h forms a stable core complex with the transcription factor AP2VIII-2 and the scaffold protein TgRFTS, a partnership critical for its chromatin-targeting function. Deletion of *TgSNF2h* or the gene encoding its essential cofactor TgRFTS disrupts nucleosome spacing, increasing the nucleosome repeat length by about 2 bp and causing widespread defects in nucleosome phasing, particularly at gene promoters. This structural perturbation diminished chromatin accessibility, directly impairing the binding of key regulatory factors, such as the epigenetic repressor Microrchidia (MORC), and leading to dysregulated expression of stage-specific genes critical for parasite development. Similarly, in *F. graminearum*, the ISWI homolog FgIsw1 governs nucleosome dynamics across the genome through ATP-dependent remodeling. Deletion of *FgIsw1* triggered a significant

increase in global nucleosome repeat length, from ~181 bp in the wild-type strain to ~199 bp in the mutants, and disrupted nucleosome occupancy at specific loci, most notably at loci from which transfer RNA (tRNA) is transcribed (tDNAs). Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq) and micrococcal nuclease quantitative PCR (MNase-qPCR) experiments confirmed that FgIsw1 is essential for maintaining proper nucleosome phasing at these tDNA loci, ensuring their accessibility for transcription. These findings reveal that ISWI-mediated control of nucleosome arrangement is not merely a housekeeping function but is required for the proper regulation of genome organization in these two pathogens (Figure 1).

Another mechanism shared by these two pathogens is the locus-specific targeting of ISWI remodelers to regulate specialized biological pathways. In *T. gondii*, chromatin immunoprecipitation sequencing (ChIP-seq) analysis revealed that TgSNF2h preferentially accumulates at the transcription start sites (TSSs) of genes, where it acts as a transcriptional insulator. By maintaining precise nucleosome organization at these loci, TgSNF2h ensures the selective recruitment of MORC, preventing any ectopic expression of stage-restricted genes (e.g. those specific to the merozoite, the invasive form specific to the final host) and preserving the fidelity of transcriptional programs specific to the tachyzoite, the invasive form specific to the intermediate host. This insulation is critical for maintaining the identity of each parasitic stage during acute infection. In *F. graminearum*, FgIsw1 binds specifically to tDNA loci, as validated by ChIP-seq and electrophoretic mobility shift assays (EMSAs), confirming direct physical interaction with tDNA segments. By stabilizing nucleosome phasing at these loci, FgIsw1 supports efficient tRNA production, ensuring a balanced tRNA pool for protein synthesis. This locus-specific regulation safeguards downstream programs—transcriptional insulation for *T. gondii* development and tRNA pool homeostasis for *F. graminearum* translation—highlighting how the loci targeted by ISWI have shifted during evolution to meet the specific needs of various pathogens.

Both studies further demonstrate that the disruption of ISWI-mediated nucleosome regulation triggers cascading functional defects that directly impair virulence. In *T. gondii*, the loss of TgSNF2h function diminished MORC binding at TSSs by over 90% at key developmental gene clusters, leading to the misexpression of stage-specific genes, impaired tachyzoite proliferation, and significant attenuation of virulence in infection models. In *F. graminearum*, the deletion of *FgIsw1* disrupted nucleosome occupancy at tDNA loci, leading to dysregulated transcript levels for ~58% of tRNAs derived from FgIsw1-enriched tDNA loci. Although transcriptome deep sequencing (RNA-seq) analysis showed that the transcript levels of deoxynivalenol (DON) biosynthesis genes (Tri genes) remained unaffected, the resulting tRNA deficiency blocked the translation of Tri proteins that are critical for DON production. This translation block abolished DON biosynthesis and decreased fungal virulence toward wheat (*Triticum aestivum*) by over 80%, as measured by disease index scoring. In both cases, the loss of ISWI function altered chromatin structure and specifically disrupted the biological pathways that underpin pathogen success (Figure 1).

These studies lay critical groundwork for future investigations into ISWI remodelers in pathogens. One key question is how environmental cues (e.g., host-derived signals for *T. gondii*, nutrient availability for *F. graminearum*) modulate the activity or localization of ISWI-containing complexes. Uncovering their upstream regulators could reveal how pathogens sense and adjust their chromatin landscapes to changing niches. Additionally, multiple ISWI complexes may not only perform sequence-directed remodeling mediated by individual accessory subunits such as those responsible for histone modification or transcription factors, but also exert global regulatory functions. Further structural and biochemical studies are needed to define the molecular determinants that enable the TgSNF2h–AP2VIII-2–TgRFTS and FgIsw1 complexes to recognize their target sites (e.g., tDNA loci or TSSs) and execute nucleosome remodeling with such precision.

Given their essential roles in virulence, ISWI-type remodelers represent promising targets for new antimicrobial strategies. High-throughput screening for compounds that disrupt the ATPase activity or complex formation of TgSNF2h or FgIsw1 may yield specific interventions against toxoplasmosis and Fusarium head blight, respectively. Additionally, comparative analysis of ISWI function in these pathogens could help identify conserved vunnerabilities in their chromatin regulatory machinery, enabling the development of broad-spectrum therapeutics. In summary, the studies on *T. gondii* and *F. graminearum* highlight ISWI-type chromatin remodelers as conserved masters of pathogenic acclimation, linking nucleosome organization to virulence through shared mechanisms of nucleosome regulation, locus-specific targeting, and functional coupling to critical pathways. Their findings open new avenues for understanding and targeting pathogen biology at the epigenetic level.

REFERENCES

1. Hu P., Sun J., Sun H., et al. (2025). Subnucleosome preference of human chromatin remodeller SMARCAD1. *Nature* **644**:818–826. DOI:10.1038/s41586-025-09100-0
2. Sia Y., Pan H., Chen K., et al. (2025). Structural insights into chromatin remodeling by ISWI during active ATP hydrolysis. *Science* **388**:eadu5654. DOI:10.1126/science.adu5654
3. Kamei M., Ameri A. J., Ferraro A. R., et al. (2021). IMITATION SWITCH is required for normal chromatin structure and gene repression in PRC2 target domains. *Proc. Natl. Acad. Sci.* **118**:e2010003118. DOI:10.1073/pnas.2010003118
4. Pachano B., Farhat D. C., Shahinas M., et al. (2025). An ISWI-related chromatin remodeller regulates stage-specific gene expression in Toxoplasma gondii. *Nat. Microbiol.* **10**:1156–1170. DOI:10.1038/s41564-025-01980-2
5. Wang J., Zhang Y., Wang J., et al. (2025). Fungal chromatin remodeler Isw1 modulates translation via regulating tRNA transcription. *Nucleic Acids Res.* **53**:gkaf225. DOI:10.1093/nar/gkaf225

FUNDING AND ACKNOWLEDGMENTS

This work was funded by the Youth Innovation Program of the Chinese Academy of Agricultural Sciences (Y2023QC04), the National Natural Science Foundation of China (32302329, 32570235), and the Agricultural Science and Technology Innovation Program (ASTIP). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

G.T. and W.L. wrote the manuscript. G.T. and W.L. conceived the project. G.T. designed and drew Figure 1 in the manuscript. W.L., edited the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.