Trends in
Parasitology

CellPress

Forum

# Alteration of host gene and protein expression by manipulative parasites

Chen-Hua Li [1] and
Robert Poulin [1,*]

**Host manipulation mechanisms remain poorly understood. We summarize recent studies using -omics approaches (transcriptomics, proteomics) to explore alteration in gene expression in hosts infected by manipulative parasites. To guide future research, we highlight the common pattern of neuromodulation, as well as other diverse combinations of functions targeted across different host manipulation systems.**

## Probing host manipulation mechanisms via transcriptomic and proteomic tools

The phenomenon by which some parasites manipulate the phenotype of their host to increase their own transmission has been reported across a wide range of parasite taxa [1]. Interestingly, modifications in the host phenotype induced by parasites often show remarkable similarities, even across widely disparate taxa of hosts and parasites, suggesting the possibility of convergence in manipulation among unrelated parasites facing similar transmission challenges. However, whether these similarities at the phenotypic level are produced by similar mechanisms remains mostly unknown. Indeed, despite decades of research, the mechanisms underlying these phenomena are still poorly understood [2]. In recent years, with the development and the broader application of transcriptomic and proteomic tools [3], research has shifted towards examining how gene expression levels in both the parasite and the host might underpin host manipulation [4,5]. Transcriptomic studies focus on sequencing mRNA and can be used to measure and compare gene expression levels in both host and parasite during and before/after the host manipulation event, identifying differentially expressed genes likely related to host manipulation [6]. Proteomic analysis provides information at the gene product (protein) level, reflecting the biological activity and downstream effects of infection more directly [6]. Due to post-transcriptional and post-translational regulation mechanisms, mRNA expression does not directly correlate with protein abundance on a one-to-one basis [7], therefore the two approaches provide comparable, but not identical, windows into gene expression changes. Both transcriptomic and proteomic studies enhance our understanding of the molecular mechanisms underlying host manipulation and help to identify key candidate genes involved in parasitic manipulation [4].

Here, we extract information from the host manipulation systems where transcriptomic and/or proteomic studies have been conducted over the past 20 years (Table S1 in the supplemental information online) to identify whether there are common molecular patterns underlying host manipulation. The systems investigated to date include parasites from ten eukaryotic phyla plus viruses that manipulate hosts from three phyla, with arthropods being the most common host group. Our goal is to highlight universal molecular mechanisms, if any, used by most or all parasites as well as idiosyncratic, taxon-specific ones, to guide future research into this fascinating phenomenon.

## A common role for neuromodulation in host manipulation

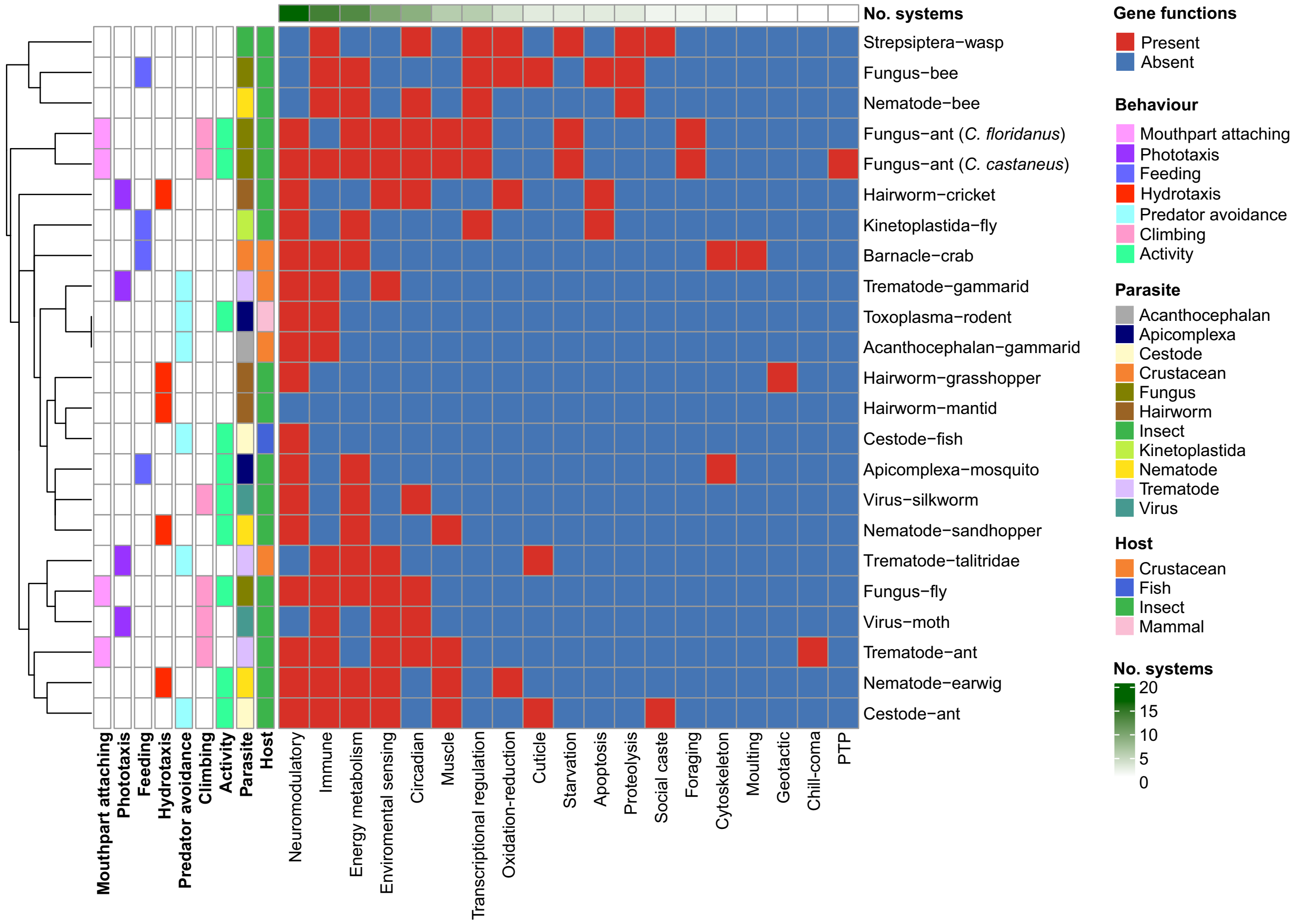
Neuromodulation appears to be a common method used by parasites to modify host behavior. Differential expression of neuromodulation-related genes and/or proteins was identified in 17 out of the 23 systems in which the host was investigated (Figure 1), and in eight out of the nine systems in which the parasite was also examined (Figure 2). These neuromodulation-related genes and/or proteins include those involved in neurotransmitter synthesis or receptors, synaptic function, signal transduction, and central nervous system (CNS) growth and functioning.

Many of the host manipulation systems involve a combination of phenotypic changes (as summarized in Figure S1 in the supplemental information online). For example, ant host activity, color, lifespan, and task performance are all altered during the manipulation by the cestode *Anomotenia brevis* [8]. Since neuromodulation is more upstream compared with some other functional changes – such as muscle action or cuticle pigmentation – it is conceivable that manipulation through the CNS is more likely to underpin multiple aspects of phenotypic changes. This also means that not all gene functions summarized are equally critical in each system, as the alteration of some gene functions could merely be secondary consequences of changes induced in upstream genes.

In addition to neuromodulation, immune, energy metabolism, and environmental sensing related genes/proteins are also frequently differentially expressed in the host among the various systems (Figure 1). Regarding the differentially expressed genes/proteins in the parasite, in addition to neuromodulation, environmental sensing, proteolysis, and transcriptional regulation were shared among three or four systems out of the nine systems (Figure 2).

## Connecting gene/protein expression to behavior?

We highlight some common phenotypic changes in the left panel of Figure 1. Activity seems to be associated with neuromodulation and energy metabolism. In the ten systems in which activity level was identified as being altered (including



Trends in Parasitology

Figure 1. Molecular strings pulled by the parasite. Host differentially expressed gene functions identified (indicated as 'present'; red color) or not (indicated as 'absent'; blue color) at the time of host manipulation in various systems. Rows represent different parasite–host systems, while columns represent different gene functions. The host and parasite groups are summarized on the left panel, together with the observed behavior manipulation. The tree on the left of the figure represents the similarity between different systems based on the shared presence or absence of differentially expressed gene functions. The total number of systems reporting alterations in each gene function is summarized at the top. Abbreviations: *C. floridanus*, *Camponotus floridanus*; *C. castaneus*, *Camponotus castaneus*; PTP, protein tyrosine phosphatase.

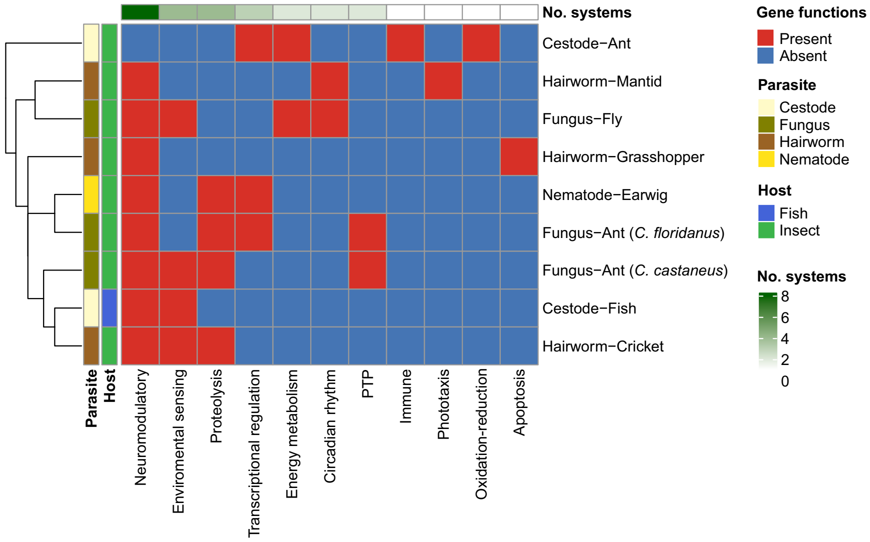
both hyperactivity and inactivity) during host manipulation, neuromodulation- and energy-metabolism-related genes/proteins were differentially expressed in ten and eight systems, respectively.

Similarly, when feeding behavior was identified as part of the altered phenotype, energy metabolism genes/proteins were differentially expressed (Figure 1). In the four systems in which host feeding behavior was altered by parasites ranging from fungus, Kinetoplastida, barnacle, and Apicomplexa, metabolism genes/proteins were all found differentially expressed. This is expected, though the direction of causality still needs to be determined – whether the parasite altered host metabolism, leading to increased feeding behavior, or the parasite altered host feeding behavior, which then changed host metabolism.

Climbing and mouthpart-attaching behavior in insect hosts are associated with circadian-rhythm-related genes, whereas phototaxis appears to be related to environmental sensing (Figure 1). However, hydrotaxis does not have an obvious association with specific gene function groups. This could indicate that phototaxis is a primary phenotype, while hydrotaxis may result from one or a combination of other phenotypes (see later).

## What can gene expression tell us about phenotypic host manipulation?

Some of the phenotypic changes could be related to each other. For example,



Trends in Parasitology

Figure 2. Changes happening within the puppeteer itself. Parasite differentially expressed gene functions identified (indicated as 'present'; red color) or not (indicated as 'absent'; blue color) at the time of host manipulation in various systems. Rows represent different parasite–host systems, while columns represent different gene functions. The host and parasite groups are summarized on the left panel. The tree on the left of the figure represents the similarity between different systems based on the shared presence or absence of differentially expressed gene functions. The total number of systems reporting alterations in each gene function is summarized at the top. Abbreviations: *C. floridanus*, *Camponotus floridanus*; *C. castaneus*, *Camponotus castaneus*; PTP, protein tyrosine phosphatase.

predator avoidance could be linked to activity level. In some cases, increased movement raises the likelihood of being eaten (e.g., *Schistocephalus*-infected fish, *Toxoplasma*-infected rodent), while in other cases, the opposite is true (e.g., *Anomotenia*-infected ant, *Levinseniella*-infected amphipod). Similarly, terms such as climbing, phototaxis, and geotaxis can all be used by different researchers to describe the same thing, relating to activity along a vertical axis. We rely on the terminology used by the authors of the original studies.

Studying the underlying mechanisms can help us to better describe phenotypic changes in hosts and differentiate between primary changes and secondary consequences. For example, in the hairworm–cricket system, it has long been known that the behavior alteration involved water-seeking [9]. The proteomic study conducted on this system found that vison-related proteins from family CRAL_TRIO were differentially expressed in the cricket during the manipulation stage [9], leading to the subsequent testing and confirmation of positive phototaxis behavior in the infected cricket [10]. The phototaxis behavior might contribute to the water-seeking behavior, as water reflects more natural light at night; however, the genes manipulated are not directly linked to hydrophilia.

## Convergence versus system-specific mechanisms

Overall, no clear pattern of convergence was identified. Different systems appear to involve distinct combinations of various gene functions involved in host manipulation. However, it is noteworthy that more gene functions appear to be altered by parasitism in social insect hosts (ants, bees, wasps; order Hymenoptera) than in other host taxa. This phylogenetic trend may reflect that host–parasite associations involving hymenopterans are generally more ancient, that these hosts are less resistant to genetic manipulation, or some other factor restricted to these insects. This observation certainly warrants further investigation.

Proteins from the Wnt family, which are related to CNS development, seem to be important in the host manipulation induced in insects by hairworms, as all proteomic studies on these parasites found proteins from Wnt family differentially expressed in both the host and the parasite [11]. Altered expression levels of proteins from the CRAL_TRIO family, which are related to vision processing, have been identified in both the hairworm–cricket system [9], and the trematode–gammarid system [10], but not in other systems in which phototaxis is altered.

Different parasite taxa may also use different genetic mechanisms to achieve the same manipulation. For example, both *Strepsiptera* infection and *Anomotaenia* infection cause an extended lifespan in wasps and ants, respectively. The former exploits host caste plasticity [12], while the latter does not [13].

There is one out of the 23 systems (the hairworm–mantid system) in which none of the functions was identified by the authors as being differentially expressed in the host; however, in the parasite itself, neuromodulation-, phototaxis-, and circadian-related genes were differentially expressed (Figure 2) [14]. This appears to be a system in which only changes in gene expression in the parasite result in host manipulation. In addition, the authors found evidence of horizontal gene transfer in the parasite's genome. By contrast, all other systems investigated to date do show at least some changes in host gene expression (Figure 1).

## The future promise of -omics research

Studies of the mechanisms underlying host manipulation that apply -omics approaches are still in their infancy, and future advances will no doubt push our understanding forward. Many genes or proteins from various systems identified as highly differentially expressed and potentially contributing to host manipulation are unannotated and unknown [8,9,14]. Further studies focusing on these novel genes and proteins, including their identification and annotation through techniques like structural prediction or knockout, could reveal new insight into how parasites achieve host manipulation. Additionally, in most host-manipulation mechanism studies, associations have been proposed between genes or proteins and particular changes in host phenotypic traits, but causality still needs to be established.

This is the first attempt to summarize the information yielded by transcriptomic and proteomic studies on host manipulation mechanisms. We aimed to find common patterns in host manipulation mechanisms among the limited number of available studies. Based on these few studies, no clear convergence pattern can be seen across the many host and parasite taxa involved. Nevertheless, some patterns might emerge with further research. For example, lifespan alteration could be related to changes in metabolism. Although only two systems reported lifespan changes, both systems also found changes in metabolism gene/protein expression. However, metabolism gene/protein expression changes were also found in 11 of the other 21 systems. More studies are needed to confirm the association between lifespan and metabolism. We propose that the search for evolutionary convergence in host manipulation strategies among unrelated parasite lineages should focus on underlying molecular mechanisms rather than phenotype-level changes, as the latter may manifest differently in different host taxa even if they are induced by similar gene-level processes. As the costs of transcriptomics and proteomics decrease and their accessibility increases, and as more and more genomic resources become available for non-model parasite species, we anticipate that these tools will allow a holistic systems biology approach to unravel the mechanistic basis of host manipulation by parasites.

## Acknowledgments

We thank Pengfei Kong for early discussions about this article.

## Declaration of interests

The authors have no conflict of interests to declare.

## Supplemental information

Supplemental information associated with this article can be found online at https://doi.org/10.1016/j.pt.2024.11.014

[1]Department of Zoology, University of Otago, PO Box 56, Dunedin, New Zealand

*Correspondence:
robert.poulin@otago.ac.nz (R. Poulin).

https://doi.org/10.1016/j.pt.2024.11.014

## References

1. Hughes, D.P. and Libersat, F. (2019) Parasite manipulation of host behavior. *Curr. Biol.* 29, R45–R47
2. Herbison, R.E.H. (2017) Lessons in mind control: trends in research on the molecular mechanisms behind parasite-host behavioral manipulation. *Front. Ecol. Evol.* 5, Published online September 11, 2017. https://doi.org/10.3389/fevo.2017.00102
3. Duraisingh, M.T. *et al.* (2023) A rising tide of parasite transcriptomics propels pathogen biology. *PLoS Biol.* 21, e3001997
4. Hughes, D.P. and Libersat, F. (2018) Neuroparasitology of parasite–insect associations. *Annu. Rev. Entomol.* 63, 471–487
5. Biron, D.G. and Loxdale, H.D. (2013) Host–parasite molecular cross-talk during the manipulative process of a host by its parasite. *J. Exp. Biol.* 216, 148–160
6. Hughes, D. (2013) Pathways to understanding the extended phenotype of parasites in their hosts. *J. Exp. Biol.* 216, 142–147
7. Canzler, S. *et al.* (2020) Prospects and challenges of multi-omics data integration in toxicology. *Arch. Toxicol.* 94, 371–388
8. Hartke, J. *et al.* (2023) Long live the host! Proteomic analysis reveals possible strategies for parasitic manipulation of its social host. *Mol. Ecol.* 32, 5877–5889
9. Biron, D.G. *et al.* (2006) 'Suicide' of crickets harbouring hairworms: a proteomics investigation. *Insect Mol. Biol.* 15, 731–742
10. Ponton, F. *et al.* (2011) Water-seeking behavior in worm-infected crickets and reversibility of parasitic manipulation. *Behav. Ecol.* 22, 392–400
11. Herbison, R. *et al.* (2019) A molecular war: convergent and ontogenetic evidence for adaptive host manipulation in related parasites infecting divergent hosts. *Proc. Biol. Sci.* 286, 20191827
12. Geffre, A.C. *et al.* (2017) Transcriptomics of an extended phenotype: parasite manipulation of wasp social behaviour shifts expression of caste-related genes. *Proc. Biol. Sci.* 284, 20170029
13. Stoldt, M. *et al.* (2021) Parasite presence induces gene expression changes in an ant host related to immunity and longevity. *Genes (Basel)* 12, 95
14. Berger, C.S. *et al.* (2021) The parasite *Schistocephalus solidus* secretes proteins with putative host manipulation functions. *Parasit. Vectors* 14, 436