



HAL
open science

Holobiont–Holobiont Interactions: Redefining Host–Parasite Interactions

Nolwenn M. Dheilly

► **To cite this version:**

Nolwenn M. Dheilly. Holobiont–Holobiont Interactions: Redefining Host–Parasite Interactions. PLoS Pathogens, 2014, 10 (7), pp.e1004093. 10.1371/journal.ppat.1004093 . hal-03129885

HAL Id: hal-03129885

<https://hal.umontpellier.fr/hal-03129885v1>

Submitted on 3 Feb 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Opinion

Holobiont–Holobiont Interactions: Redefining Host–Parasite Interactions

Nolwenn Marie Dheilly*

MIVEGEC (UMR CNRS/IRD/UM1/UM2 5290), Montpellier, France

The term holobiont (Greek, from *holos*, whole; *bios*, life; *-ont*, to be; whole unit of life) describes a long-term physical association between different living organisms [1]. Theoretically, this definition encompasses all symbiotic associations (along the mutualism–parasitism continuum) spanning all taxa. However, in most cases, the term holobiont is restricted to the host and its associated mutualistic symbionts. The hologenome theory of evolution considers that the holobiont is the unit under natural selection in evolution [2,3]. I argue that this opens new perspectives on the study of host–parasite interactions. Evidence suggests that all of the diverse microorganisms associated with the host and parasite play a part in the coevolution. This new paradigm has the potential to impact our comprehension of the development and evolution of disease.

It has been established in different model species that immune system maturation requires the presence of mutualistic bacteria [4–6]. The tsetse fly *Glossina moritans* carries an obligate mutualist, the bacteria *Wigglesworthia glossinidia*, which is necessary for maturation of the immune system during development [6,7]. In vertebrates, species-specific gut bacteria are necessary for the maturation and the maintenance of a healthy immune system [4,8–13]. Organisms are associated with a great variety of microorganisms, including viruses and unicellular eukaryotes, and we are starting to realize that they also play an important role in shaping a healthy immune system [14–16].

Thus, symbionts indirectly protect the host against various pathogens via immune activation (Figure 1A, 1B). In some cases, even parasites improve the fitness of their host; this process is called conditional mutualism [17]. For example, the hepatitis G virus limits the progression of HIV to AIDS [18,19], the hepatitis A virus suppresses infection by the hepatitis C virus [20], and the murine cytomegalovirus protects mice against infection by *Listeria monocytogenes* and *Yersinia pestis* [21].

Host-associated microorganisms also contribute directly to the defense against pathogens (Figure 1C). The bacteriophage

carried by the bacteria *Halmitonella defensa*, *Acyrtosiphon pisum* secondary endosymbiont (APSE) is a conditional mutualist of the pea aphid *A. pisum* [22–24]. It encodes toxins targeting the developing larva of the parasitic wasp *Aphidius ervi* [25,26]. Human gut bacteria directly antagonize bacterial pathogens by producing antibacterial factors, by competing for elements necessary for pathogen growth (competitive exclusion), and by limiting their adhesion to host cells [9]. In addition, mucus-associated bacteriophages participate in the first line of defense against bacteria in various species, from cnidarians to mammals [27]. Thus, the “holo-immunome” must be studied for a comprehensive understanding of host resistance to infections.

Host-associated microorganisms are also affected by parasitosis (Figure 1D). In the coral *Oculina patagonica*, infection by *Vibrio shiloi* induces coral bleaching by directly attacking the photosynthetic microalgal endosymbionts [28,29]. Symbiotic bacterial communities associated with the lichen *Solorina crocea* are also affected by the fungal parasite *Rhagadostoma lichenicola* [30]. HIV and SIV infections are frequently associated with gastrointestinal disorders that can be explained by an alteration of the gut microbial community [31–33]. As discussed above, such disruptions of host–symbiont interactions favor pathogenesis, therefore indirectly participating in the disease.

Finally, parasites are also associated with microorganisms that will directly benefit from an improved fitness of their parasitic host. These symbionts can directly participate in the disease caused by the

parasite (Figure 1E). For instance, parasitoid wasps of the Ichneumonidae and Braconidae families have independently evolved mutual associations with DNA or RNA viruses (unpublished work) and play an essential role in the parasite’s success and evolution [34–35]. Entomopathogenic nematodes are associated with bacteria that produce toxins that help degrade tissues for the nematode to feed on [36,37]. Similarly, the plant-pathogenic fungi *Rhizopus* sp. has an endosymbiotic bacteria that produces toxins that have a key role in the disease [38].

Until recently, the role of parasite-associated microorganisms in human diseases had been underestimated, but examples are now starting to emerge. The *Leishmania* RNA virus promotes the persistence of *Leishmania vienna* parasites by inducing a TLR3-mediated inflammatory response that renders the host more susceptible to infection [39]. Similarly, *Trichomonasvirus*, an endosymbiotic of the protozoan parasite *Trichomonas vaginalis* is responsible for the strong proinflammatory response that causes preterm birth [40]. Microorganisms associated with such medically important parasites can now be targeted to limit the impact or development of the disease.

The theoretical framework provided by considering not only the host but also the parasite as a holobiont revealed that some interactions have been underestimated and others have not yet been explored. For example, can microorganisms associated with the host directly interact with microorganisms associated with the parasite? Can the host defend itself against

Citation: Dheilly NM (2014) Holobiont–Holobiont Interactions: Redefining Host–Parasite Interactions. *PLoS Pathog* 10(7): e1004093. doi:10.1371/journal.ppat.1004093

Editor: Glenn F. Rall, The Fox Chase Cancer Center, United States of America

Published: July 3, 2014

Copyright: © 2014 Nolwenn Marie Dheilly. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This work was funded by the Agence Nationale de la Recherche (ANR) Blanc, SVSE7, Project Bodyguard to F. Thomas. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The author has declared that no competing interests exist.

* Email: ndheilly@hotmail.fr

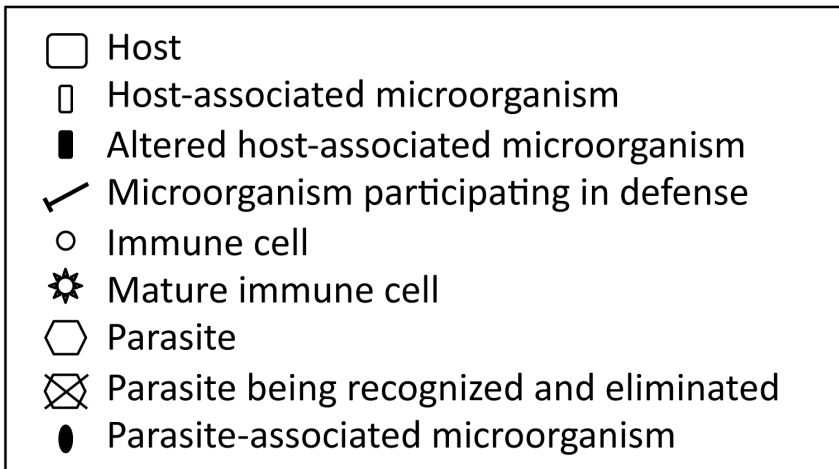
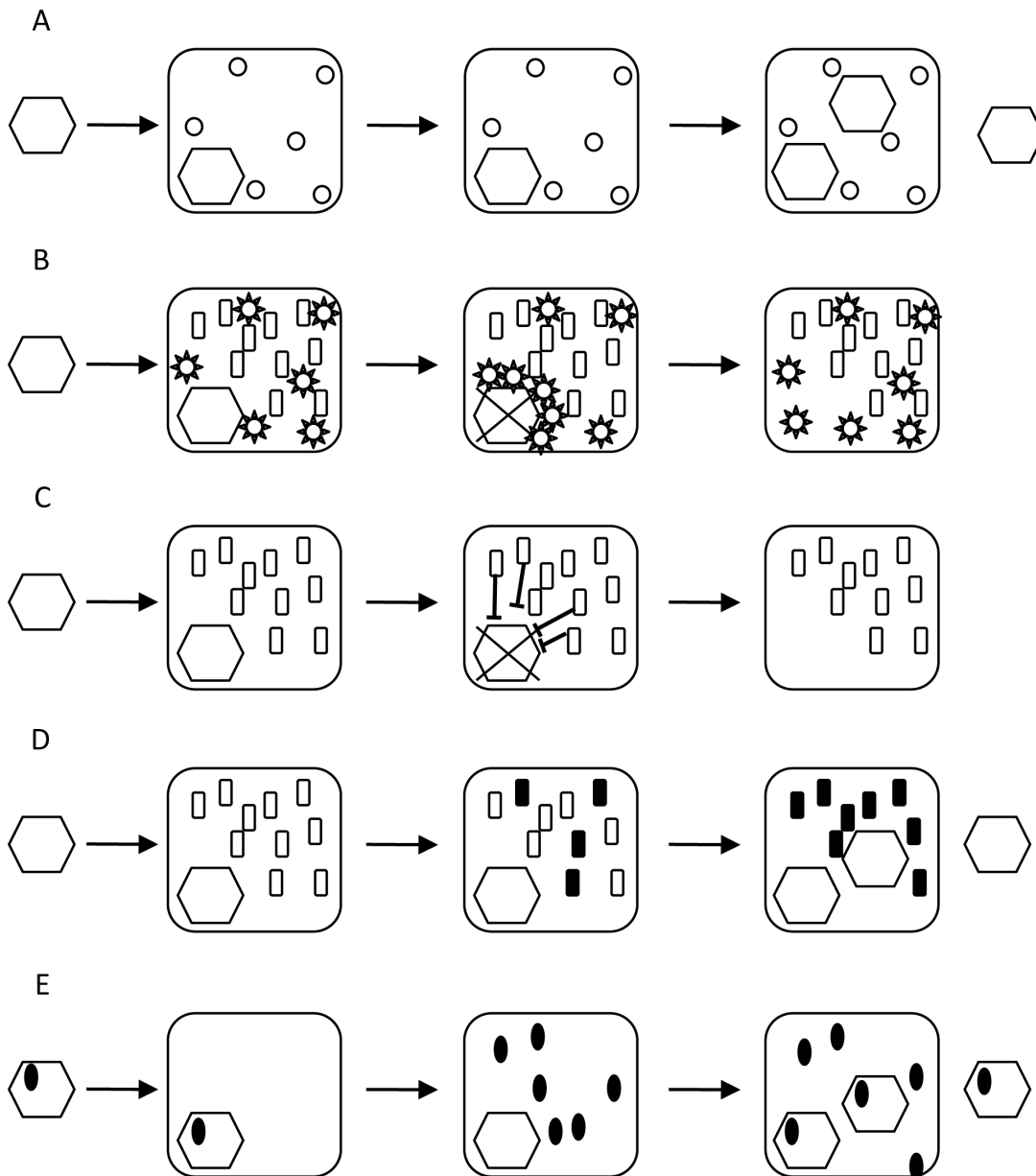


Figure 1. Role of microorganisms associated with the host or the parasite in the host–parasite interaction. (A) Host–parasite interaction without associated microorganisms. (B) Host-associated microorganisms participate indirectly in the immune defense by promoting immune system maturation. (C) Host-associated microorganisms participate directly in the immune defense. (D) Parasite interferes with host-associated microorganisms. (E) Parasite-associated microorganisms participate in the disease.
doi:10.1371/journal.ppat.1004093.g001

infection by recognizing the microorganisms associated with the parasite? Can parasite-associated microorganisms indirectly promote the disease (by increasing its fecundity, for example)? Parasitologists, microbiologists, and immunologists have the monumental task of revealing the myriad interactions occurring between holobiont hosts and holobiont parasites. This knowledge promises to greatly impact our ability to develop new treatments and therapies.

These interactions within interactions have major implications for ecologists and evolutionary biologists, because any

host–parasite interaction will be dependent on all other interactions in the system [41,42]. The short generation time of microorganisms, along with the genetic diversity and novelty they provide [43,44], can play an important role in the adaptation and evolution of hosts and parasites in their evolutionary arms race [45]. This coevolution may also be driven by fluctuating selection [46], in which hosts and parasites interact with different microorganisms over thousands of years, constantly evolving to favor the most advantageous symbiont at the time. In addition, associated microorganisms may be pathogenic

to non-adapted individuals and drive speciation [35,47,48]. Thus, the study of microorganisms associated with hosts and parasites is no longer optional; it is, rather, an obligatory path that must be taken for a comprehensive understanding of the ecology and evolution of hosts and parasites. It is a necessary step for the prevention and prediction of disease outbreaks.

Acknowledgments

I thank F. Thomas for his support and comments on the original manuscript.

References

- Margulis L (1991) Symbiogenesis and symbiontism. In: L. Margulis RFE, editor. *Symbiosis as a source of evolutionary innovation: speciation and morphogenesis*. Cambridge: MIT press. pp 1–14.
- Zilber-Rosenberg I, Rosenberg E (2008) Role of microorganisms in the evolution of animals and plants: the hologenome theory of evolution. *FEMS Microbiol Rev* 32: 723–735.
- Brucker RM, Bordenstein SR (2013) The capacious hologenome. *Zoology* 116: 260–261.
- Chung H, Pamp SJ, Hill JA, Surana NK, Edelman SM, et al. (2012) Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* 149: 1578–1593.
- Schnupf P, Gaboriau-Routhiau V, Cerf-Bennus N (2013) Host interactions with Segmented Filamentous Bacteria: An unusual trade-off that drives the post-natal maturation of the gut immune system. *Sem Immunol* 25: 342–351.
- Weiss BL, Wang J, Aksoy S (2011) Tsetse immune system Maturation requires the presence of obligate symbionts in larvae. *PLoS Biol* 9: e1000619.
- Aksoy S (2000) Tsetse—A haven for microorganisms. *Parasitol Today* 16: 114–118.
- Abt MC, Osborne LC, Monticelli LA, Doering TA, Alenghat T, et al. (2012) Commensal bacteria calibrate the activation threshold of innate antiviral immunity. *Immunity* 37: 158–170.
- Buffie CG, Pamer EG (2013) Microbiota-mediated colonization resistance against intestinal pathogens. *Nat Rev Immunol* 13: 790–801.
- Ganal SC, Sanos SL, Kalfass C, Oberle K, Johner C, et al. (2012) Priming of Natural Killer Cells by Nonmucosal Mononuclear Phagocytes Requires Instructive Signals from Commensal Microbiota. *Immunity* 37: 171–186.
- Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL (2005) An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 122: 107–118.
- Mazmanian SK, Round JL, Kasper DL (2008) A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 453: 620–625.
- Round JL, Mazmanian SK (2009) The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 9: 313–323.
- Rook GAW (2009) Review series on helminths, immune modulation and the hygiene hypothesis: The broader implications of the hygiene hypothesis. *Immunol* 126: 3–11.
- Virgin HW, Wherry EJ, Ahmed R (2009) Redefining chronic viral infection. *Cell* 138: 30–50.
- Duerkop BA, Hooper LV (2013) Resident viruses and their interactions with the immune system. *Nat Immunol* 14: 654–659.
- Herre EA, Knowlton N, Mueller UG, Rehner SA (1999) The evolution of mutualisms: exploring the paths between conflict and cooperation. *Trends Ecol Evol* 14: 49–53.
- Tillmann HL, Heiken H, Knapik-Botor A, Heringlake S, Ockenga J, et al. (2001) Infection with GB Virus C and reduced mortality among HIV-infected patients. *N Engl J Med* 345: 715–724.
- Xiang J, Wünschmann S, Diekema DJ, Klinzman D, Patrick KD, et al. (2001) Effect of coinfection with GB Virus C on survival among patients with HIV infection. *N Engl J Med* 345: 707–714.
- Deterding K, Tegtmeyer Br, Cornberg M, Hadem J, Potthoff A, et al. (2006) Hepatitis A virus infection suppresses hepatitis C virus replication and may lead to clearance of HCV. *J Hepatol* 45: 770–778.
- Barton ES, White DW, Cathelyn JS, Brett-McClellan KA, Engle M, et al. (2007) Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature* 447: 326–329.
- Polin S, Simon J-C, Outreman Y (2014) An ecological cost associated with protective symbionts of aphids. *Ecol Evol* 4: 826–830.
- Weldon SR, Strand MR, Oliver KM (2013) Phage loss and the breakdown of a defensive symbiosis in aphids. *Proc Roy Soc B Biol Sci* 280: 20122103.
- Dion E, Polin SE, Simon J-C, Outreman Y (2011) Symbiont infection affects aphid defensive behaviours. *Biol Lett* 7: 743–746.
- Oliver KM, Degnan PH, Hunter MS, Moran NA (2009) Bacteriophages encode factors required for protection in a symbiotic mutualism. *Science* 325: 992–994.
- Degnan PH, Moran NA (2008) Diverse phage-encoded toxins in a protective insect endosymbiont. *App Environ Microbiol* 74: 6782–6791.
- Barr JJ, Auro R, Furlan M, Whiteson KL, Erb ML, et al. (2013) Bacteriophage adhering to mucus provide a non-host-derived immunity. *Proc Nat Acad Sci U S A* 110: 10771–10776.
- Banin E, Israely T, Kushmaro A, Loya Y, Orr E, et al. (2000) Penetration of the coral-bleaching bacterium *Vibrio shiloi* into *Oculina patagonica*. *App Environ Microbiol* 66: 3031–3036.
- Banin E, Israely T, Fine M, Loya Y, Rosenberg E (2001) Role of endosymbiotic zooxanthellae and coral mucus in the adhesion of the coral-bleaching pathogen *Vibrio shiloi* to its host. *FEMS Microbiol Lett* 199: 33–37.
- Grube M, Köberl M, Lackner S, Berg C, Berg G (2012) Host–parasite interaction and microbiome response: effects of fungal infections on the bacterial community of the Alpine lichen *Solorina crocea*. *FEMS Microbiol Ecol* 82: 472–481.
- McKenna P, Hoffmann C, Minkah N, Aye PP, Lackner A, et al. (2008) The macaque gut microbiome in health, lentiviral infection, and chronic Enterocolitis. *PLoS Pathog* 4: e20.
- Knox TA, Spiegelman D, Skinner SC, Gorbach S (2000) Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. *Am J Gastroenterol* 95: 3482–3489.
- Gori A, Tincati C, Rizzardini G, Torti C, Quirino T, et al. (2008) Early impairment of gut function and gut flora supporting a role for alteration of gastrointestinal mucosa in Human Immunodeficiency Virus pathogenesis. *J Clin Microbiol* 46: 757–758.
- Beckage NE, Drezen J-M (2012) Parasitoid viruses: symbionts and pathogens. *Waltham: Academic Press*. 312 p.
- Jancek S, Bézier A, Gayral P, Paullusson C, Kaiser L, et al. (2013) Adaptive selection on bracovirus genomes drives the specialization of *Cotesia* parasitoid wasps. *PLoS ONE* 8: e64432.
- An R, Sreevatsan S, Grewal P (2009) Comparative in vivo gene expression of the closely related bacteria *Photobacterium temperata* and *Xenorhabdus koppenhoeferi* upon infection of the same insect host, *Rhizotrogus majalis*. *BMC Genomics* 10: 433.
- Adams BJ, Fodor A, Koppenhöfer HS, Stackebrandt E, Patricia Stock S, et al. (2006) Biodiversity and systematics of nematode-bacterium entomopathogens. *Biol Control* 37: 32–49.
- Partida-Martinez LP, Hertweck C (2005) Pathogenic fungus harbours endosymbiotic bacteria for toxin production. *Nature* 437: 884–888.
- Ives A, Ronet C, Prevel F, Ruzzante G, Fuentes-Marraco S, et al. (2011) Leishmania RNA virus controls the severity of mucocutaneous leishmaniasis. *Science* 331: 775–778.
- Fichorova RN, Lee Y, Yamamoto HS, Takagi Y, Hayes GR, et al. (2012) Endobiont viruses sensed by the Human host ' beyond conventional antiparasitic therapy. *PLoS ONE* 7: e48418.

41. Moller AP (2008) Interactions between interactions: predator-prey, parasite-host, and mutualistic interactions. *Ann N Y Acad Sci* 1133: 180–186.
42. Oliver K, Noge K, Huang E, Campos J, Becerra J, et al. (2012) Parasitic wasp responses to symbiont-based defense in aphids. *BMC Biol* 10: 11.
43. Taylor FJR (1979) Symbiogenesis revisited: A discussion of the evolutionary impact of intracellular symbioses. *Proc Roy Soc Lond B Biol Sci* 204: 267–286.
44. Margulis L, Fester R (1991) Symbiosis as a source of evolutionary innovation: speciation and morphogenesis. L. Margulis RFE, editor. Cambridge: MIT press.
45. Ferrari J, Vavre F (2011) Bacterial symbionts in insects or the story of communities affecting communities. *Phil Trans Roy Soc B Biol Sci* 366: 1389–1400.
46. Thompson JN (1999) The evolution of species interactions. *Science* 284: 2116–2118.
47. Brucker RM, Bordenstein SR (2013) The Hologenomic Basis of Speciation: Gut Bacteria Cause Hybrid Lethality in the Genus *Nasonia*. *Science* 341: 667–669.
48. Le Clech W, Braquart-Varnier C, Raimond M, Ferdy J-B, Bouchon D, et al. (2012) High Virulence of *Wolbachia* after Host Switching: When Autophagy Hurts. *PLoS Pathog* 8: e1002844.