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REVIEWS

Physiological Aspects of *Wolbachia pipientis*–*Drosophila melanogaster* Relationship

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Abstract—The intracellular bacterium *Wolbachia pipientis* is one of the most common prokaryotic symbionts of invertebrates. It is able to affect host species reproduction, thus contributing to the spread of the bacteria in host populations via increasing the number of infected females. However, while the main effects of *Wolbachia* are well documented, the mechanisms of reproductive anomalies it evokes and positive effects it exerts on the host fitness remain largely understudied. This review addresses various aspects of *Wolbachia* effects on host physiology and fitness with a special focus on the symbiotic system *Wolbachia pipientis*–*Drosophila melanogaster*, specifically *Wolbachia* influence on host hormonal status and host resistance to stress, viral infection, fecundity, and lifespan.

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INTRODUCTION

Wolbachia pipientis [1] is an intracellular, maternally inherited alpha-proteobacterium that occurs in approximately 40–60% of arthropod species [2], including *Drosophila melanogaster*, and is one of the most common prokaryotic symbionts of invertebrates (Fig. 1). *Wolbachia* has been dubbed a master manipulator because it is able to control the biology, morphology, and even some aspects of its host's behavior. At the same time, the host in turn can gain an advantage over uninfected individuals in its adaptability.

EFFECT OF *WOLBACHIA* ON HOST'S REPRODUCTION

The co-evolution of *W. pipientis* and host species has led to the development of a variety of mutual adaptations. In the host organism, most evident adaptations concern a modification of the reproductive function. The four basic phenotypes known to date are cytoplasmic incompatibility (CI), feminization, androcide (selective death of males during embryogenesis or larval development), and thelytokous parthenogenesis [3–5]. Among these effects, CI is the most studied [5, 6].

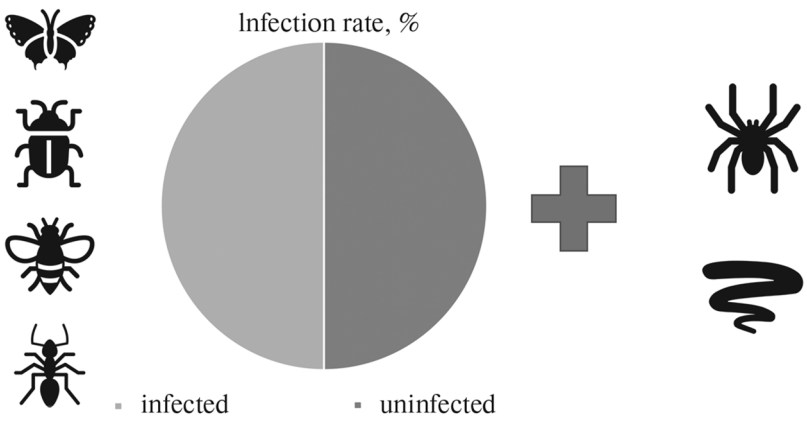

Fig. 1. Natural occurrence of the endosymbiotic bacterium *Wolbachia pipientis* in insects, arachnids and nematodes.

In insects, CI arises when *Wolbachia*-infected males mate with uninfected females or those carrying another *Wolbachia* strain, which leads to embryo death [6]. As a result, *Wolbachia*-infected females that are protected against CI gain a reproductive advantage over uninfected females. Another variant of CI, bidirectional CI, occurs when crossing parents that carry different bacterial strains. It has been hypothesized that such a type of CI can contribute to host speciation by causing reproductive barriers [7]. The CI level depends on many factors. For example, a high level of sperm infection causes a high CI level [8, 9]. Another discovery has been made when studying a *Wolbachia wPip* strain that infects the mosquitoes *Culex pipiens*. The genome of these bacteria has been found to contain a transcription regulator that affects the expression of the host's *grau* gene responsible for CI manifestation [10]. A high CI level positively correlates with a high *Wolbachia* titer [11–14]. The *Wolbachia* titer in the host organism depends on various factors. One and the same *Wolbachia* strain may have different titers in different host genotypes [15–17], and within the same host, the titer varies from tissue to tissue, e.g., reproductive tissues show higher titers compared to somatic tissues [18, 19]. In addition, *Wolbachia* titer may depend on the ambient temperature. For example, *D. nigrosparsa* raised at temperatures below 19°C had a higher *Wolbachia* titer compared to individuals grown at high temperatures [20]. Also, *D. melanogaster* individuals raised at 13°C were found to have a higher *Wolbachia* density compared to those raised at 31°C [21]. By changing the *Wolbachia* titer in eggs, temperature also affects the degree of androcid manifestation in *D. bifasciata* [22]. In *D. melanogaster*, *Wolbachia* density varies depending on a diet [23]: flies raised on sucrose-enriched food were shown to have an increased bacterial titer in oogenesis, while those raised on yeast-enriched food had a decreased one. The mortality rate in *D. melanogaster* infected with the *Wolbachia w*MelPop strain positively correlates with the bacterial titer [24]. The titer can also change with host age, as observed in many arthropods, including *Drosophila* spp. [15, 25–28]. Since it has previously been shown that in *D. melanogaster* females, the division of germline stem cell declines with age [29], while *Wolbachia* is most represented in host's reproductive tissues [30–32], the decrease in *Wolbachia* titer in flies approaching four weeks of age can be explained by a decrease in germline stem cell division.

EFFECT OF *WOLBACHIA* ON HOST FITNESS

Depending on specific host-bacteria interactions, macrosymbionts can benefit from the *Wolbachia* symbiont. For example, *D. melanogaster* infected with *w*Mel had higher fecundity and mating rates compared to uninfected individuals [2]. The cicadas *Laodelphax striatellus* infected with the *wStri* strain also had a higher fecundity than uninfected insects [33]. The beetles *Callosobruchus chinensis* infected with *Wolbachia w*BruCon, *w*BruOri, and *w*BruAus strains were reported to

have larger body size and lifespan [34]. At the same time, the infection of *D. nigrosparsa* with *Wolbachia w*Mel had no effect on fly fecundity level and their heat and cold stress tolerance, although increasing their motor activity [20].

In *D. melanogaster* and *D. simulans*, *Wolbachia* titer positively correlates with host antiviral resistance [19, 35–39], including an increase in insect resistance to viruses dangerous to humans (Dengue, yellow fever, and West Nile fever viruses) [28, 35, 40, 41]. The presence of *Wolbachia* in *Drosophila* and mosquitoes leads to increased host resistance to the malaria pathogen (*Plasmodium vivax*) [38]. As shown in various *Drosophila* species and the woodlouse *Armadillidium vulgare*, the symbiont's impact on host immunocompetence and survival varied significantly within the same population, depending on the host-infecting *Wolbachia* strain [42, 43], which suggests an actively ongoing evolutionary process in the formation of *Wolbachia*-host system's resistance to various pathogens. Recent studies [44] have shown that temperature is a strong modulator of the antiviral protection provided by *Wolbachia* in *D. melanogaster* infected with *Drosophila* C virus (DCV). *Drosophila* development at 25°C leads to strong antiviral protection in terms of survival and DCV resistance, while the development at 18°C strongly reduces or even negates such a protection. This has been observed with different *D. melanogaster* genotypes, *Wolbachia* variants (*w*Mel and *w*MelCS), and viruses, and may therefore represent a common phenomenon [44].

To shed light on the mechanism underlying these changes, Pan et al. [45] conducted studies on the mosquitoes *Aedes aegypti*, which transmit a number of severe human diseases, including those caused by yellow fever and Dengue viruses (YFV and DENV). The authors investigated how *Wolbachia* infection affects the host (*Ae. aegypti*) and elicits DENV resistance. It was shown that in *Wolbachia*-infected *Ae. aegypti*, the transcription of genes related to the regulation of immune responses and redox reactions is activated. The infection with this bacterium induces oxidative stress and increases reactive oxygen species (ROS) levels in the host mosquito. An increase in ROS production is due to the activation of the Toll signaling pathway, which is required to mediate antioxidant expression and counteract oxidative stress. This immune pathway is also responsible for the activation of the antimicrobial peptides defensins and cecropins. There is evidence that these antimicrobial peptides are involved in the suppression of DENV proliferation in *Wolbachia*-infected mosquitoes. These results show that the symbiotic bacterium can manipulate the host defense system to facilitate its own persistent infection, which results in a reduced ability of mosquitoes to be infected with pathogens dangerous to humans [45].

In another study of the mechanism of antiviral protection associated with *Wolbachia* infection and also performed on *Ae. aegypti*, the mosquitoes were infected in laboratory conditions with the *Drosophila*-specific pathogenic *w*MelPop strain [46]. It turned out that in the presence of *Wolbachia*, the synthesis level of miRNAs involved in the regulation of the density of distribution of these bacteria in *Ae. aegypti* tissues increases. These short single-stranded RNAs encode no proteins, but are implicated in the regulation of a large number of genes. For this reason, they play a crucial role in many vital processes, including immune defense, programmed cell death, etc. The same microRNAs increase mosquito DENV resistance [47, 48].

However, *w*MelPop is a strain that was only identified in the laboratory. The natural *Wolbachia* strains, commonly used in antiviral protection studies, are *w*Mel and *w*MelCS isolated from *D. melanogaster*, *w*Au, isolated from *D. simulans*, *w*AlbB isolated from *Ae. albopictus*, and *w*Stri isolated from the cicadas *L. striatellus* [49]. Martinez et al. [50] analyzed the antiviral protection of many natural *Wolbachia* strains drived from different *Drosophila* species after transferring them to the same genetic background of *D. simulans*. It was found that the protection is determined by not the host genotype but the *Wolbachia* strain [50]. It is noteworthy that most studies showing the ability of different *Wolbachia* strains to protect insect hosts against many RNA viruses were carried out under laboratory conditions, and only little evidence has been obtained thus far for the existence of *Wolbachia* antiviral effect in nature.

In addition, there have been described cases when *Wolbachia* infection did not protect the host

from viruses and, on the contrary, contributed to further infection [51]. In their work, Graham et al. [51] provided data on field populations of the dangerous crop pest, African moth *Spodoptera exempta*, which show that the prevalence and intensity of infection with nuclear polyhedrosis virus (*SpexNPV*) positively correlate with the infection with three *Wolbachia* strains. The authors also demonstrated that the infection with one of these strains increases *SpexNPV*-induced host mortality by a factor of 6–14. These data suggest that, instead of protecting their lepidopteran hosts from viral infection, *Wolbachia* makes them more susceptible thereto.

Wolbachia infection has been repeatedly shown to affect *Drosophila* lifespan. These effects, however, are contradictory and include both increases [19, 52, 53] and decreases [19, 54, 55] in longevity.

The lifespan-regulating effects of *Wolbachia* may depend on the host genetic background [56, 57]. Fry and Rand [56] used reciprocal hybrid crosses between the two *D. melanogaster* strains, one of which (Z53), when infected with *Wolbachia*, lives longer and the other (Z2) does not, and noted that *Wolbachia* can increase fly longevity by reducing its fecundity. The positive effect of *Wolbachia* infection on fly longevity was far more pronounced in hybrids of these strains than in the parental line Z53. Moreover, this favorable effect of infection was more evident when females and males were kept separately, which excluded courtship and mating. Under these conditions, almost all *Wolbachia*-infected insects lived longer than uninfected flies.

The longevity of an organism can be influenced by the genetic background and the environment. The two most common factors that affect longevity and hence arouse great interest are oxidative stress caused by various abiotic exposures and infections [58, 59]. Capobianco et al. [60] investigated how different combinations of *Wolbachia* infection and oxidative stressors affect lifespan in two wild-caught *D. melanogaster* strains, Burlington and Plattsburgh. Naturally *Wolbachia*-infected and cured Burlington and Plattsburgh strains were treated with paraquat or L-arginine to induce two different types of oxidative stress. Both paraquat and L-arginine affect the ROS pathway inside *D. melanogaster*. Paraquat produces free oxygen radicals when it is metabolized in the cytoplasm. Thus, paraquat is a proven and useful tool for to elevate the superoxide anion content in cells [61]. Feeding on the nitric oxide precursor L-arginine [62] induces nitric oxide, which can enhance the insect immune response to plasmodium [63] and parasitoid infection [64]. Nitric oxide is a small molecule that plays multiple roles in biological processes, including signal transduction and the ability to react with superoxide anions to form peroxynitrite (ONOO-) [65]. Peroxynitrite, a potent and toxic oxidant, is relatively slow to react with most biological molecules. The authors found that the removal of *Wolbachia* infection shortens the lifespan of flies with one genetic background but not with the other. *Wolbachia* infection makes only one of the strains more paraquat-sensitive. However, it was the strain uninfluenced by *Wolbachia* when treated with paraquat that proved to be protected by this infection against L-arginine-induced stress [60]. Consequently, *Wolbachia* modifies the protection against free radicals via two different mechanisms that depend on the host genetic background. This supports the idea that the factors able to regulate aging (infection and oxidative stress) are not universal, but specific to the genetic structure of the individual.

It has also been shown that the effect of *Wolbachia* on host fitness also depends to some extent on the genotype of the endosymbiont [66–69]. Serga et al. [66] demonstrated that *D. melanogaster* females infected with *w*MelCS have lower fecundity compared to those infected with *w*Mel, which, in the authors' opinion, may be the reason for the predominance of *w*Mel in *D. melanogaster* populations.

However, when studying the effect of different *Wolbachia* genotypes on *D. melanogaster* survival under heat stress, it was found that one of the *w*MelCS genotype isolates, *w*MelPlus strain, provides the host insect with increased stress tolerance [67, 70] and fecundity [68] in comparison with the *w*Mel genotype and other strains of the *w*MelCS genotype.

Apart from fecundity, longevity, and antiviral protection, *Wolbachia* influences other aspects of host insect vital activity: in *D. melanogaster* and

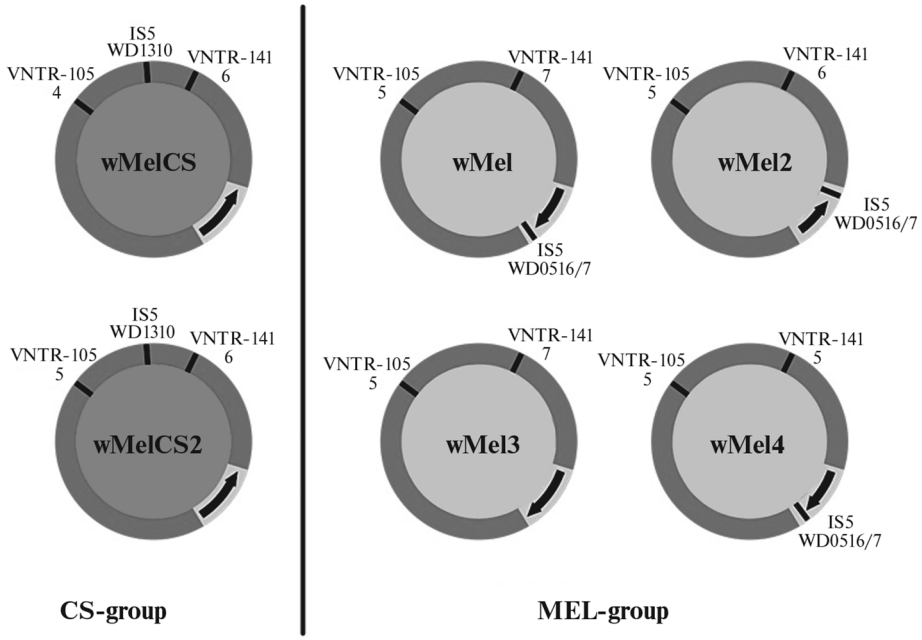

Fig. 2. Chromosomal maps of the six different *Wolbachia pipientis* genotypes isolated from *Drosophila melanogaster* (after Riegler et al., 2005, with additions). The genotypes differ by a single large chromosomal inversion, two loci with a variable number of tandem repeats (VNTR-105 and VNTR-141), and two different IS5 transposon insertion sites (WD1310 and WD0516/7).

D. simulans, the bacterium affects dietary iron metabolism. When the fruit flies were placed on food with a deficiency or excess of iron salts, uninfected individuals laid fewer eggs compared to the infected [71, 72]. In bed bugs *Cimex lectularius*, it has been shown that *Wolbachia* *w*Cle can provide an insect host with vitamin B, which is essential for its development [73]. There are also data on the ability of *Wolbachia* to influence the behavior of its hosts. For example, in *D. paulistorum* and *D. melanogaster* it was shown that females and males infected with different *Wolbachia* strains avoid crossing that leads to CI [74, 75]. *Wolbachia*-infected *D. melanogaster* females also demonstrate changes in oviposition substrate preference, while *Wolbachia*-infected males are more competitive than uninfected ones [76]. The beetles *Callosobruchus chinensis* infected with *Wolbachia* *w*BruCon and *w*BruOri are significantly more active than uninfected ones, which increases their mating success [77]. *Ae. aegypti* artificially infected with *w*MelPop are 2.5-fold more active compared to uninfected ones [78].

All these data indicate that the physiological and behavioral features of *Wolbachia*-infected insects, which can be observed both under laboratory conditions and in nature, are provided by an entanglement of different genetically determined mechanisms of interaction between the two organisms. Of course, these complicated insect-bacteria interrelationships require further in-depth study.

THE *DROSOPHILA MELANOGASTER*–*WOLBACHIA PIPIENTIS* SYSTEM

Particular attention is paid now to the symbiotic *D. melanogaster*–*Wolbachia pipientis* system. Analysis of the *Wolbachia* genomes detected in *D. melanogaster* revealed six genotypes of monophyletic origin: *w*Mel, *w*Mel2, *w*Mel3, *w*Mel4, *w*MelCS, and *w*MelCS*2* (Fig. 2), with two of them (*w*Mel and *w*MelCS) being ubiquitous and the *w*Mel genotype occurring in the vast majority of infected individuals [79–83]. The *w*Mel2 and *w*Mel4 genotypes have been detected in *D. melanogaster* populations only in the Asian regions [17, 79, 80, 82], *w*MelCS2—in Eastern Europe and Central Asia, the Caucasus and the Altai [79, 80, 82, 84], and *w*Mel3—only in a single laboratory *D. melanogaster* strain [79]. A pathogenic *w*MelCS variant, the *w*MelPop (from the word

"popcorn") strain, was also isolated in the laboratory and so dubbed for its ability to reproduce unrestrainedly in cells of the *Drosophila* organism, leading to cell rupture and, as a consequence, degradation of nervous and muscle tissues, as well as premature fly death [54]. As a genetic marker, it is indistinguishable from *w*MelCS [85]; however, it reduces insect lifespan approximately by half even at optimal temperature (25°C), and by another half when temperature is increased to 29°C [15, 54]. The *w*MelPop genotype also has a negative effect on host fitness, reducing host survival under stress yet before the onset of its premature death, which *w*MelPop induces on day 9–10 [67], and increasing the frequency of programmed cell death in the developing *Drosophila* ovarian follicles [86]. At the same time, the transfer of *w*MelPop-infected flies kept at 29°C to lower-temperature conditions (16°C) can partially restore their lifespan [55]. In addition, *w*MelPop was observed to be more pathogenic when transfected in *D. simulans* and *Ae. albopictus* compared to its natural host, *D. melanogaster* [87, 88]. A study of the dynamics of *Drosophila* brain cell colonization with bacteria of the *w*MelPop strain showed that they get there at the early stages of insect development, however begin to divide actively only at the imago stage, gradually destroying the host nervous system, with the rate of bacterial cell division increasing as temperature rises [55].

Recently, Duarte et al. [89] developed a novel forward genetic screen and identified new over-proliferative *Wolbachia* variants. The authors provided a comprehensive characterization of two of the obtained mutants, *w*MelPop2 and *w*MelOctoless, and determined the genetic substrate of their overproliferation. The *w*MelPop2 genotype has an amplification of the Octomom region containing eight *Wolbachia* genes, which, as previously shown, leads to overproliferation in the case of *w*MelPop [24, 28]. In *w*MelOctoless, by contrast, the same Octomom region was deleted. A detailed phenotypic characterization of these strains showed that both *Wolbachia* variants reduced host lifespan and increased its antiviral protection. Moreover, the authors demonstrated that the *Wolbachia* proliferation rate in *D. melanogaster* depends on the interaction between the number of Octomom copies, host developmental stage, and temperature. These findings confirm and further develop the ideas on the ambiguous role of this genomic region in the control of *Wolbachia* proliferation.

A unique *Wolbachia* *w*MelPlus strain has also been recently found to increase the stress resistance of *D. melanogaster* [67, 68, 70]. This strain represents a variant of the *w*MelCS genotype and is indistinguishable therefrom as a genetic marker.

Numerous studies have shown that the *Wolbachia* infection rate in natural *D. melanogaster* populations varies from 30 to 60% across the entire distribution range of the species [2, 80–83, 90–93]. The reasons for such a wide distribution of the symbiont are still not fully elucidated. However, the studies of this symbiosis have yielded extremely interesting results. For example, the symbiont can restore fertility in females of a certain genotype [94], influence the fertility level of *Drosophila* females by changing their hormonal background [68], increase the fitness of flies with a reduced production of the insulin-like growth factor [95], or rescue flies infected in laboratory conditions with high doses of RNA viruses [35]. However, these and other known facts cannot fully explain why the infection in *D. melanogaster* populations is ubiquitously maintained at a high level [2, 66, 82]. It should be noted that the CI phenomenon, which could explain the spread and maintenance of *Wolbachia* in populations, is manifested in *D. melanogaster* at a high level only under special laboratory conditions, while under conditions approximating the natural, it is extremely low or undetected at all [90, 91].

In 2009, Ilinskii and Zakharov [96] evaluated the CI level in *D. melanogaster* caused by the three most common *Wolbachia* genotypes, *w*Mel, *w*MelCS and *w*MelCS2. They showed that *w*Mel and *w*MelCS genotypes are able to elicit a weak CI (< 10%), whereas *Wolbachia* *w*MelCS2 lacks this ability.

EFFECT OF *WOLBACHIA* ON *DROSOPHILA MELANOGASTER* HORMONAL STATUS

Effect on catecholamines

In insects, catecholamines, dopamine and octopamine, are stress hormones, along with

juvenile hormone (JH), 20-hydroxyecdysone (20HE), insulin and adipokinetic hormone, which are directly involved in the control of adaptation [97–99]. Dopamine, apart from being involved in stress development, also plays an important role in controlling sleep quality and quantity. In the mammalian mesencephalic tegmentum, dopamine-containing neurons are important for excitation [100]. Like in mammals, dopamine in flies promotes wakefulness [101], indicating that this and other neurotransmitter pathways [102] share common functions in sleep regulation in both insects and different mammalian species.

The effect of *Wolbachia* genotype on *Drosophila* survival under heat stress is mediated by changes in catecholamine metabolism in the latter [67, 103]. The dependence of *Wolbachia* effect on the level and biosynthesis of octopamine in *D. melanogaster* on endosymbiont genotype was also shown by Rohrscheib et al. [104].

Transcriptional analysis of the dopamine biosynthesis pathway showed that its two main genes, *Pale* and *Ddc*, were significantly activated in *Wolbachia*-infected flies [105]. A study of the effect of *Wolbachia* on sleep duration and quality showed that it elicited an increase in total sleep time in both male and female *D. melanogaster*. Such an increase in sleep duration was due to an increase in the number of nocturnal sleep episodes, but not to an increase in the duration of individual sleep episodes. Accordingly, *Wolbachia* infection also reduced the excitation threshold in their host flies. However, *Wolbachia* infection affected neither the circadian rhythm nor post-deprivation sleep recovery. Taken together, these results indicate that *Wolbachia* mediates the expression of dopamine-related genes and reduces the sleep quality in host insects [105].

Effect on 20-hydroxyecdysone signaling pathway

Drosophila lifespan is well known to be largely dependent on the 20HE signaling pathway, in which 20HE is a steroid hormone acting as the main regulator of insect development and reproduction. This pathway is also involved in the manifestation of *Wolbachia*-induced reproductive phenotypes [106, 107].

Drosophila with heterozygous mutation in the EcR^{V559fs} gene encoding the 20HE receptor, have an increased lifespan and stress resistance with no obvious locomotor and fertility deficits [108]. Female flies of the DTS-3/+ strain carrying a mutation in the molting defective (*mld*) gene involved in 20E biosynthesis, also demonstrate increased longevity when cultured at 29°C. It has been suggested that *Wolbachia* produces specific regulators able to interact both directly and indirectly with the 20E receptor, thus modulating signaling therethrough [109]. These findings confirm that the ecdysteroid pathway may be involved in the lifespan modulation provided by *Wolbachia* in *D. melanogaster*.

Effect on juvenile hormone signaling pathway

Wolbachia is able to stimulate gene expression of the juvenile hormone (JH) signaling pathway and influence the JH metabolic level in *D. melanogaster* [68, 110]. JH is known to be related with ecdysteroid pathways [111–114] and insulin signaling [112]. Liu et al. [110] showed that in *D. melanogaster*, *Wolbachia* infection leads to a significant activation of the *Jhamt* and *Met* genes encoding the enzyme of JH synthesis and its receptor, playing a key role in the JH signaling pathway. The results of this study suggest that *Wolbachia* can enhance JH signaling in *Drosophila*.

Effect on protein-carbohydrate metabolism

Drosophila lifespan is highly dependent on nutritional conditions, such as the balance between dietary proteins and carbohydrates [115]. Ponton et al. [116] demonstrated that *Wolbachia* modulates the effect of the protein to carbohydrate (P/C) ratio on *D. melanogaster* lifespan. Flies, whose dietary P/C ratio was 1 : 16, lived longer compared to those with a 1 : 1 P/C ratio, while flies there were allowed to choose between the two food supplements (pure yeast or sucrose solution) had a medium lifespan. This is consistent with the previous results [117] showing that, when offered a choice of dietary supplements, flies regulated the intake of macronutrients to maximize not their longevity but egg-laying capacity. No differences were observed between the survival curves of infected and uninfected insects fed with a P/C 1 : 16 mixture or allowed to choose between the two dietary supplements. However, among the insects

fed with a P/C 1 : 1 diet, uninfected flies lived longer compared to the infected. It has been suggested that these results may reflect host-symbiont competitiveness for carbohydrates and explain why infection has a negative effect on host longevity. *Wolbachia* has a limited number of metabolic pathways [118] and is thus highly dependent on its host for metabolic support [38, 118, 119]. For example, *Wolbachia* utilizes host sugars not only for glycolysis [120], but also for lipid II synthesis [121, 122], which the authors suggest to be essential for bacterial division. In the same study, the infected flies raised on a P/C 1 : 1 diet had a higher reproduction rate compared to their uninfected counterparts. If flies were allowed to choose between yeast and sucrose solutions, uninfected flies consumed more protein than infected flies. Carbohydrate intake was almost indistinguishable in infected versus uninfected flies. The average P/C ratio preferred by infected and uninfected flies was 1 : 20 and 1 : 9, respectively. Ponton et al. hypothesized that changing the feeding behavior of *Wolbachia*-infected flies may diminish the lifespan-shortening effect of infection by decreasing the reproduction [116].

Effect on insulin/insulin-like growth factor signaling pathway

The linkage between the fly feeding type and their lifespan is probably mediated by the insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) pathway, which is known to play a decisive role in the regulation of nutrient uptake and metabolism [123]. In addition, numerous studies have shown that the IIS pathway plays a pivotal role in the regulation of growth, reproduction, stress tolerance, and lifespan in all multicellular organisms, including *D. melanogaster* [124–126].

There is evidence that *Wolbachia* boosts the activity of the insulin signaling system [95, 127]. When studying how *Wolbachia* interacts with the *D. melanogaster* IIS pathway, Grönke et al. [127] found that the loss of insulin-like proteins produced in the brain significantly increases lifespan, but only in the presence of *Wolbachia*.

Ikeya et al. [95] explored the effect of *Wolbachia* infection on a number of IIS-related phenotypes in control and IIS-mutant *D. melanogaster*. They showed that in the presence of *Wolbachia*, the ubiquitous expression of a dominant negative form of the *Drosophila* insulin receptor (InRDN) led to a moderate dwarfism, reduced fecundity and increased longevity in females, i.e. to all phenotypes typical for decreased IIS. In the absence of *Wolbachia*, the moderate effects of InRDN expression were enhanced, resulting in the emergence of flies with phenotypes characteristic of pronounced IIS deficiency, including extreme dwarfism, sterility, increased fat content, and decreased longevity. The absence of *Wolbachia* in mutant flies led to a reduction in fecundity and weight of adult insects compared to infected flies of the same genotypes, but had no effect on lifespan [95]. In other words, it can be assumed that *Wolbachia* partially compensated for the defects caused in the host organism by impaired insulin signaling.

CONCLUSION

The impact of *Wolbachia* on intraspecific host competition is mediated through changes in the hormonal status of the latter. *Wolbachia* controls many pathways and processes that are required for the viability of its host, such as stress resistance, immune responses, energy metabolism, protection against oxidative stress, and other key survival functions. By all appearances, the effect of *Wolbachia* is generally aimed at increasing host fitness by increasing its fecundity and tolerance to environmental factors, which is not always accompanied by an increase in lifespan, and sometimes even shortens it.

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AUTHORS' CONTRIBUTION

Writing the manuscript (E.V.B.); editing the manuscript (N.E.G.).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, both evident and potential, related to the publication of this article.

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