evolutionary shortcut as an underlying mechanism for host co-option of EVEs. A common feature behind their success is the fact that, as viruses, they had evolved self-serving compatibility to the immune system that is easily usurped by hosts. Above all, the results of Chuong *et al.* [3] are formative because they reveal a systematic and widespread evolutionary process, which includes multiple ERVs being co-opted by several genes across the mammalian phylogeny, including those that are IFN-γ-inducible. What such discoveries show is that incorporating the unique dynamics involved behind co-opting products of the arms race will be necessary to elucidate the web of interactions that drive the coevolution of viruses and hosts.

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Host–Symbiont Interactions: Male-Killers Exposed

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Male-killing is one strategy used by maternally transmitted bacterial symbionts to boost transmission and spread in populations. In *Drosophila melanogaster*, *Spiroplasma* target males by hijacking an essential, male-limited epigenetic process. A new study reveals clues to the mode of killing.

Arthropods are hosts to many types of bacterial symbionts that are vertically transmitted through the maternal germ line [1]. Bacterial symbionts spread in populations by offering some benefit to their host or by manipulating host reproduction. These complex relationships can have a large impact on the evolution and ecology of both the host and the parasite (reviewed in [2]). Some of the most notable bacterial symbionts — *Wolbachia*, *Cardinium* and *Spiroplasma* — are reproductive parasites that bias their transmission by

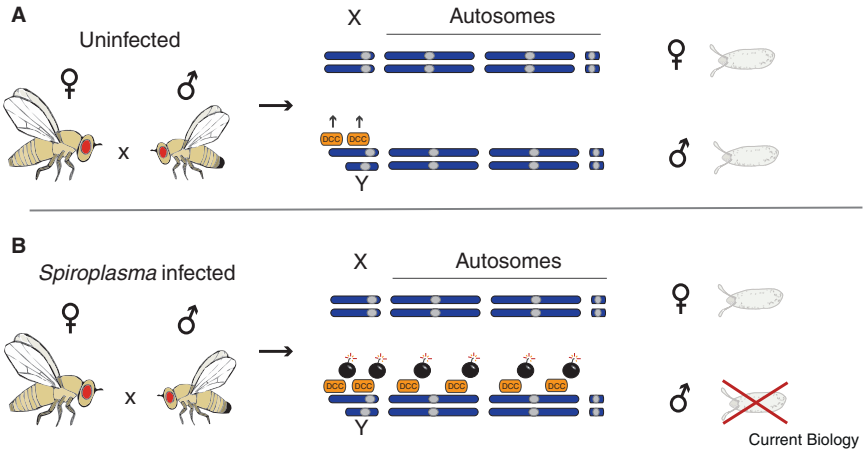

Figure 1. *Spiroplasma* hijacks the dosage compensation system in male *Drosophila melanogaster* embryos.
(A) Females (X:Autosome ratio of 1) and males (X:Autosome ratio of 0.5) require similar levels of most X-encoded gene products. Males overcome hemizygosity for the X chromosome by assembly of the Dosage Compensation Complex (DCC). The DCC is recruited to X-linked genes and modifies chromatin to increase expression. (B) *Spiroplasma*-infected male embryos display mislocalization of DCC components that is accompanied by genome-wide misregulation. A study in this issue [6] reveals that *Spiroplasma* achieves male-killing through toxic gain of function that 'weaponizes' the DCC.

manipulating their hosts in ingenious ways. The strategy of these parasites is to increase the reproduction and survival of infected females over that of uninfected females, which can be accomplished through cytoplasmic incompatibilities, selective male-killing, transformation of males into females or induction of parthenogenesis (reviewed in [3]). Some *Wolbachia* and *Spiroplasma* are even beneficial to their hosts and spread in populations by offering the host protection from other infections or parasites (reviewed by [4]). A remarkable example of this is *Spiroplasma* protection of *Drosophila neotestacea* from sterilization by a nematode parasite. This benefit has fueled the dramatic spread of *Spiroplasma* in *D. neotestacea* across the North American continent over the last 25 years [5]. Bacterial symbionts can have profound ecological and evolutionary consequences — driving reproductive changes and accelerating the evolution and speciation of their hosts [2]. Little is understood about precisely how symbionts manipulate host sex determination and reproduction. A new study reported in this issue of *Current Biology* by Cheng *et al.* [6] focuses on the mode of male killing by the MSRO strain of *Spiroplasma* (*melanogaster* sex ratio organism) — a strain that produces broods that are almost entirely female [6,7]. Intriguingly, a functional dosage compensation system is required for male-killing to occur [8]. This finding was satisfying as it identified a male-limited process manipulated by *Spiroplasma*, but the actual mechanism of killing has not been studied in detail until now.

Because dosage compensation is a well-studied epigenetic system, its involvement in male-killing is particularly intriguing. Dosage compensation equilibrates the expression of X-linked genes between XY males and XX females. In *D. melanogaster*, this occurs through the action of a ribonucleoprotein complex, variously termed the MSL (Male Specific Lethal) complex or DCC (Dosage Compensation Complex), that binds transcribed X-linked genes and modifies chromatin to elevate expression (Figure 1A) [9]. Mutations that inactivate dosage compensation are lethal to males, but females are unaffected. The timing, localization and behavior of the DCC in the presence of *Spiroplasma* all indicate that male-killing is through a novel, gain-of-function process that depends on the DCC, rather than a loss of compensation (Figure 1B). For one thing, the lethal period in *Spiroplasma* infection precedes that of mutants that inactivate the DCC by several days. Although the DCC becomes active 3 h after embryo deposition, males unable to form this complex die at the larval/pupal transition, about five days later. This delay in lethality may reflect partial compensation by non-DCC dependent mechanisms [10]. In contrast, the first signs of abnormality in *Spiroplasma*-infected males appear shortly after the onset of compensation, and male embryos die a few hours later [11]. Interestingly, DCC localization is disrupted in infected males [6]. Rather than exclusive localization to the X chromosome, the MSL proteins become diffusely distributed throughout the nucleus. Finally, artificial induction of DCC formation in females makes them susceptible to killing by *Spiroplasma*. Formation of the DCC in females reduces female viability and fertility due to elevated expression from both X chromosomes [12]. These females can be rescued by mutations that disable the DCC. If *Spiroplasma* killed males by inactivating the DCC, it would be predicted to rescue females that form DCC, rather than making them susceptible to embryonic killing. This finding nicely illustrates the hijacking of DCC function and eliminates the possibility that other male-limited factors, such as masculine differentiation or the Y chromosome, participate in *Spiroplasma*-induced male killing.

To explore the effects of *Spiroplasma* on gene expression, Cheng *et al.* used a clever trick to collect populations of male-enriched embryos from infected mothers. They discovered that killing coincides with dramatic misregulation throughout the genome. Particularly notable are dozens of autosomal and X-linked genes that increase over two-fold in expression. This can be contrasted with the situation in males mutated for any component of the DCC, which suffer a modest reduction in X-linked gene expression but little disruption of autosomal genes [13,14].

Precisely how *Spiroplasma* achieves this remarkable feat remains to be discovered. An added complication is that, except for the syncytial embryo and the ovary, *Spiroplasma* is extracellular [15]. One possibility is that Spiroplasma epigenetically marks chromatin in the early embryo, making subsequent expression of the DCC toxic. Alternatively, extracellular *Spiroplasma* could produce a toxin capable of penetrating host cells and interacting with the dosage compensation machinery.

Interestingly, the strain of *Spiroplasma* that protects *D. neotestacea* against parasites generates a Shiga-like toxin that penetrates cells and selectively depurinates nematode rRNA [16]. Destruction of nematode ribosomes reduces the parasite burden to tolerable levels.

An added incentive to understand the mechanisms by which symbiotic bacteria manipulate their hosts is that this field is becoming crucially important for the control of vector-born diseases. Some maternally transmitted symbionts offer protection against RNA viruses, nematodes and wasps as well as fungal and bacterial pathogens (reviewed in [4]). Researchers are working to exploit these and other features of bacterial symbionts in efforts to limit transmission of dengue fever, malaria and filarial diseases (reviewed in [17]). For example, the mosquito that transmits dengue fever, *Aedes aegypti*, is not normally infected with *Wolbachia*. However, *A. aegypti* can be infected with a *Wolbachia* strain from *D. melanogaster*, and this reduces dengue virus replication within the mosquito host (reviewed in [18]). The possibility of using *Spiroplasma* infection in a similar manner to interrupt transmission of malaria, river blindness or other diseases caused by nematodes is exciting [19]. Taking advantage of symbiont–host relationships, such as male-killing, to drive infections through natural populations of disease vectors is a potentially powerful tool to interrupt transmission.

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