Varroa mite evolution: A neglected aspect of worldwide bee collapses?

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Highlights:

- Breeding bees for *Varroa* tolerance has largely ignored potential mite adaptation
- *Varroa* genetic diversity is greater than previously envisioned and they adapt rapidly
- We suggest that tolerance is best viewed as a 'shared trait' of hosts and parasites
- Focusing on the interaction between partners can inform research and breeding

Abstract

While ectoparasitic *Varroa* mites cause minimal damage to their co-evolved ancestral host, the eastern honey bee (*Apis cerana*), they devastate their novel host, the western honey bee (*Apis mellifera*). The host switch caused worldwide population collapses, threatening global food security. *Varroa* management strategies have focused on breeding for bees for tolerance. But, can *Varroa* overcome these counter-adaptations in a classic coevolutionary arms race? Despite increasing evidence for *Varroa* genetic diversity and evolvability, this eventuality has largely been neglected. We therefore suggest a more holistic paradigm for studying this host-parasite interaction, in which '*Varroa*-tolerant' bee traits should be viewed as a shared phenotype resulting from *Varroa* and honey bee interaction.

Keywords: coevolution, honey bees, host switch, parasites, tolerance

Introduction

Honey bee populations decline in many countries worldwide. This phenomenon has both ecological and economical impacts, as honeybees are the main pollinators in most agricultural systems, as well as in natural habitats (Paudel et al. 2015; Potts et al. 2010; Hung et al. 2018). It is now well established that the reasons for this decline are multifactorial, but primarily driven by *Varroa* mites and viruses that they vector (Steinhauer et al. 2018). In the colony of its original host, the eastern honey bee (*Apis cerana*), *Varroa* mites are tolerated while causing minimal damage (Rosenkranz et al. 2010). However, due to the globalization of beekeeping, eastern honey bees and their mites have come into contact with the western honey bee (*Apis mellifera*). This caused exceptionally rapid switches by two mites (*Varroa destructor* and *Varroa jacobsoni*) to this new host, causing colony collapse and damage estimated in billions of dollars (Gallai et al. 2009). As the use of chemical pesticides has been severely reduced in many countries, one of the notable control approaches is to breed for "*Varroa* tolerant" bees (Carreck 2011). This review aims to highlight the mites' role as actively adapting members of the coevolutionary interaction with honey bees, an observation that has significant pest control implications.

'*Varroa*-tolerant' bees and their genetic basis

Honey bees have experienced diverse selective pressures, but domestication by humans led to a major turning point in their evolution. From the first record of honey bees domestication in Egypt 2600 BCE, bee colonies were selected for traits beneficial to humans. At first probably this may have been an incidental consequence of beekeeping, but later as a result of sophisticated breeding programs. The main desired traits were high honey yield and gentle temperament, but also tolerance of diseases and pathogens (vanEngelsdorp & Meixner 2010). While bee diseases have been a continuing problem for centuries, the emergence of the *Varroa* mite as a particularly devastating pest in *A.*

mellifera colonies has caused particular concern. Beekeepers as well as bee researchers have bred for traits that may help the bee colony to cope and survive mite infestation, particularly as a long-term and sustainable alternative to pesticides. This approach has solid theoretical justification, given that millions of years of coevolution have allowed the ancestral host, the eastern honey bee (*Apis cerana*) to tolerate the mite, and some subspecies of *A. mellifera*, such as the African and Africanized varieties are naturally resistant (Mondragón et al. 2006). In addition, several previously susceptible populations have evolved to tolerate *Varroa* (Seeley 2017; Brettell & Martin 2017; Locke 2016; De Jong & Soares 1997; Mikheyev et al. 2015). In that spirit, some breeding programs have been selecting bee colonies using "live and let die" strategy, in which the colonies remain untreated and only a small portion of the surviving colonies will allow to contribute queens and drones for the next generations (Kefuss et al. 2004). For a few of the '*Varroa*-tolerant' lines the mechanism of *Varroa* tolerance was investigated, and, increasingly, the genetic basis underlying the tolerance is becoming understood, potentially improving the efficiency of these programs.

The bee breeding programs have resulted in a number of widely known and commercially used lines. In the US the three '*Varroa*-tolerant' lines: the *Varroa* Sensitive Hygiene (VSH), the Russian honey bees, and the Minnesota Hygienic lines (Spivak et al. 2009; Rinderer et al. 2010). In Europe, several tolerant lines were bred by natural selecting from local lines, such as in France (Kefuss et al. 2015), and in Norweig (Swenson et al. 2018). In addition, *Varroa*-targeted breeding programs have been concentrated by the COLOSS initiative, that leads several pan-European experiments to assess the *Varroa* tolerance capacity of local bees (http://coloss.org).

Over the past decade, as molecular methods have improved and became less costly, our knowledge of bee genetics increased with the growing understanding of the bee genome (reviewed by (Grozinger & Robinson 2015; Niño & Cameron Jasper 2015)). Altogether, these advances enabled the identification of genetic markers, those are aimed to improve breeding for healthier bees, and shorten this years-long process. An obvious great attention was given for the search of markers for '*Varroa*-tolerant' bees, by trying to correlate specific markers to specific useful traits (Zakar et al. 2014) (Figure 1). More recently, a few studies exploited the approach of genome-wide association study (GWAS) to detect specific markers, those include SNPs for bees' hygienic behavior (Spötter et al. 2016), mitochondrial DNA SNPs that discriminate between *Varroa* susceptible and tolerant bee colonies (Kim et al. 2019), and ecdysone-induced gene in bee pupa that was found to affect *Varroa* reproduction (Conlon et al. 2019).

Varroa genetic variance

While bee genetic architecture is well investigated, little is known about how *Varroa* have evolved in the last 60 years since its shift to *A. mellifera*. *Varroa* were generally believed to be clonal populations with low genetic variability according to surveys using randomly amplified polymorphic DNA (RAPD) markers (Kraus & Hunt 1995), mitochondrial DNA, and microsatellites (Solignac et al. 2005). *Varroa* colonies regularly sib-mate and have correspondingly high inbreeding coefficients (Broeckx et al. 2019). However, more recent studies using different sampling regimes (Dietemann et al. 2019; Gajić et al. 2019), and whole-genome data (Techer et al. 2019), show *Varroa* genetic is much more diverse than thought before. Regardless of underlying genetic diversity, extensive evidence exists that *Varroa* experience high selective pressures and rapidly evolve in response to pesticides treatments. Pyrethroids resistant mites were reported across Europe (Martin 2004), the UK (Thompson et al. 2003), and the middle east (Israel) (Mozes-Koch et al. 2000). Interestingly, this resistance can be reversed, when stop exposing for a few years, suggesting a potential cost (Milani & Della Vedova 2002). In addition, mites evolved rapid resistance for other chemical families such as organophosphorus (Elzen et al. 2002; Spreafico et al. 2001), and Formamide (Rodríguez-Dehaibes et al. 2005; Maggi et al. 2010). And in some cases, mites showed resistance to multiple active chemicals, which makes impossible to rotate between available pesticides (Sammataro et al. 2005). Consequently, *Varroa* mites do have a potential for rapid evolution, at least *vs*. chemicals, and deserves further consideration.

"Varroa tolerant" traits as host-parasite shared traits

A key property of coevolutionary systems highlighted in the host-parasite literature is the "shared control" of some traits, namely those that emerge from the joint action of the interacting genotypes (Restif & Koella 2003). Classically, antagonistic coevolution can result in arms races centered around key traits such as host resistance/tolerance, and pathogen virulence. However, while this is well-established in other agricultural systems such as plant diseases (Lambrechts et al. 2006; Sacristán & García-Arenal 2008), it has received less attention in the study of invertebrate parasites such as *Varroa* mites. Although all bee tolerance traits involve direct interaction with *Varroa*, until recently the possible contribution of *Varroa* genetics to these phenotypes was generally overlooked (Figure 1). However, this has been changing recently. Beaurepaire et al. (2019) have noted the ability by *Varroa* to adapt as a possible factor in a host-parasite arms race, as changes in the genetic structure of mite population in '*Varroa*-tolerant' colonies were higher compared to mites in susceptible colonies, a realization that has led to recent integrative work examining the effect of host genetics on the shared phenotype . For example, Broeckx et al (2019) compared reproducing and non-reproducing mites using DNA microsatellites but found no difference. Recent work has also tried to disassociate the bee-*Varroa*-virus complex by examining the virus effect only (Remnant et al. 2019; Thaduri et al. 2019). While this work provides illuminating insights into bee-virus interactions, we would like to caution that an artificial uncoupling between the *Varroa* and bee genomes ignores the possibility that they actually interact, with important consequences for the course of infection. This may lead to failure in detecting important loci that facilitate the *Varroa* and bee adaptation, and misinterpretation of results for breeding programs and research of '*Varroa*-tolerant' bees. This idea can be extended further, since social immunity requires the interaction between bee brood, adult bees and *Varroa*, requiring careful consideration of the contribution of each.

In general, coevolution favors a stable equilibrium between host and parasite (Restif & Koella 2003). The equilibrium point depends on diverse genetic and environmental factors and cannot be predicted or generalized (Read 1994; Thompson 2005; Techer et al. 2019). However, in the original association between *Varroa* and *A. cerana*, *Varroa* virulence is fairly attenuated (Rath 1999; Lin et al. 2018). It is therefore reasonable to hypothesize that this will be the ultimate equilibrium state also for *A. mellifera*. In fact, mathematical modeling suggests that a benign *Varroa* haplotype will outcompete the virulent one (Vetharaniam & Barlow 2006). As a result, it could be that in some cases of reported '*Varroa*-tolerant' *A. mellifera* colonies in the wild, the survival of the bees can be also explained by less virulent mite population. *Varroa* may be evolving to reduce honey bee colony mortality to provide itself with a longer-lasting resource. Therefore, observed naturally occuring resistance may result from bee or *Varroa* evolution.

Incorporation of *Varroa* genetics may broaden our understanding of traits that were so far explained by mechanisms and genetics of the bee only. For example, a few studies showed that '*Varroa*-tolerant' bees have better ability to recognize mite-infested cells compared to control bees (Martin et al. 2002; Mondet et al. 2016). However, this could also be explained by the variance in *Varroa* camouflage abilities, or variance in *Varroa* cuticular profile between colonies (Kather et al. 2015; Le Conte et al. 2015), in addition to differences in bee sensitivity to *Varroa* presence. *Varroa* genetic variance can also explain inconsistency in '*Varroa*-tolerant' traits in bee lines, and "unsuccessful" breeding programs (Odemer 2019), or failures to import '*Varroa*-tolerant' lines, as often experienced in breeding programs (Meixner et al. 2015). However, as these cases are likely underreported, they are harder to interpret. In one natural population, Seeley (2007) found that there was no difference in *Varroa* growth rates in apparently resistant feral colonies and sensitive commercial strains. While the population in question has undergone a strong selective event after arrival of *Varroa* (Mikheyev et al. 2015), whether this or milder mite strains result in its apparent persistence remains unclear. Recovery of natural bee-swarms a few years after *Varroa* introduction were recorded in a few instances, and were suggested to be partially due to variance in *Varroa* virulence (Fries et al. 2006; Villa et al. 2008).

Implications and conclusions

In conclusion, we suggest that the design of bee breeding programs for desired '*Varroa*-tolerant' traits should be addressed from a broader perspective that include both host and parasite genetics, and treated as a shared traits. *Varroa* genetic variance should studied and included as one of the factors influencing the capacity of bees to tolerate *Varroa* mite, in addition to environmental conditions (Le Conte et al. 2007; Currie & Tahmasbi 2008) and bee nutrition (Alaux et al. 2011; Huang 2012). Understanding *Varroa* genetic architecture and quantifying its possible contribution to '*Varroa*-tolerant' traits should enable improved breeding programs that will account for possible coevolutionary interactions in the future. Given that *Varroa* is a fact of life for *A. mellifera,* evolution of less virulent strains of *Varroa* over time, as suggested by mathematical modeling (Vetharaniam & Barlow 2006) may decrease the severity of their impact. When studying bee-*Varroa* interactions regular genetic monitoring of both players should be conducted before and during breeding programs. Such temporal surveys will give us a clue about *Varroa* population genetic dynamics in response to changes in selective pressures, either through pesticide treatment or '*Varroa*-tolerant' phenotypes. These data can help improve our *Varroa* management, for example by rational pesticide rotation, and directed selection of bee lines according to the current *Varroa* population. In the long term, such genetic monitoring of the mite-bee population will enable us to predict eruptions of mite infestation, or resistance events for novel pesticides before they occur, by modeling. However, all the available genetic tools to study *Varroa* are low-resolution and new methods are urgently needed.

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* of special interest

** of outstanding interest

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Figure 1. Mechanisms of *Varroa* tolerance by bees: much known about the bee, little about the mite. Typically a '*Varroa*-tolerant' colony will possess a few of the following desired traits: (1) hygienic behavior (removal of dead and diseased brood), (2) grooming behavior, (3) suppression of *Varroa* reproduction and (4) short post-capping stage duration. The bee-genetic basis of these traits is well studied (reviewed by (Grozinger & Robinson 2015; Niño & Cameron Jasper 2015; Zakar et al. 2014)). However, although *Varroa* participates in all these interactions, the role of its genetics has been neglected.