



Review

Parasite resistance and tolerance in honeybees at the individual and social level[☆]Christoph Kurze^{a,*}, Jarkko Routtu^a, Robin F.A. Moritz^{a,b,c}^a Institute for Biology, Martin Luther University Halle-Wittenberg, Hoher Weg 4, D-06099 Halle (Saale), Germany^b German Institute for Integrative Biodiversity Research (iDiv), Deutscher Platz 5e, D-04103 Leipzig, Germany^c Department of Zoology and Entomology, University of Pretoria, Roper St., 0002 Pretoria, South Africa

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ABSTRACT

Organisms living in large groups, such as social insects, are particularly vulnerable to parasite transmission. However, they have evolved diverse defence mechanisms which are not only restricted to the individual's immune response, but also include social defences. Here, we review cases of adaptations at the individual and social level in the honeybee *Apis mellifera* against the ectoparasitic mite *Varroa destructor* and the endoparasitic microsporidians *Nosema ceranae* and *Nosema apis*. They are considered important threats to honeybee health worldwide. We highlight how individual resistance may result in tolerance at the colony level and vice versa.

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1. Introduction

The host–parasite dynamics in social organisms are different compared to those of solitary ones. In particular, large colonies of social insects provide optimal conditions for parasite growth and

horizontal transmission due to the incubator-like environment of the nest, which is crowded with often tens of thousands of susceptible hosts (Schmid-Hempel, 1998). The honeybee *Apis mellifera* provides an important model system for host–parasite relationships, primarily because of its role in agriculture and ecosystem functioning. Bees are crucial pollinators for approximately 70% of all crop species worldwide as well as for the wild flora (Klein et al., 2007; Potts et al., 2010). Thus, the alarming reports of worldwide losses of managed honeybees have sparked scientific debates and stimulated intensive research on honeybee health in the past decades.

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Although the role of pathogens and parasites in recent honeybee declines is still not fully understood (Lundin et al., 2015; Moritz and Erler, 2016), pathogen epidemiology and host–parasite interactions have been studied in considerable detail (Ball and Bailey, 1991; Fries, 2010; Rosenkranz et al., 2010; Evans and Schwarz, 2011). Honeybees are vulnerable to a broad spectrum of parasites and pathogens, but two parasites clearly stand out in scientific discussions on honeybee health over the last decade (2005–2015), the ectoparasitic mite *Varroa destructor* and the endoparasitic *Nosema ceranae* with more than 800 and 400 publications, respectively, listed in the Web of Science (www.thomsonreuters.com/WebOfScience). Both parasites have been introduced into *A. mellifera* only a few decades ago and they are therefore suitable for revealing swift reciprocal adaptations. In this review, we will focus on the rapid adaptations in host defence against both parasites.

There are two host defence strategies to be distinguished, resistance and tolerance. Resistant hosts are able to limit the parasite burden, whereas tolerant hosts are able to limit the harm caused by a given parasite burden (Råberg et al., 2009). Host tolerance is described as a reaction norm to illustrate host fitness alterations as a function of parasite burden, i.e. for more tolerant hosts, fitness decreases less with increasing parasite intensity (for detailed reviews see Råberg et al., 2009; Kutzer and Armitage, 2016). Although a trade-off between tolerance and resistance was reported in mice and in *D. melanogaster*, tolerance is not generally associated with a cost (Kutzer and Armitage, 2016). Both strategies are likely leading to different host–parasite dynamics (Best et al., 2014). Whereas resistance may lead to an antagonistic host–parasite coevolution through Red Queen (RQ) oscillations of host and parasite genotype frequencies (Agrawal and Lively, 2002; Salathé et al., 2008), tolerance should slow RQ dynamics down by eliminating the negative frequency dependence due to marginal fitness effects on both host and parasite within a certain range of infection intensity (Råberg et al., 2009; Best et al., 2014).

When applying theoretical models to honeybees, one needs to consider the social structure of the host population and male haploidy (Schmid-Hempel and Jokela, 2002; Kidner and Moritz, 2013). Interestingly, resistance may only rarely result in RQ dynamics when high susceptibility of the host population and transmission rates reach a certain threshold (Kidner and Moritz, 2013). We are not aware of any theory addressing tolerance similarly with multilevel selection and haplodiploidy. Yet, a distinction between resistance and tolerance is essential for our understanding of host–parasite interactions. In societies of social insects it is also important to differentiate between resistance and tolerance at the individual and at the colony level. A colony composed of resistant individuals is likely to also be resistant at the colony level. However, if not all individuals of a colony are resistant, the colony may still tolerate an infection without experiencing negative fitness effects such as in the case of the *Varroa*-tolerant honeybee colonies from Gotland (see Section 3.2). In contrast, a colony composed of tolerant individuals might also become resistant against endoparasites if the infection can be cleared at the colony level as suggested for *Nosema*-tolerant honeybees from Denmark (see Section 4.2). We will therefore embark on dissecting the defence mechanisms against *Nosema* and *Varroa* and assessing how these determine resistance and tolerance at both the individual and the colony level.

2. The parasites

2.1. *Varroa destructor*, an ectoparasitic mite

V. destructor (formerly also *V. jacobsoni*) (Anderson and Trueman, 2000) is an obligate ectoparasite of brood and adult hon-

eybees, which is currently considered to have the most negative impact on apiculture (Dainat et al., 2012; Kielmanowicz et al., 2015). *Varroa*-infested colonies have been reported to die after 2–3 years if not systematically treated (Rosenkranz et al., 2010). *V. destructor* has originally coevolved with *Apis cerana* in Asia, but has nearly reached worldwide distribution now, with the exception of Australia and some isolated islands, after two host shift events to *A. mellifera* in Korea and Japan about 60–100 years ago (Oldroyd, 1999; Roberts et al., 2015a).

The life cycle of this haplodiploid mite is highly adapted to the development of drone and worker brood, allowing only a narrow time window for reproductive success (reviewed by Rosenkranz et al., 2010). Briefly, after invasion of a suitable host cell just before capping, the female mite starts feeding on the 5th instar larval haemolymph and initiates oogenesis within a few hours (Garrido and Rosenkranz, 2004). Specific host signals trigger egg-laying of the mite, starting with an unfertilised haploid male egg after approximately three days and followed by up to four or five fertilised diploid female eggs in 30 h intervals (Frey et al., 2013). The offspring mites hatch a few hours after oviposition and pass through proto- and deutonymph stages until they become sexually mature following a final moult after approximately seven days. As soon as the first female reaches sexual maturity the male mates with it, triggered by female sex pheromones, until the next female is mature (Ziegelmann and Rosenkranz, 2014). Fertilised females are released when the host honeybee hatches and can be transmitted between individual honeybees within the same colony or might even be spread to a new host colony through foraging and drifting honeybees (Rosenkranz et al., 2010).

V. destructor infestations have a strong negative effect on the fitness of honeybees both at the individual and the colony level. Infested honeybee pupae experience severe nutritional deficiencies during development depending on the parasitisation rate, as both adult female mite and offspring feed on their haemolymph (Garedew et al., 2004). This feeding activity at the early sensitive life stage, together with additional secondary infections, can alter the host physiology and may reduce the immunocompetence, flight and navigation performance when adult, which will ultimately result in decreased honeybee survival (e.g., Duay et al., 2002; Amdam et al., 2004; Kralj and Fuchs, 2006; Annoscia et al., 2012). Alongside with direct effects of *Varroa* parasitisation come indirect effects, because *Varroa* acts as an incubator and important vector of honeybee viruses (Martin et al., 2012; Mondet et al., 2014). Best studied is the fatal interplay between mite and deformed wing virus (DWV) (de Miranda and Genersch, 2010; Martin et al., 2012; Nazzi et al., 2012; Francis et al., 2013; Kielmanowicz et al., 2015).

2.2. *Nosema apis* and *N. ceranae*, two intracellular microsporidians

N. apis is a long-known parasite of *A. mellifera*, whereas *N. ceranae* is presumed to have more recently undergone a host switch from *A. cerana* to *A. mellifera* (Fries, 2010). Today, *N. ceranae* has reached global distribution and has progressively become more prevalent over the past decade (Klee et al., 2007; Paxton et al., 2007). *N. ceranae* has also been found to infect other honeybee (Chaimanee et al., 2010; Traver and Fell, 2015) and bumblebee species (Plischuk et al., 2009; Li et al., 2012; Fürst et al., 2014). As *N. ceranae* has only recently been described and can only be reliably identified by polymerase chain reaction, a clear distinction between both *Nosema* species especially in older publications might be difficult (Fries, 2010).

The role and magnitude of the damage of *N. ceranae* infections in honeybee colonies has been controversially discussed. Major implications of *N. ceranae* infections in colony losses have been mainly reported in Mediterranean regions (e.g., Higes et al., 2008;

Bacandritsos et al., 2010; Soroker et al., 2011), but have been ruled out in countries with a temperate climate (e.g., Genersch et al., 2010; Dainat et al., 2012; Budge et al., 2015). This suggests that climate may influence its virulence (Martín-Hernández et al., 2009; Gisder et al., 2010). Irrespective of this, some studies suggested a higher virulence of *N. ceranae* than *N. apis* (Paxton et al., 2007; Martín-Hernández et al., 2011; Williams et al., 2014), whereas other studies neither reported higher proliferation rates for *N. ceranae* nor increased host mortality (Forsgren and Fries, 2010; Milbrath et al., 2015; Natsopoulou et al., 2015). Nevertheless, the asymmetric interspecific competition between both *Nosema* species in sequential co-infections may provide an alternative explanation for the global invasion success of *N. ceranae* (Natsopoulou et al., 2015).

Both *Nosema* species undergo analogous life cycles and are typically horizontally transmitted via the faecal–oral route by ingestion of spores from the environment (Bailey, 1955; Fries, 2010; Graystock et al., 2015), but might possibly also be sexually transmitted (Roberts et al., 2015b). Ingested *Nosema* spores germinate in the midgut lumen and penetrate the membrane of epithelial cells with their polar tube to inject their sporoplasm (Fries et al., 1992). The spherical sporoplasm develops into a spindle-shaped meront, which replicates several times until first oval sporonts and the new generation of spores are formed after 4 days post-infection (Fries et al., 1992; Gisder et al., 2011). Ultimately they are released into the lumen via cell lysis, where they may infect neighbouring cells or may be defecated (Fries, 2010). Although *Nosema* species are known to have lost sexual reproduction (Ironside, 2007), recent reports of recombination in *N. ceranae* raise new questions about its life cycle (Sagastume et al., 2011; Gómez-Moracho et al., 2015).

Despite the controversies mentioned above, *N. ceranae* infections have been shown to negatively affect honeybee health at the individual level, which may also lead to reduced colony fitness under certain conditions. Depending on the intensity of the *Nosema* infection, honeybees may experience nutritional and energetic stress (e.g. Mayack and Naug, 2009; Martín-Hernández et al., 2011; Kurze et al., 2016), and/or immunosuppression (Antúnez et al., 2009; Chaïmanee et al., 2012; Holt et al., 2013; Aufauvre et al., 2014), which possibly makes them also more vulnerable to other pathogens such as black queen cell virus (BQCV). Additionally, *N. ceranae* appears to inhibit apoptosis in its host cell, which might be a mechanism of self-protection, thus enhancing its reproductive success (Higes et al., 2013; Kurze et al., 2015). Recent transcriptome and proteome data also suggest modifications in epithelium renewal and apoptosis-related pathways in association with *N. ceranae* infections (Dussaubat et al., 2012; Holt et al., 2013; Aufauvre et al., 2014; Vidau et al., 2014).

3. Defence against an ectoparasite

3.1. Social level

A. mellifera resistance to *V. destructor* is characterised by many different mechanisms ranging from colony level to individual responses. A major resistance mechanism at the colony level is swarming, as it reduces the mite intensity (lost in the swarming bees) and simultaneously having a broodless period in the old hive hindering mite reproduction. Colony level tolerance in the new nesting site is caused by reproductive timing and type as mainly worker brood is produced initially, where the mites have lower fitness (Fries et al., 2003). Another type of swarming is non-reproductive (absconding). When absconding, all adult individuals of the colony, including the queen swarm, leave the brood and most of the stores behind and establish a new nest elsewhere (Fig. 1A). In this process all parasites in the brood and pathogens in the stores are also left behind. Absconding is therefore a most

efficient natural colony level defence mechanism against *Varroa*. It is particularly pronounced in African honeybees where colonies readily leave the hive whenever conditions become unfavourable (Hepburn and Radloff, 1998).

The best studied behaviourally controlled resistance mechanism is the so-called *Varroa* sensitive hygiene (VSH, formerly called suppressed mite reproduction) and grooming behaviour (Fig. 1A), collectively called social immune response (Cremer et al., 2007). VSH is a social level trait where typically only few paternal lines express the task at a specific time of their adult life due to temporal polyethism. For example, hygienic behaviour consists of a sequence of different subcomponents (detection, opening and removing), which may be inherited independently and performed by different workers in the colony (Moritz and Fuchs, 1998; Oxley et al., 2010; Tsuruda et al., 2012). There is also a cost to VSH behaviour, as with very low mite detection thresholds, relatively large numbers of uninfected pupa are removed as well (Vandame et al., 2002). The heritability of VSH has been estimated to be rather low at $h^2 = 0.18$ in *A. mellifera* (Boecking et al., 2000). *A. cerana*, having a long coevolutionary history with *V. destructor* and *V. jacobsoni*, removes the *Varroa* mites from the worker brood to such an extent that the mites will not even enter the worker brood but instead reproduce exclusively in the drone brood (Peng et al., 1987). The *A. cerana* drone cell cap is hard and has a specific form with an opening at the top, which may be an adaptation to mite infection. If more than one *Varroa* female enters an *A. cerana* drone cell, the drone will not be able to open the cell cap since workers are not helping the drones to emerge. This mechanism most effectively reduces high infection rates of *Varroa* and keeps the *Varroa* population typically below 800 individuals per colony (Rath, 1999).

Grooming behaviour is the ability of adult honeybees to remove phoretic mites from themselves or other bees. The mite is large relative to the size of the honeybee so it is likely that the camouflage of cuticular carbohydrates plays a significant role in its phoretic lifecycle phase as well as in the brood. Indeed, *V. destructor* can rapidly change its cuticular hydrocarbon profile, i.e. odour, when moving from one host colony to another (Kather et al., 2015; Le Conte et al., 2015). *Varroa* mites are also highly adapted in holding on to bees and bore between the abdominal sclerites of the host during long phoretic phases. However, in spite of the parasite adaptations honeybees, in particular *A. ceranae*, are able to detect and remove the *Varroa* mites (Le Conte et al., 2015). The traits associated with behavioural resistance are usually complex colony level traits. They are not only complex because the behaviour as such is composed of different coordinated subtasks, but also because the queen is highly polyandrous resulting in a composite genotypic colony structure (Adams et al., 1977).

3.2. Individual level

The most solid case of resistance to *V. destructor* has independently emerged as a consequence of natural selection on the island of Gotland (Sweden) and in Avignon (France). In both cases the resistance to the parasite is based on a – slightly different – inhibition of the mite's reproduction, with *V. destructor* entering the brood but failing to produce offspring or exhibiting delayed egg-laying (Le Conte et al., 2007; Locke and Fries, 2011; Locke et al., 2012) (Fig. 1A). Part of this resistance may also be due to tolerance of the resistant honeybee populations to virus load (Locke et al., 2014). However, in these populations individual resistance of drones is a main driver of tolerance on the colony level, mainly due to reduction of mite population growth rate (Locke et al., 2012). *V. destructor* has an eight- to ten-fold preference for drone brood, as the drones are larger in size and their post-capping development lasts 14 days instead of 12 days in worker bees. In the Cape honeybee, *A. mellifera capensis*, worker development even lasts

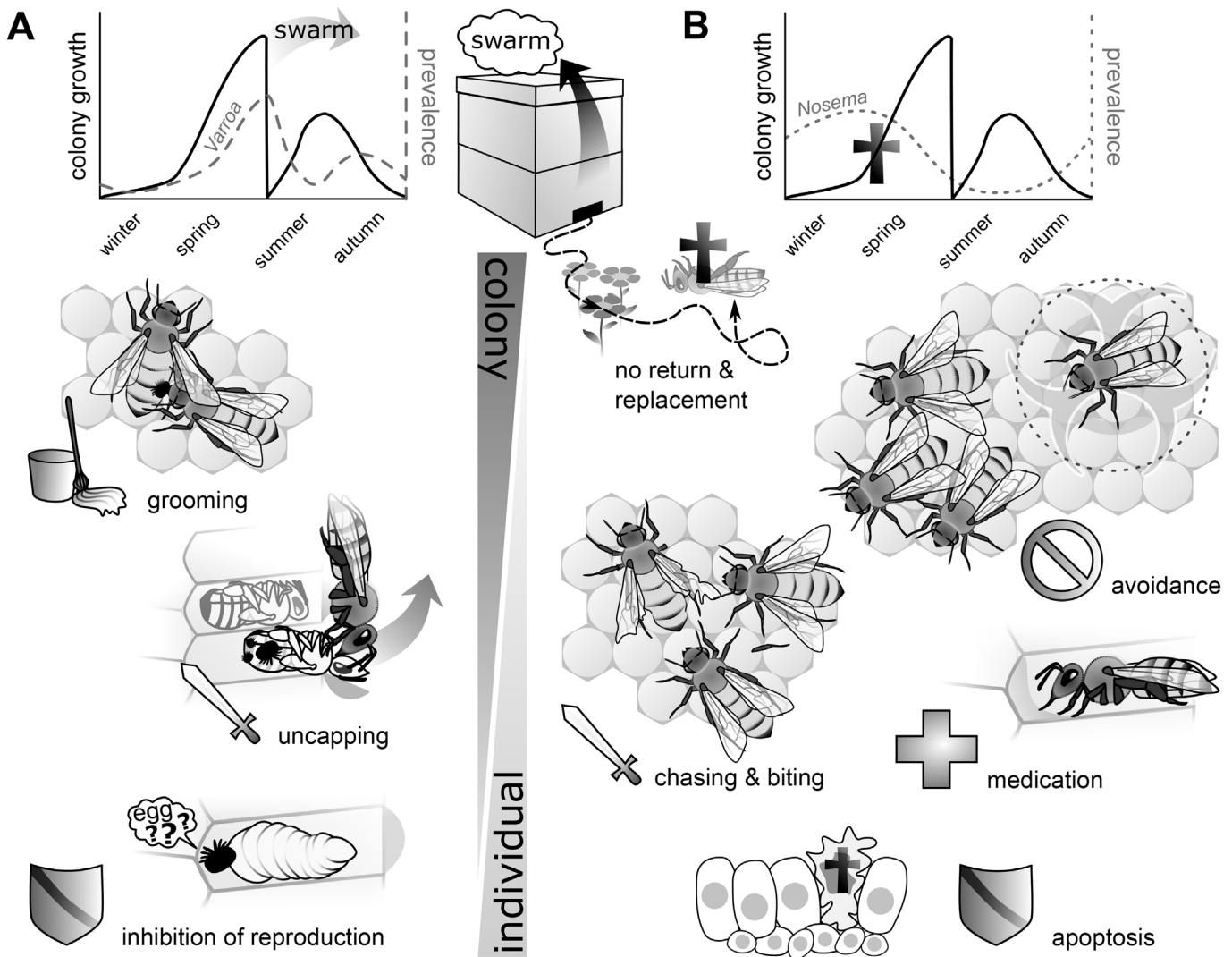


Fig. 1. Defences against (A) *Varroa* and (B) *Nosema*, ranging from the colony level to the individual level. (A) Swarming/absconding and leaving infested brood behind in the hive; grooming behaviour to remove and kill mites from nest mates; *Varroa*-sensitive hygienic behaviour (VSH) by detecting and uncapping infested brood cells to remove the pupae from the colony and kill all immature mites; inhibition of the mite's reproduction where *V. destructor* enters the brood cell but fails to produce offspring. (B) Replacement of old workers through rapid colony growth in spring/infected bees may not return to the colony as they age faster and become foragers sooner; infected bees display modified cuticular hydrocarbons and can be either attacked/killed or avoided; bees choose specific honeys for self-medication; escape from the inhibition of apoptosis by *N. ceranae* in midgut epithelial cells.

only 9 days on average. Hence, only a single reproductive mite offspring can develop per worker cell, which drastically inhibits the growth of the mite population in *A. m. capensis* colonies (Moritz and Hänel, 1984). In addition, drones are also fed more often and longer by nurse bees that may involuntarily carry mites to the brood, thus increasing the probability of a mite infection (Cervo et al., 2014). Therefore, any traits of resistance to *V. destructor* that are expressed in the drone brood will have a strong influence on *V. destructor* population growth rate, fundamentally interfering with the host–parasite coevolution.

Resistance of individual drones may enable the whole colony to tolerate *Varroa* and survive under the infection, as even a low frequency of resistant drones directly reduces the growth rate of the mite population. The colony may become tolerant because it can be infected but the infection only rises to a certain limit depending on the mite reproduction in the worker brood. Yet, if the genes determining drone resistance also result in worker resistance, colonies are expected to become fully resistant. In this case, natural selection should be particularly swift because of the haploid male genome.

Potential resistance gene(s) will spread more rapidly in the population due to fitness advantages of resistant drones (Kidner and Moritz, 2015).

V. destructor has only a very narrow time window for starting reproduction after enclosure in the brood cell (Rosenkranz et al., 2010). Within 5 h after the capping of the brood cell, the mite consumes the first haemolymph meal and only a few hours later oogenesis begins. If the female mite fails to initiate ovary activation in this narrow time window, it will remain infertile. The ovary activation has been suggested to depend on cuticular hydrocarbon stimuli (Aumeier et al., 2000; Frey et al., 2013). Hence, a lack of such stimuli might be one way to prevent mite reproduction. However, it is also possible that specific compounds in the first haemolymph meal can inhibit the activation of the mite's reproductive cycle. Clearly, understanding the underlying physiological processes that interfere with the crosstalk between the mite and the host larva will be fundamental to comprehend this important step in host–parasite coevolution. This is the most critical phase in

the reproductive cycle of the mite, where the host has the opportunity to evolve true resistance.

4. Defence against an endopathogen

4.1. Social level

The colony dynamics do not only influence the prevalence of brood parasites like *Varroa*, but also affect the prevalence of *Nosema* infections in adult bees (Fig. 1B). Although the prevalence of *N. apis* and *N. ceranae* may differ, also depending on the climatic conditions (Fries, 2010; Gisder et al., 2010), typically *Nosema* prevalence dynamics in temperate climates (also in the southern hemisphere) are characterised by an increase of *Nosema* infections during winter, reaching a high peak in spring before the old winter workers are replaced by many uninfected young workers (Borchert, 1928; Bailey, 1955; Doull and Cellier, 1961). However, these dynamics may disappear under climatic conditions favourable for *N. ceranae* (Martín-Hernández et al., 2007; Higes et al., 2008). In principle there are two options for a healthy worker to reduce chances for parasite transmission within the colony: either remove infected workers from the colony or avoid contact with infected workers (Fig. 1B). Infected workers appeared to be attacked, including biting, stinging and chasing, by their uninfected nestmates, which in some cases even resulted in lethal attacks in these experimental groups (Müller et al., 2015). Such agonistic behaviour, which was associated with significantly altered expressions of cuticular hydrocarbons, was also observed in DWV-infected and generally immune-challenged honeybees (Richard et al., 2008, 2012; Baracchi et al., 2012). However, healthy workers were also observed to avoid highly infected nestmates (Müller et al., 2015). Interestingly, although *N. ceranae* and *N. apis* infections indeed resulted in changes of hydrocarbon profiles in honeybees, these specific cues may not always lead to altered social interaction between nestmates (Murray et al., 2015). Thus, the recognition of infected individuals likely reflects an adaptive social immune response towards *Nosema* infections.

A special case of social immunity is self-medication. Honeybee products such as honey, bee bread (pollen stored in the combs) and propolis contain naturally antibiotic, antifungal, and antiviral compounds of plant products, which are crucial for food and nest hygiene and may also be considered as medication (reviewed by Erler and Moritz, 2015). For example, honeybees collected more antiparasitic resin when they were infected with the fungal pathogen *Ascosphaera apis*, which causes chalkbrood disease, thereby reducing the infection intensity (Simone et al., 2009; Simone-Finstrom and Spivak, 2012). Likewise, specific antiparasitic honey types were preferably chosen by *N. ceranae*-infected workers in comparison to healthy individuals in laboratory tests (Gherman et al., 2014).

4.2. Individual level

Another mechanism promoting the reduction of infected workers in the colony is that *N. apis*-infected workers age more quickly and begin risky foraging earlier in life (Wang and Moeller, 1970; Woyciechowski and Moroń, 2009), which may also be the case for *N. ceranae*-infected workers (Wolf et al., 2014). Furthermore, *N. ceranae*-infected foragers may often be too weak to return to the hive, showing significantly reduced homing abilities (Wolf et al., 2014). This may be due to the energetic stress imposed by *Nosema* spp. (Mayack and Naug, 2009; Kurze et al., 2016). Thus, if infected workers that tolerate the infection sufficiently to allow for flight ability do not return from flights, this would limit the transmission

of *Nosema* to newly emerged uninfected workers and may lead to a “clearance” of the infection in the hive and colony resistance.

Besides external defence mechanisms, honeybees possess an innate immune system for internal defence. Their immune system, although consisting only of a reduced set of immune genes (Evans et al., 2006), displays nuanced patterns of selection between bee taxa, which likely reflect different parasite pressures and life history traits among them (Barribeau et al., 2015). Also, *N. ceranae* would be expected to impose a strong selection pressure on the immune system of honeybees. Although *N. ceranae* infections are associated with the suppression of immune genes (Antúnez et al., 2009; Chaimanee et al., 2012; Holt et al., 2013; Aufauvre et al., 2014) and the inhibition of apoptosis in sensitive honeybees (Higes et al., 2013; Kurze et al., 2015), recent transcriptome and proteome analyses revealed increased expression levels of antioxidants, which might indicate an alternative immune response (Dussaubat et al., 2012; Vidau et al., 2014).

Possible defence mechanisms against *N. ceranae* infections were studied in some detail in honeybees that were artificially selected for resistance over two decades in Denmark, resulting in a decrease from 60–80% down to 10% *Nosema* prevalence in these colonies (Hatjina et al., 2014). When infecting individual drones from this breeding line with *N. ceranae*, they showed significantly higher survival and expression levels of genes of the innate immune system, in particular of the *Toll* pathway, than *Nosema*-sensitive honeybees after one week of infection (Huang et al., 2012). Surprisingly, *N. ceranae* developed similarly high infection levels in these drones as in sensitive honeybees, suggesting tolerance rather than resistance at the individual level (Huang et al., 2012; Kurze et al., 2015). Another indication for tolerance is that the energy budget appears not to be negatively affected like in sensitive honeybees (Mayack and Naug, 2009; Martín-Hernández et al., 2011; Kurze et al., 2016).

If these bees are truly tolerant, how can this lead to resistance observed at the colony level? According to a quantitative trait loci (QTL) mapping study based on drones from a hybrid queen between both genotypes, major QTL (on chromosome 14) were associated with 31 genes, including the candidate gene Aubergine (*Aub*), which is known to be involved in post-transcriptional gene silencing via RNA interference (Huang et al., 2014). Indeed, *Aub* has been shown to be associated with resistance against intestinal bacterial infections in *Drosophila melanogaster* (Cronin et al., 2009). As apoptosis has been suggested to play an important role in the pathogenesis of *N. ceranae* infections (Higes et al., 2013), this could be another target of selection. Interestingly, tolerant workers appear to escape the manipulation of apoptosis by *N. ceranae* in the midgut epithelium, having similar rates of apoptosis as uninfected controls. In contrast, apoptosis was significantly reduced in negative association of the inhibitor of apoptosis protein (*iap*) gene expression in sensitive honeybees (Kurze et al., 2015). If this different response would really keep the *Nosema* infection intensity at bay through regular defecation of infected cells outside the hive, this adaptation could possibly reduce the transmission success of this intracellular pathogen and may explain the low prevalence observed in colonies of this breeding lineage.

5. Concluding remarks

While the majority of research in ecological immunology is based on individual responses, the additional complexity of immune responses at the social level makes social insects an appealing study system for future investigations of host–parasite dynamics and coevolution. This may also reveal new perspectives for studying other social organisms. They appear to have not only adapted at the individual level to resist or tolerate parasites, but their adaptations at the social level are also crucial to reduce or

avoid parasite transmission. The case study on *Varroa* resistance (i.e., the mite's delayed egg-laying) in Sweden illustrates how individual resistance may lead to tolerant colonies due to the inhibition of *Varroa* reproduction. In contrast, colonies selected for *Nosema* resistance in Denmark (i.e., low prevalence at colony level) appear to be tolerant at the individual level (i.e., they developed high infection intensities, but energy metabolism and survival was not impaired). This may suggest that tolerant individuals buffer the impact of an infection on colony fitness, leading to a potentially swifter replacement of infected individuals and reduced parasite transmission under certain conditions. A better understanding of these mechanisms in social insects may not only be interesting for questions on host–parasite evolution, but could also be important for improving honeybee health in the long term.

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