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Social Immunity: Emergence and Evolution of Colony-Level Disease Protection

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Abstract

Social insect colonies have evolved many collectively performed adaptations that reduce the impact of infectious disease and that are expected to maximize their fitness. This colony-level protection is termed social immunity, and it enhances the health and survival of the colony. In this review, we address how social immunity emerges from its mechanistic components to produce colony-level disease avoidance, resistance, and tolerance. To understand the evolutionary causes and consequences of social immunity, we highlight the need for studies that evaluate the effects of social immunity on colony fitness. We discuss the role that host life history and ecology have on predicted eco-evolutionary dynamics, which differ among the social insect lineages. Throughout the review, we highlight current gaps in our knowledge and promising avenues for future research, which we hope will bring us closer to an integrated understanding of socio-eco-evo-immunology.

1. INTRODUCTION

The eusocial wasps, bees, ants, and termites (110) are evolutionarily and ecologically successful, having persisted and diversified over millions of years to now inhabit almost every ecosystem on the globe (82, 158). The success of the social insects is due in no small part to their social lifestyle, which makes it easier for them to colonize new habitats and fill ecological niches, among other benefits (158). However, sociality is not without its drawbacks (2, 64). For a long time, a social lifestyle has been thought to increase the risk of disease (2, 53). This is because pathogens (i.e., disease-causing agents such as fungi, bacteria, and viruses) exploiting social interaction networks within animal groups can spread more easily between infectious and susceptible individuals, compared with solitary species (2, 53, 130).

In 1987, Hamilton (64) pointed out that this problem is exacerbated in social insects by the low genetic diversity in their colonies. He reasoned that because they are typically single families, a pathogen able to infect one insect genotype should be able to spread and infect all others (64, 130). Later, Schmid-Hempel (130) identified several other aspects of social insect biology, such as living within homeostatic nests in pathogen-rich environments, that further increase the risk of disease outbreaks. At the same time, Schmid-Hempel (130) developed a framework for how sociality affects host–pathogen interactions and evolutionary dynamics in social insects.

Despite these apparent vulnerabilities, social insects seem to cope with diseases remarkably well, and epizootics killing colonies are rare (44). To understand this observation from an ecological perspective, Boomsma et al. (15) assessed how the life history and ecology of the different social insect lineages affect the pathogenic pressure they experience. Their major conclusions were that, as hosts, ants and termites share many similarities, and the same is true of bees and wasps. These similarities should predispose the ants and termites on one hand, and bees and wasps on the other, to a comparable set of pathogens with equivalent transmission routes and, in turn, select for comparable host defenses. On the basis of a growing number of studies, Boomsma et al. (15) outlined the behavioral and physiological adaptations that insect colonies express, in addition to the immunological defenses of colony members, that reduce disease susceptibility at both the individual and colony level.

In 2007, Cremer et al. (33) introduced the term social immunity to describe the colony-level disease protection that is achieved through the collective defenses of colony members (33). These defenses were categorized into behavioral, physiological, and organizational components, which function jointly to prevent the uptake, establishment, and replication of pathogens in the colony. Building on the pioneering work of Schmid-Hempel (130), Schmid-Hempel & Schmid-Hempel (134), and Naug & Camazine (100), Cremer et al. (33) highlighted the role of colony organization as a unique feature of social immunity, which should be under selection to prevent disease spread within colonies. In 2009, Cremer & Sixt (34) conceptualized the remarkable number of similarities between social immunity and the organismal immunity of a multicellular body, arguing that, in effect, social immunity functions as the immune system of the colony (see Section 2.1) (34).

Over the following decade, studies on social immunity have steadily increased. In addition to earlier work using mostly honey bees (46, 159) and bumble bees (131), several well-established host models have been developed for the termites (122, 123, 162) and ants (28, 50, 89, 147, 149, 154), while the wasps have so far remained understudied. In this review, our aim is to cover the expansion of studies on social immunity and recent advances in the field. Section 2 discusses the evolution of social immunity and how it differs from other group-level disease defenses. It then examines how social immunity emerges from its components to provide colony-level protection by avoidance, resistance, or tolerance. Section 3 considers how social immunity affects eco-evolutionary dynamics between social insects and their pathogens. Finally, Section 4 highlights current challenges and prospective avenues for future social immunity research.

2. SOCIAL IMMUNITY

2.1. The Immune System of the Colony

Social immunity results from the collectively performed defenses of colony members (33, 130). It is composed of behavioral, physiological, and organizational defenses that are carried out by workers, either together or toward one another to reduce the risk of disease (33). Social immunity measures often initially involve nest hygiene and sanitary care behaviors that prevent or reduce the disease risk of colony members, for example, when they are contaminated with a pathogen (143, 145, 162). However, if this first line of defense fails, selection may favor the elimination of the infected individual to protect the colony (9, 31, 107, 125, 138, 149). Social immunity can therefore be characterized as a care–kill dichotomy, depending on whether the individual can be cured or is a threat to the fitness of a colony (34, 130).

Conceptually, social immunity is analogous to the immune system of a complex multicellular organism (e.g., a metazoan body) and may even have evolved in response to comparable selective pressures (20, 34). This is because social insect colonies, similar to a multicellular body, comprise two functional components: the queens and males specialized for reproduction and the nonreproducing workers that perform all tasks related to colony maintenance (130). This division of labor mirrors that of the cells in a body, with the queens and males functioning as germline cells (or gonads) and the sterile workers as somatic tissue (11, 13, 34, 157). In both cases, neither the germline nor soma elements can survive or replicate without the other, so that when they reproduce, bodies make more bodies, and colonies make more colonies (11, 20, 67). For this reason, a social insect colony, although comprising many individuals, can be considered a single reproductive unit that functions similar to an organism (111). These organismal qualities emerge from the division of labor between the functional germline and soma, which characterizes both facultative and obligate (11) eusocial insects (the latter of which qualify as superorganisms; see 11, 13, 67, 157). Therefore, across these levels of biological organization—organismal bodies and organismal insect colonies—immune systems and social immunity have evolved convergently to mitigate the impact of disease and to maximize fitness, respectively (34).

2.2. Evolution of Social Immunity

In recent years, the term social immunity has occasionally been broadened to capture a wider range of behaviors performed by animals living in groups of varying social complexity, including families in which all offspring disperse, as well as communally breeding groups (32, 96). Under such sensu lato definitions, any behavior performed by an individual that reduces the disease susceptibility of another may be considered social immunity. Although we do not question the importance of these traits and their roles in host–pathogen evolution, we argue that social immunity, as originally defined for eusocial insects (33, 34), is a derived trait that evolved when the unit of selection shifted from the individual to the colony, caused by the separation of germline and soma, which is an unconditional characteristic of superorganisms (20). Such sensu stricto social immunity is therefore necessary and essential to protect the entire reproductive entity and maximize its fitness (20). In superorganisms, the interests of all individuals are thus sufficiently aligned for cooperation to be high and conflicts low (20, 67, 111). Hence, unconditionally altruistic traits—for example, the expression of sickness signals by infected individuals triggering their own elimination—can evolve via kin selection because they enhance the survival and fitness of the colony. However, the eliminated individual still gains indirect fitness by increasing the likelihood that copies of its genes are transferred into the next generation via its kin. Ultimately, social insect workers therefore perform social immunity to maximize their inclusive fitness. Unconditionally altruistic

traits are thus an important characteristic of social immunity of the obligate eusocial species, while we may predict that the facultative eusocial species, which have context-dependent rather than unconditional reproductive division of labor (13), would express context-dependent altruism in their cooperative disease defenses. Moreover, in groups in which all individuals undergo individual reproduction, such as communal breeders (3, 96) and family groups, selection acts predominantly at the individual level, so that conflicts of interests can prevent the emergence of altruistic traits if they come at too high of a cost to the direct fitness of the individual (111, 155) (**Figure 1**). Yet it is exactly these traits that are necessary to make social immunity truly effective and analogous to the evolution of organismal immune systems (20, 34).

2.3. Emergence of Social Immunity from Its Components

Colonies operate without central control, and workers have no global picture of when or where certain tasks need to be accomplished (59). Instead, colony organization emerges from the

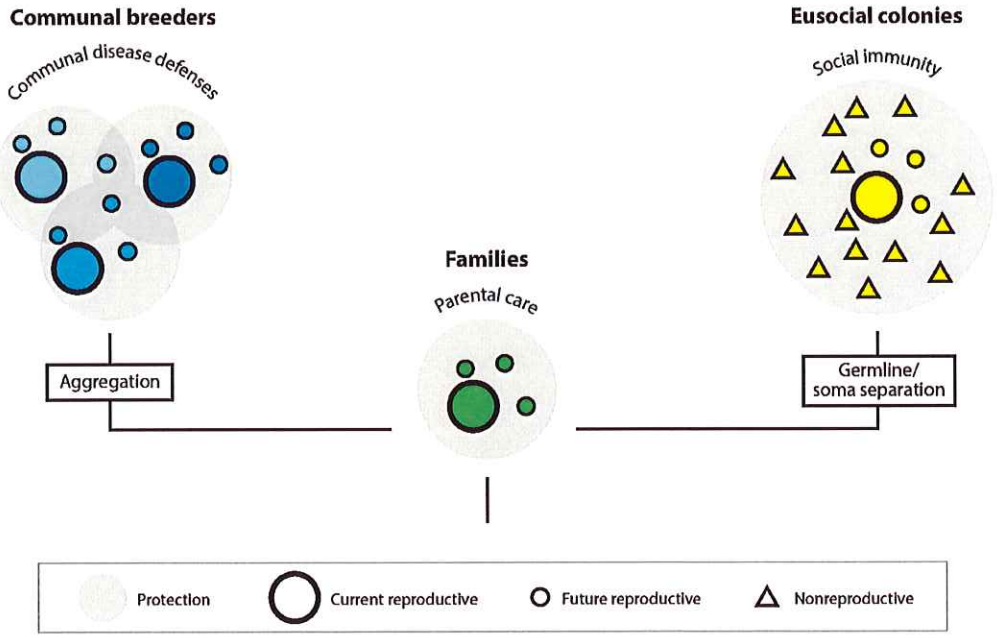

Figure 1

Disease protection in groups. Behaviors that prevent disease in group members are present in different forms of social organization. In families with dispersing offspring, parents provide unidirectional protection from disease to their offspring by parental care, thereby also enhancing their own fitness. The offspring then disperse instead of helping their parents, and the social group breaks up. In communal breeders, the protection provided by the different group members is additive and a by-product of the aggregation (e.g., disinfection by all group members, reducing pathogen load in a communal breeding area) (75). As the potential for conflicts in these aggregations is high, we predict that cheaters should arise and undermine these communal disease defenses by trying to take advantage of the benefits without paying the costs. In superorganismal societies, such as the obligate eusocial colonies of social insects, which evolved from family groups by the separation into reproductive individuals (queens and males; germline) and nonreproductive workers (soma) (11, 12, 13, 27), colony-level protection arises from social immunity. As the level of selection is the reproductive entity of germline and soma, we here see the evolution of unconditionally altruistic traits.

responses of individuals to local cues and dyadic interactions between colony members (59, 63). We suggest that social immunity, like any other complex, concerted task in the colony, is produced through the same means. Yet despite a wealth of knowledge on the diversity of individual and collectively expressed defenses (15, 33, 46, 159), we have a poor understanding of how they combine to achieve colony-level protection. The organizational immunity hypothesis (33, 100, 134) suggests that the inherent organizational structure of colonies into task-related communities (8, 95) and the ability to alter interaction networks in response to pathogen entry should limit intracolony disease transmission between the members of a social insect colony (128, 139). Despite strong theoretical support, empirical evidence for this hypothesis has so far remained scarce owing to the difficulty of studying whole colonies (139, 150).

The key to coordinating social immunity responses likely depends on the ability of colonies to effectively communicate information about pathogens. Communication about disease might occur directly between insects during one-on-one interactions—for example, via behavioral changes or the exchange of regurgitated crop content (trophallaxis), which contains not only food but also chemicals used in communication, microRNAs, and hormones (83). In addition to this peer-to-peer information exchange, we propose that the broadcasting of disease information should have evolved to allow for a rapid flow of information through the colony. This is because a host's response needs to be faster than the replication and transmission of the pathogen to prevent a systemic infection. In the body, this is achieved through signaling early in the infection process to generate both local and global immune responses that identify and clear the pathogen (132). Evidence for similar processes in social insects is limited, but pathogen-exposed termites use vibrational cues to trigger a colony-level disease response (121). However, chemical communication is typically the main form of communication used by social insects to coordinate tasks (87) and could also play a central role in social immunity.

Communication of disease-related information through chemicals should be particularly efficient, as volatile signals can be broadcast within the airspace of the nest to reach many individuals at once (86). Currently, there is no evidence of insects recruiting others to social immunity tasks in a systemic way by releasing volatile chemicals, but several studies have shown that insects exhibit changes in their comparably nonvolatile cuticular hydrocarbon profiles upon infection or immune stimulation (9, 107, 116, 117). These changes are used by nestmates to specifically target the immune-challenged individuals and perform either sanitary care or aggressive acts (116), or elimination behavior (9, 107). As shown for infected ant brood, these nonvolatile signals seem to function in an analogous way to the find me/eat me signal that infected cells use to communicate their infection to the immune cells, triggering their elimination (107, 113). Furthermore, cuticular hydrocarbon changes in immune-stimulated honey bee workers cause an upregulation of immune genes in their queen (68). Hence, cuticular chemical cues can act as signals to elicit both social immunity behaviors and the individual immune responses of other colony members. Beyond this, we propose that more systemically acting volatiles should also have evolved to facilitate the emergence of colony-wide reactions, analogous to the cytokine response of the immune system, sending a systemic signal to other cells throughout a vertebrate body (132). Studies investigating how disease information is spread within colonies should help improve our understanding of the coordination and emergence of social immunity.

2.4. Colony-Level Avoidance, Resistance, and Tolerance to Disease

Emergent colony-level protection arises via different defensive strategies that can be categorized as avoidance, resistance, or tolerance. To fight disease, colonies employ these strategies in combination, but here we consider them separately to pinpoint to their distinct roles in social immunity.

Avoidance is typically considered the first line of disease defense in animals (37). In social insects, individuals can reduce the uptake of pathogens into the colony by avoiding contaminated areas and food (145), closing nest entrances, and denying contaminated/infected insects entrance into the colony (41, 152). In general, examples of pathogen avoidance in social insects are relatively few, and recent reports have even found the opposite—that is, a preference of contaminated nest sites under some circumstances (23, 106). Overall, avoidance seems a relatively unexplored area of disease defense, and more work is needed to understand its relevance in social insects. Yet the ubiquity of pathogens, among other factors, makes complete avoidance unlikely; colonies will still need to resist or tolerate diseases (15).

Resistance combines all responses that reduce pathogen load and can be achieved by decreasing the probability of infection or by lowering the amount of or clearing pathogens after infection (94). At the colony level, resistance is achieved by sanitizing the nest with antimicrobials and removing dead individuals to reduce the probability of microbial growth and the potential for infection (24, 30, 39, 40, 48, 49, 109, 151). In addition to general nest hygiene, targeted sanitary care of contaminated insects, such as cleaning the body surface by allogrooming and prohibiting pathogen germination or growth by disinfection, reduces their risk of infection (62, 101, 115, 143, 145, 154, 160, 162). These measures are thought to be more important for ants and termites, which nest in direct contact with soil and decaying wood that contain a large number and diversity of generalist pathogens, such as fungal spores (77) (see Section 3.1). If hygiene and sanitary care fail and colony members become infected, the colony can reduce pathogen load by preventing infections from spreading to uninfected colony members. To that end, infected brood is removed or destroyed and infected adults are aggressively excluded (9, 107, 137, 144, 149). Moreover, contaminated workers also leave the brood chamber (147), and moribund individuals exclude themselves from the colony (18, 66, 125). Such social disintegration may be triggered in part by a loss of attraction of sick individuals to social cues from the nest and their nestmates (84). The resulting reduced interaction rate with susceptible nestmates could lower the risk of disease spread (100). Infected honey bees also switch faster to out-of-hive tasks, which could reduce disease transmission within the hive (99). Moreover, an experimental increase in colony pace, achieved through a faster turnover of workers, reduced pathogen load in the colony (25). Hence, social insects have evolved many resistance mechanisms to reduce pathogen load and prevent infections by a wide diversity of pathogens.

Tolerance is the capacity of a host to limit the negative impact of an infection on its fitness without directly affecting pathogen load itself (94, 112, 136). Although the underlying mechanisms of tolerance are often unclear, they revolve around reducing the damage that arises either directly from the pathogen or indirectly through an immune response aimed at the pathogen (61, 94, 136). Tolerance has so far received less attention than resistance from studies of animal disease defense but has become a growing area of research (136). We predict that tolerance may play an important role in social immunity, as colony-level tolerance mechanisms would allow colonies to cope with worker losses due to infection (18, 66) or the elimination of infected workers due to self-removal or elimination by their nestmates (107, 138, 149). Damage to the worker force could also arise through collateral damage if healthy workers are erroneously killed or damaged by social immunity behaviors, similar to immunopathology in a body (61). Evidence of social immunopathology is lacking but could exist because the antimicrobials that social insects use can be toxic to the insects themselves (e.g., cytotoxic formic acid) (65, 143) and because the mechanisms that are used to detect and eliminate infected colony members may not be perfect (107, 144).

Although colony-level tolerance mechanisms are unknown, we predict that they should involve the efficient replacement of lost workers with new ones to avoid a decrease in factors affecting fitness, such as colony productivity. Typically, social insect colonies exhibit temporal polyethism

(8, 95, 158), in which the youngest workers perform in-nest tasks (like nursing the brood) but progress to more dangerous out-of-nest tasks as they age (like guarding and foraging). We postulate that these different groups of workers, similar to different organs in a body (94), should have distinct intrinsic tolerance capacities. For example, the eldest workers, the foragers, can be replaced by younger workers switching to foraging tasks (57, 95, 158), while the youngest workers, the nurses, are mostly regenerated from brood (158). Moreover, because the nurses raise their own replacements, a loss of these workers is expected to severely limit the colony's ability to regenerate its worker force. Thus, it would be interesting to examine whether tissue-specific tolerance (94) exists between the different worker groups in social insect colonies and how flexibly a loss in either task group can be recovered.

Tolerance mechanisms can function after the damage has occurred, such as a transient increase in worker production following an infection (26). However, replacement individuals may already be produced prophylactically. In some species, as much as 45% of the worker force appears to be inactive workers (29) and could potentially act as a buffer for soma damage. Moreover, tolerance mechanisms may ameliorate damage arising not only from the complete loss of workers but also from reductions in functionality. For example, the negative effects of parasitized workers that no longer contribute to colony productivity appear to be tolerated by the colony through the compensatory actions of healthy workers (129).

Unlike the workers, the queen is often irreplaceable and her loss cannot be tolerated. Similar to irreplaceable cells in a body, such as the brain and the gonads, queens are therefore thought to receive special immune protection, known as an immune privilege (33, 34, 94). Hence, tolerance may not always be possible, and generally, it is expected to function up to a certain point, beyond which the damage caused by disease is no longer tolerated. Resistance mechanisms should then activate to reduce pathogen load (94).

Avoidance, resistance, and tolerance act together to defend the colony, and the relative investment into each strategy depends on a number of factors (94). For example, to tolerate the loss of workers, a colony needs to be sufficiently large and able to produce new workers fast. Hence, species with small colonies and young colonies with few workers investing into growth are expected to tolerate worker losses poorly, so they might invest relatively more into resistance mechanisms if the costs of resistance do not cause trade-offs with reproduction. Investment into resistance versus tolerance also depends on pathogen infection mode and virulence—that is, the harm it causes in the host upon successful infection. As examples, colonies may tolerate infections of relatively low virulence by producing more workers to buffer the reduced activity of infected workers and occasional deaths, while obligate-killing pathogens should select for resistance (15). Studies on the role of tolerance in social immunity and its interaction with other defense strategies could prove to be an exciting avenue for future research.

2.5. Fitness Effects of Social Immunity

To understand how social immunity is selected for and evolves, we need to study its long-term consequences on colony fitness. Ultimately, social insect fitness is measured as the number of new daughter colonies a parental colony contributes to the next generation (21, 58). Ideally, to understand the evolutionary importance of social immunity, fitness would be compared between colonies expressing and lacking social immunity or that at least differ in the level of expression of behaviors, such as the hygienic bee lines (137, 138). Performing such experiments over several generations, while excluding potentially confounding effects, is challenging in most cases, as many species rely on poorly understood environmental factors to trigger mating, so that only parts of their life cycle can be observed in the laboratory.

Nonetheless, fitness estimates, such as the number of reproductive offspring (daughter queens and males) produced per colony, can provide good, short-term proxies for colony fitness. These estimates can be obtained from field (153) and laboratory colonies by counting their numbers and determining classical life-history parameters such as body size or immune function (7, 19, 108). The latter is particularly important when predicting the likelihood a colony will survive the nonreproductive (ergonomic) colony-founding phase, only after which it reproduces and gains fitness itself (21).

To increase the chances of a colony gaining fitness, founding queens and longer-lived males (e.g., termite kings) may be immune-primed by their maternal colony to enhance their survival against a later pathogen challenge (93). So far, only maternal transgenerational immune priming (TGIP) from the mother queens to their offspring has been described for social insects (54, 126), but TGIP can also occur via the father in other insects (124). However, because the parents' role in social insect colonies ends with mating (males) and egg laying (queens) in mature colonies, TGIP may be more likely to occur via the nurses that actually raise and care for the brood (98). Worker-mediated TGIP may be particularly important and necessary in social insects as the queens are exceptionally long-lived and mate once at the beginning of their lives (76), and there is a protracted delay between egg laying and the emergence of adults. Hence, the immunological experience of the parents may be out of sync with the current pathogen pressure facing emerging offspring and reflects only a small fraction of the pathogen diversity. However, the combined immunological experience of the worker force is more likely to reflect the prevailing pathogen community. Thus, we propose that studies are needed to test for the existence and importance of tripartite—maternal, paternal, and sibling—TGIP in social insects and its impact on fitness.

3. ECO-EVOLUTIONARY DYNAMICS OF SOCIAL INSECT HOST–PATHOGEN INTERACTIONS

Pathogen transmission can take two major pathways: It can occur either horizontally between interacting hosts of the same generation or vertically from the reproducing individuals to their offspring. In social insects, these transmission dynamics can be considered at the level of individuals within their colony, but also at the level of transmission between colonies within a population. Within social insect colonies, horizontal transmission of infectious pathogens can easily occur via the close social contacts between colony members. Within-colony vertical transmission, by contrast, relates to the transfer of pathogens from the reproductive queen(s) to the (reproductive and nonreproductive) offspring. At the population level, horizontal disease transmission between colonies can occur directly between individuals from different colonies interacting with one another (such as during drifting or robbing events) or indirectly through environmental transmission (like on shared floral resources). Vertical transmission between social insect colonies refers to any form of disease transmission from a maternal colony to its offspring colonies (15, 130). It can entail (*a*) individual-level vertical transmission to the daughter queens or their accompanying workers (in the case of colony founding by budding or swarming) and (*b*) individual-level horizontal transmission between the rearing workers in the maternal colony and the queens (or workers) that later disperse to found a daughter colony. Understanding how pathogens are transmitted and interact with their social insect hosts both within and between colonies is important, as these factors affect the selection pressures producing and maintaining social immunity. Social insect lineages are expected to vary their host–pathogen interactions owing to substantial differences in their life histories. Here, we highlight the major life-history parameters of the different social insects and the effects they are expected to have on host–pathogen interactions (see References 15 and 130 for a comprehensive overview). We then explore how this may select for social immunity and how social immunity in turn influences the evolution of pathogens.

3.1. Host Life Histories and Pathogen Exposure, Transmission, and Virulence

Host life history influences where and how pathogens are encountered and recruited. For instance, both ants and termites are highly territorial, reducing the number of opportunities for direct horizontal transmission between colonies. This means that they encounter and acquire most pathogens from the environment (15, 123), via durable long-lasting stages that "sit and wait" until they are encountered by a host (47, 130). These pathogens are typically fungi that can actively penetrate the host cuticle or spore-forming bacteria that cause infections after ingestion (per os). Environmentally transmitted pathogens encounter new hosts stochastically and thus typically evolve broader host ranges (generalism) to increase their chances of reproduction (14). Hence, many of the pathogens ants and termites experience will be generalists (**Figure 2**). Several selection pressures thus affect pathogen virulence, and the overall outcome cannot easily be generalized (15). Pathogen virulence typically decreases with infection of multiple host species (85; but see 55), whereas environmental transmission selects for increased pathogen virulence (47, 130).

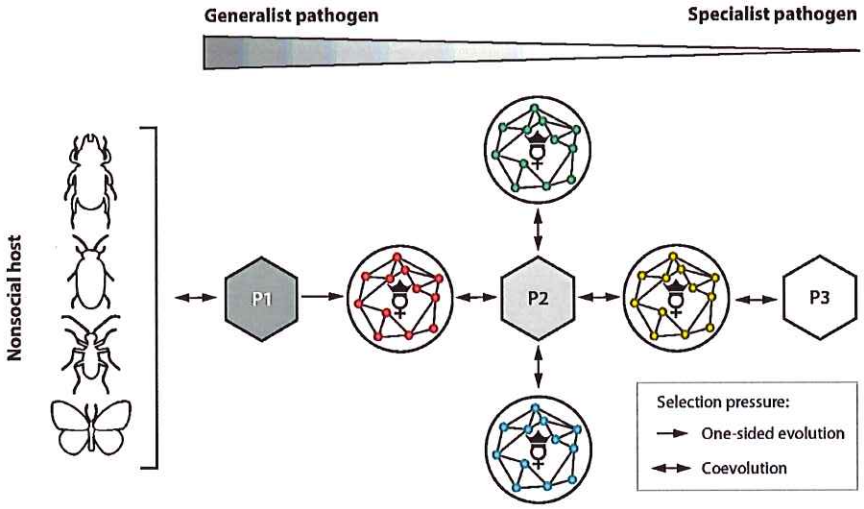

Figure 2

Host–pathogen evolution. Pathogens (*hexagons*) can interact with hosts at different degrees of host range, from broad (generalism) to limited (increasing specialism). The degree of host specificity defines pathogens' evolutionary dynamics with their hosts (142). Generalist pathogens such as P1 can exploit multiple nonsocial hosts, thereby reaching high abundance in the environment; this consequently poses a chronic threat. This exerts a strong unidirectional disease pressure and therefore a strong selective pressure on social insect hosts (*circles*) (selection pressure is indicated by the *arrow* pointing toward the social host). Social insect hosts have thus evolved highly effective resistance mechanisms against such generalists, making it unlikely for the pathogen to complete its life cycle when infecting a social insect host (a dead end for the pathogen). Importantly, this limits the likelihood that the pathogen can evolve counteradaptations, resulting in one-sided, asymmetric evolution of the host. Pathogens of intermediate degree of specialisms such as P2 can infect multiple social hosts (indicated by different colors), with which they may diffusely coevolve (51). Specialist pathogens such as P3 that infect only a single social host species coevolve and engage in a symmetric arms race with their social host. Social insect host colonies are shown as a social interaction network between the workers (*dots*) and the queen (*crowned female*). Different nonsocial insects depicted by insect outlines that were adapted from photographs by Didier Descouens, available at Wikimedia Commons [CC BY-SA 4.0 (**http://creativecommons.org/licenses/by-sa/4.0/**)]; therefore, the outlines also license with CC BY-SA 4.0.

In contrast, bees and wasps are expected to encounter and recruit more pathogens that are transmitted per os directly between insects of different colonies (15)—for example, when they drift from one colony and enter another (1, 52, 102). In addition, indirect horizontal transmission is facilitated by the use of shared food resources, such as flowers (15). These transient food patches are visited by insects of multiple colonies and species; thus, they act as disease hubs, promoting the transmission of pathogens between them (15, 78). Transmission mostly occurs via the fecal–oral route (42, 135): Infected insects contaminate resources, such as flowers, leaving behind infectious propagules that can infect susceptible insects using the same resource in the near future. The stable, frequent transmission of pathogens between colonies of the same or closely related species, such as within Apidae and Vespidae, will favor more specialist pathogens in bees and wasps than in either ants or termites (15, 130). Pathogen virulence is expected to increase under frequent horizontal transmission (16, 17), yet high virulence evolution is expected to be counteracted by the necessity of infected bees and wasps to still be able to forage to disseminate the pathogen.

Ants and wasps should also encounter pathogens from their food as they hunt or scavenge on other insect and arthropod species (15). In addition, ants tend honeydew-producing insects, such as aphids, as a source of carbohydrates. These intimate interactions with other species may lead to disease spillover events. However, infection likelihood and virulence are hard to predict. For example, a generalist virus acquired from feeding on an infected corpse may cause virulent infections. However, ants that encounter obligate aphid pathogens (e.g., *Pandora neoaphidis*) while collecting honeydew are unlikely to contract the disease themselves (20).

Vertical transmission may play a key role in the spread and persistence of pathogens in social insect populations. Vertical transmission to daughter colonies can occur via infected daughter queens themselves, or—in species where workers accompany the queen during colony foundation—also via the workers. The differences between these types of colony foundation may affect the evolution of virulence in vertically transmitting pathogens. When queens found colonies alone, selection should favor pathogens with relatively benign effects, as the queens need to survive and reproduce before the pathogen can disperse again through daughter queens (15, 130). However, this constraint may be relaxed in species where workers from the parental colony leave with the daughter queens, because the workers may buffer the negative impacts of virulent pathogens. However, pathogen virulence should still depend on the relative frequency of horizontal-to-vertical transmission events (88).

As previously mentioned (15, 130), predicting the virulence of social insect pathogens is difficult because they have diverse and complex host interactions. Virulence can conceivably evolve in any direction (15, 130) and may even be context dependent (22). However, overall differences between host–pathogen associations across the social insects are clear and will skew the types of pathogens the different social insect lineages encounter—namely, more generalists for ants and termites and more specialists for bees and wasps (15). This skew is also present in established model systems for the study of social immunity and likely reflects natural host–pathogen associations. To gain a fuller understanding of social host–pathogen evolution, we nonetheless encourage future studies that investigate (*a*) all groups of social insect hosts, giving also stronger focus on the wasps, and (*b*) the full range of pathogens social insects encounter, including pathogens that persist in social insect populations that appear to defy the abovementioned association bias (e.g., viral infections in ants and termites).

3.2. Social Immunity and Host–Pathogen Evolution

How pathogens select for social immunity and, in turn, how social immunity influences pathogen evolution require further study (133). However, variation in the expression of social immunity

behaviors, such as grooming (18), exists between colonies, which selection can in theory act upon. Genetic differences between patrilines can increase the diversity of defenses expressed within colonies (70), and social immunity traits such as hygienic removal of brood in honey bees are heritable and can be artificially selected for, with direct fitness consequences to colony-level disease protection (138). Hence, pathogen-induced selection, acting on standing variation in social insect populations, is likely maintaining and driving the evolution of social immunity.

The evolutionary outcomes of host–pathogen interactions will depend on many factors, such as the type of pathogen and its host specificity. For example, generalist entomopathogenic fungi with broad host ranges release large quantities of infectious conidiospores from corpses to maximize their chances of infecting a new host in the future (14) (see the sidebar titled Generalist Fungal Pathogens in Ants). The high abundance of these spores in the environment should place a strong, persistent disease pressure and hence selection pressure on ant and termite colonies to evolve social immunity traits that efficiently prevent disease outbreaks. However, this evolutionary process is asymmetric: One-sided adaptations may evolve in the host to combat the high pathogen burden, whereas the pathogen itself does not evolve any reciprocal specialist traits because it switches hosts across generations. Social immunity defenses in both ants and termites, such as sophisticated nest hygiene and mutual cleaning, are highly efficient resistance mechanisms that reduce the pathogen load in the colony and thus the risk of infection of colony members. Moreover, if infection still occurs, the insects can prevent generalist pathogens from replicating within the colony (107), meaning that such infections are likely evolutionary dead ends (**Figure 2**).

On the contrary, several specialist fungi that cause endemic infections in ants can persistently infect the same colony across years (see the sidebar titled Specialist Fungal Pathogens in Ants). They do this by manipulating their hosts into leaving the nest before becoming infectious, so that they avoid the social immunity defenses that prevent generalist pathogens from reproducing. Whether host manipulation evolves specifically to overcome social immunity defenses is unknown, though it is observed in nonsocial hosts as well (69). However, in response, there is evidence that ant

GENERALIST FUNGAL PATHOGENS IN ANTS

Recently, the ecological relevance of generalist fungi in social immunity research has been questioned (90). However, generalist fungal pathogens have been infecting ants for millions of years (105), and to date, the cosmopolitan *Metarhizium* and *Beauveria* are the best-studied genera (103, 119). These obligate-killing pathogens produce high numbers of infectious propagules (approximately 12 million per infectious cadaver), which reach high abundances in the environment, either freely in the soil (up to 5,000 infectious conidiospores per gram of soil) (71–73, 77, 114) or in association with plants (97). Once in contact with insect cuticle, they attach and actively penetrate into their host, where they can cause lethal infections (6, 10). In the field, deadly infections are estimated to affect as many as 10% of ant workers (35, 73). These reports are likely underestimates, however, as cadavers are inconspicuous in the field (e.g., lost in leaf litter or kept in colony graveyards) (141) and can be destroyed by ants to prevent sporulation (107). Because these fungi can be reared in the laboratory, they are excellent model systems to study social immunity against generalists. Most studies use topical applications of between 2% and 20% of the conidiospores released by a single cadaver to reach a 50% lethal dose (LD_{50}) in the laboratory (72, 81, 143, 144, 149). Yet because many conidiospores immediately fall off during this mode of application (80), the actual infective LD_{50} is much less, far below 1% of a cadaver-load of conidiospores; indeed, deadly infection can also occur at low conidiospore numbers (<5 per insect), albeit with a much lower probability (LD_2) (81). Studying these generalists under controlled laboratory conditions allows for detailed investigations into the evolution of collective host defenses against the constant disease threat and hence pressure these pathogens impose on social insects.

SPECIALIST FUNGAL PATHOGENS IN ANTS

Several specialist fungal pathogens of ants exist (4, 36) and are categorized as low-virulence pathogens, which may not place strong selection pressure on their hosts, or highly virulent pathogens, which seem to have evolved adaptations to evade social immunity. Species of the order Laboulbeniales (such as *Rickia* spp. and *Laboulbenia* spp.) anchor their large thalli into the cuticle of living ants and have low virulence (43), potentially even being beneficial for their hosts by providing protection against generalist pathogens (79). In contrast, *Pandora* spp. (91) and *Ophiocordyceps* spp. (4) are obligate killers. In parallel, they have evolved the ability to manipulate their hosts into leaving the nest and climbing nearby plant stems, where the insects attach, die, and become infectious (5, 91). Conspicuous fruiting bodies then emerge and release relatively few, large ascospores that infect foraging workers (89). Their conspicuous cadavers make them an excellent field study system, as the number of corpses around ant nests can easily be determined (45, 89) and is relatively few per colony (36, 89). Thus far, infections in the laboratory have been established only via a nonnatural route of injection of hyphae (38, 60). It would therefore be highly valuable to establish controlled laboratory infections via the natural infection route by, for example, using topical applications of cuticle-attaching and cuticle-penetrating ascospores—as in the generalist fungi (see the sidebar titled Generalist Fungal Pathogens in Ants)—to study all aspects of their biology. Specialist fungi are interesting complementary models to generalists, as they help to explore coevolution between social insects and their pathogens and, in particular, to understand how specialist pathogens can evolve to evade social immunity.

colonies have evolved a reciprocal behavior—they appear to search around the colony and attempt to remove infected corpses before the pathogen becomes infectious (92). This behavior is therefore suggestive of a classical evolutionary arms race between a pathogen overcoming social immunity and a host evolving a new, antagonistic social immunity defense in response. Such symmetric coevolution occurs when pathogens are specialized to infect a single host species. In addition, coevolution can occur through diffuse interactions between multiple linages (74)—for example, between multiple species of bees and wasps that exchange pathogens on flowers (**Figure 2**).

Social insect colonies are thus exposed to a wide diversity of pathogens, whose host range can be limited or broad. Hence, evolutionary interactions between social insects and their pathogens are likely to be complex. For example, coinfections by multiple pathogens in a single host are expected to be common (118). How coinfections of colonies influence the evolution of social immunity is an interesting question. Generally, behavioral responses are effective against a broad range of pathogens. As an example, grooming and chemical disinfections may reduce infection probability of most pathogens that infect via the cuticle, relatively independent of the exact pathogen strain or species (50, 161, 163). Ants also show increased grooming levels with pathogen experience (115, 154, 156), and we suggest this behavior should also cross-protectively act against other, comparable pathogens entering the colony. Hence, the evolution of social immunity may play an important role in fighting multiple pathogens present in a colony.

4. CONCLUSIONS AND FUTURE OUTLOOK

With a well-established conceptual framework, an increasing knowledge of social host–pathogen interactions, and novel technological developments (15, 33, 34, 130, 139), we feel it is timely and feasible to experimentally address how social immunity emerges from its mechanistic components. That is, how do different social immunity actions, based on dyadic interactions and local cues, scale up, interact, and synergize to reach colony-level protection? To answer this, we need to take whole-colony perspectives, in which we analyze how the organization of social insect colonies contributes

to social immunity (33). Novel technologies such as automated monitoring, machine learning, and network analyses (95, 120, 127, 146) offer us powerful tools to address the organizational immunity hypothesis, as well as a refined view of how local interactions and information exchange can produce emergent properties (95, 104). Combining these technologies with methods to quantify pathogen spread (25, 56, 81) offers a potentially promising approach for understanding how disease defenses function at the colony level (139).

To understand how social immunity evolves and, in turn, affects pathogen evolution, we require long-term studies measuring the fitness of both parties. Although challenging, this can be approached using both field and laboratory studies. Longitudinal field studies over multiple years (across time) (58) or local adaptation approaches (across space) could be used to address whether and how social immunity responses adapt to and evolve with specific pathogen communities. In the laboratory, evolution experiments, including coevolution and one-sided evolution, can elucidate evolutionary interactions that are hard to study in the field. For example, serial infections by generalist pathogens of the same social insect host could be used to investigate how pathogens, in the absence of host switches, as is symptomatic for specialists, evolve adaptations to overcome social immunity defenses. Indeed, with ongoing biodiversity losses caused by invasive social insects (140, 148), changes in the prevailing host community are likely to disrupt established host–pathogen dynamics.

To gain a fuller insight into the complexity of host–pathogen interactions in social insects, next-generation sequencing techniques provide potentially powerful tools to tackle current gaps in our knowledge of the molecular underpinnings of the observed patterns. Furthermore, comparative genome analyses will allow us to determine how, for example, the evolution of the immune system is affected by social immunity. To conclude, we believe that developing a single socio-eco-evo-immunological framework for social immunity will expand our understanding of its role in social evolution and host–microbe interactions.

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