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Molecular Evolution of Insect Sociality: An Eco-Evo-Devo Perspective

Amy L. Toth^{1,2,*} and Sandra M. Rehan³

¹Department of Ecology, Evolution, and Organismal Biology, Iowa State University, Ames, Iowa 50011; email: amytoth@iastate.edu

²Department of Entomology, Iowa State University, Ames, Iowa 50011

³Department of Biological Sciences, University of New Hampshire, Durham, New Hampshire 03824; email: sandra.rehan@unh.edu

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*Corresponding author

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Abstract

The evolution of eusociality is a perennial issue in evolutionary biology, and genomic advances have fueled steadily growing interest in the genetic changes underlying social evolution. Along with a recent flurry of research on comparative and evolutionary genomics in different eusocial insect groups (bees, ants, wasps, and termites), several mechanistic explanations have emerged to describe the molecular evolution of eusociality from solitary behavior. These include solitary physiological ground plans, genetic toolkits of deeply conserved genes, evolutionary changes in protein-coding genes, *cis* regulation, and the structure of gene networks, epigenetics, and novel genes. Despite this proliferation of ideas, there has been little synthesis, even though these ideas are not mutually exclusive and may in fact be complementary. We review available data on molecular evolution of insect sociality and highlight key biotic and abiotic factors influencing social insect genomes. We then suggest both phylogenetic and ecological evolutionary developmental biology (eco-evo-devo) perspectives for a more synthetic view of molecular evolution in insect societies.

DNA methylation:

a form of epigenetic modification by which methyl groups are enzymatically added to DNA, with effects on chromatin structure and gene expression

Evolutionary conservation:

the presence of shared genetic elements or gene functions across species as a result of common ancestry

Queens:

reproductive females in a eusocial insect colony; most social insect species have a single queen, but others can have multiple queens

Workers:

nonreproductive and sometimes sterile individuals in a social insect colony that perform specialized tasks, including foraging, nest maintenance, nest defense, and brood care

Age polyethism:

when individuals show different behaviors at different ages; most notably, workers of many social insect colonies transition from brood care to foraging behavior with age

Caste determination:

the process by which developing offspring are differentiated into reproductive queens and nonreproductive workers

EUSOCIALITY AS A MODEL FOR STUDYING THE EVOLUTION OF COMPLEXITY

Studying molecular evolution in eusocial insects provides one of the best opportunities for answering fundamental questions related to how biological complexity arises in evolution. Such fundamental questions include, (a) Are major transitions in evolution accomplished via radical shifts in genome sequence and organization or by small changes in sequence and gene regulation? (b) What types of molecular mechanisms are invoked during different transitional steps in social evolution—in other words, are different molecular processes operating during the origin and subsequent elaboration of eusociality? (c) Are the same or different molecular processes involved during multiple, independent origins of sociality, and is there a set of deeply conserved genes, or genetic toolkit for sociality? (d) Are there any special or unusual features of social insect genomes or their solitary ancestors (e.g., high recombination rates, DNA methylation, rates of molecular evolution) that facilitate the evolution of sociality?

Eusocial Insect Taxa and Levels of Sociality

Although eusociality has been described and studied in other insects (31), Hymenoptera (ants, bees, and wasps) and Isoptera (termites) are the best-studied eusocial insects from both a behavioral and genetic perspective and include species with varying levels of social organization (156). They are thus the most useful taxa for studying the molecular evolution of sociality and are the focus of this review (**Figure 1**).

The societies of Hymenoptera and Isoptera provide a remarkable example of convergent evolution. Comparisons between independently evolved social lineages can be extremely useful for understanding the roles of evolutionary conservation versus convergence in social evolution (136). Within the Hymenoptera, there have been multiple, independent origins of eusociality both across and within the major hymenopteran lineages. Ants (family Formicidae), bees (superfamily Apoidea), and wasps (families Vespidae and Crabronidae) have all evolved social behavior independently, and representatives of each of these lineages share a large number of convergent social features such as the presence of queens and workers, age polyethism, preimaginal caste determination, and cooperative nest defense using the sting (156). Eusociality evolved once within the ants, once within the Crabronidae (and sociality is rare and not well developed in this group), once or twice within the Vespidae (52), and four times in the bees (reviewed in 70) [twice in the family Apidae (25, 108) and twice in the family Halictidae (43)]. Because it is hyperdiverse and contains numerous representative species with different grades of sociality, the Hymenoptera is the best group for studying the molecular evolution of eusociality (**Figure 1**).

Previous authors have defined sociality using diverse terminology (32). For the purposes of this review, we focus on four distinct levels of social complexity: subsocial, incipiently social, primitively social, and advanced eusocial (109) (see **Table 1** for descriptions). These four levels of sociality are broad definitions intended to provide a context for comparing evolutionary transitions by highlighting convergent features shared by many social lineages. However, each lineage has specific characteristics for many social traits, and therefore behavioral phenotypes differ in some important ways across lineages. It is thus extremely important to study evolutionary transitions between the levels of sociality within monophyletic groups of taxa because each has followed a different evolutionary trajectory (109) (**Figure 1**). Only then, through broader comparative studies, can we truly understand whether there are common patterns across independent origins of sociality.

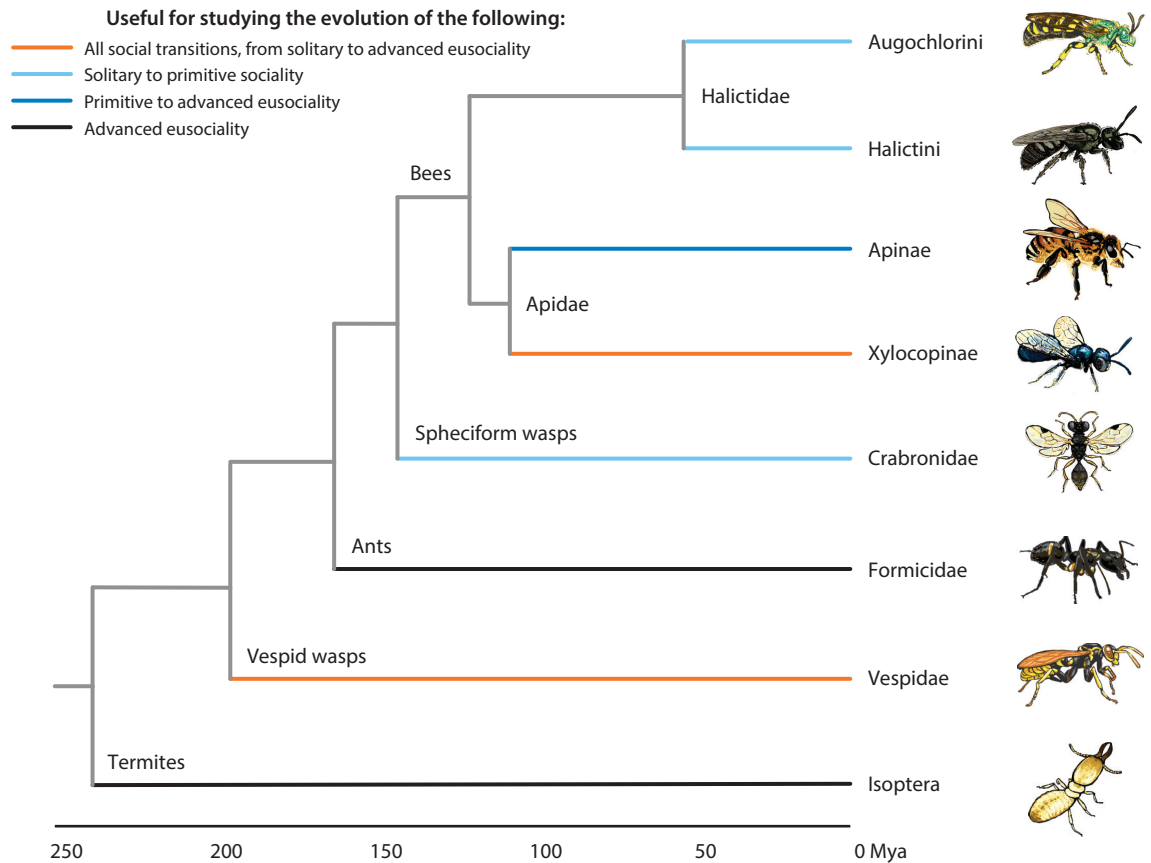


Figure 1

Phylogenetic overview of social species and levels of sociality. Lineages in which all members are eusocial are shown in black (ants and termites). Lineages ranging from solitary to primitively social are shown in light blue (halictid bees and spheciform wasps). Lineages containing species ranging from solitary to advanced eusocial, but without the full social spectrum within a monophyletic lineage, are shown in dark blue (corbiculate bees in the subfamily Apinae). Lastly, lineages ranging the full social spectrum from solitary to advanced eusocial within a monophyletic lineage are shown in orange (xylocopine bees and vespine wasps). Approximate evolutionary timeline (based on 88) allows for estimation of relative divergence times of different lineages. Insect images by Amy C. Geffre.

Transitions in Social Evolution

Early stages of social evolution are important for understanding origins of sociality and the transition from solitary to parental to incipient societies. Individual solitary and subsocial parents must complete all nest construction, foraging, and egg-laying tasks to successfully reproduce (133), although the proximate mechanisms underlying the transition from solitary to subsociality are poorly understood.

Incipiently social insects switch between reproductive and nonreproductive behavioral states (149), and this may occur by physiological switches and changes in hormonal titers (150). It is further posited that observed behavioral and physiological changes are regulated by changes in the expression of multiple sets of pleiotropically linked genes (40). Although there are numerous incipiently social species across both bee and wasp lineages and ample points of comparison to be

Table 1 Features and relevance to social evolution of several different levels of insect sociality

Level of sociality	Main features	Relevance to social evolution
Subsociality	Prolonged parental care and parent–offspring interaction	Parental care as a precondition for the evolution of eusociality
Incipient sociality	All individuals retain the ability to reproduce and forage and can also live solitarily Simple division of reproduction and foraging tasks Cooperatively care for brood; may not have reproductive division of labor or overlapping generations	Useful for understanding earliest stages in social evolution because they form cooperative social groups but do not possess castes
Primitive sociality	May initiate nests either solitarily or jointly and then transition into cooperative colonies upon the emergence of workers Relatively small colony size Composed of two distinct castes, reproductive dominants and foraging subordinates, but retain caste flexibility into adulthood	Useful for understanding intermediate stages of social evolution Provide insight into key adaptations in the transition to an obligately social lifestyle Provide insight into the evolution of the first caste systems
Advanced eusociality	Distinct reproductive and worker castes Complete reproductive division of labor with loss of reproductive totipotency Large colony size Reproductives monopolize reproduction, and workers are functionally sterile and forage for colony food provisions	Useful for understanding the evolution of permanent and highly differentiated castes Provide insight into the evolution of derived eusocial specializations, including specialized worker subcastes Lost ability to revert to primitive social forms (i.e., the evolutionary “point of no return”)

examined in these lineages, incipiently social species are rarely studied and the molecular basis of simple societies have only begun to be addressed.

Later stages of social evolution are important to our understanding of the elaboration of eusociality, in which individuals become specialized and work together as a colony unit. This transition from primitively social to advanced eusocial groups has been termed an evolutionary “point of no return” (54). This represents a major transition in evolution beyond which colony-level selection acts to produce novel social traits (157).

Different selective forces and molecular mechanisms may be involved during different stages of social evolution (109). These differences in individual versus colony performance and multilevel selection suggest multiple forms of molecular changes may differ between early and later stage social transitions.

Molecular Evolution of Eusociality in a Comparative Context

The first studies of molecular evolution in social insects focused on a few model advanced eusocial insects such as the honey bee and the fire ant (111). Although these studies have been fruitful for understanding the molecular basis of some derived social traits such as queen number differentiation, reproductive division of labor, and age polyethism, it is clear that studies of a wider variety of species are required to fully understand different phases in the evolution of insect sociality. There have been enormous recent advances in sequencing technology and molecular techniques leading to an ever-wider variety of social insects for which there are genomic data, including some more primitively social species (20, 65, 100, 107, 127, 128, 148).

Because of the complex nature of species evolutionary histories, we emphasize that it is crucial that such comparisons be made within a well-grounded phylogenetic context (**Figure 1**). Each

Reproductive division of labor:

discrete roles in a social colony, where royal castes (queens, kings) monopolize reproduction and workers specialize on nonreproductive tasks

independent origin of sociality is unique and will likely have distinct social traits because of its evolutionary history (21, 25, 43, 52, 108). Therefore, comparing the genetics of highly eusocial organisms, such as honey bees, with distantly related solitary species can provide a before and after comparison across an evolutionary chasm, but it will not tell us what kinds of intermediate changes were associated with each social transition. By studying genes associated with the earliest steps into sociality as well as those in related but more advanced species, we will be able to determine whether the transitions from solitary to simple to complex sociality represent incremental changes or genetic revolutions.

Thus, we are at a critical juncture in our study of molecular evolution in insect societies, in which there are sufficient data for a review and synthesis, but it is still early enough to influence research directions by presenting a broader view of the numerous hypotheses about the genomic basis of social evolution in insects. For example, many researchers are now generating data sets that can actually test multiple hypotheses about genomic routes to eusociality (**Table 2**), but they may miss opportunities for new insights by focusing on one major hypothesis while ignoring others. In addition, our review can serve to guide analyses and new research in this area by highlighting the complementarity of the different hypotheses while emphasizing the need for studies on solitary and incipiently social species, using a carefully framed phylogenetic context.

Table 2 Summary of existing studies on molecular mechanisms related to social transitions in evolution

Class	Molecular mechanism	Subsocial to incipiently social	Incipiently to primitively social	Primitively to advanced eusocial
Sequence-based	Novel genes	<i>Ceratina</i> (107)	<i>Polistes</i> (15, 39, 100)	Bees (50, 63, 65) Ants (20, 100, 123, 159)
	Protein evolution	<i>Ceratina</i> (107)	Bees (65, 162)	Bees (65, 162) Ants (123)
	Recombination	None	None	<i>Apis</i> (18, 50, 66, 113, 126, 154, 159)
	Gene networks	None	<i>Polistes</i> (99)	<i>Apis</i> (62, 90) Ants (100, 117)
	Social chromosomes	None	None	Ants (104, 142)
	Genetic caste determination	None	None	Bees (67, 126, 135) Termites (84) Ants (24, 56, 118, 126)
	Genomic imprinting	None	None	<i>Apis</i> (41, 72)
Expression-based	Maternal heterochrony	<i>Ceratina</i> (106)	<i>Polistes</i> (139)	<i>Bombus</i> (161)
	Ovarian ground plan	<i>Ceratina</i> (106)	<i>Polistes</i> (138, 139, 150)	<i>Apis</i> (4, 5, 46)
	Genetic toolkits	None	<i>Polistes</i> (15, 137, 138)	Bees (15, 99, 136) Termites (115, 145, 165) Ants (92)
	Transcription factors	None	None	<i>Apis</i> (9, 69, 125) Ants (123)
	DNA methylation	<i>Ceratina</i> (107)	<i>Polistes</i> (100, 128)	<i>Apis</i> (51, 77, 79, 85) Ants (19, 78, 100)
	Histone acetylation	None	None	Ants (122, 124)

Phenotypic

plasticity: the ability of one genotype to produce more than one phenotype in response to changing environments

DNA SEQUENCE CHANGES IN SOCIAL EVOLUTION

What types of sequence changes underlie the evolution of complex phenotypes? Some argue that protein-coding changes are prime movers in phenotypic evolution (53), whereas others emphasize a leading role for regulatory changes (26, 110). There have been numerous studies of molecular evolution of insect social traits related to changes in protein-coding sequences, the structure and dynamics of social insect genomes, and alterations of gene networks. Below, we review, in an evolutionary context, some of the major results addressing the types of DNA sequence changes associated with social traits before moving on to gene regulation in the subsequent section.

Genetic Caste Determination

One of the key social traits that has been the focus of molecular studies in social insects is the formation of castes. Despite huge phenotypic differences between reproductive and nonreproductive castes, most caste differences are the result of environmental rather than genetic differences. Caste differences thus represent a classic example of phenotypic plasticity, and environmental caste determination (relying on gene expression rather than heritable, genotypic differences) is considered the rule in most eusocial insects. Despite this, several notable exceptions, in which genotypic differences do affect caste fate (genetic caste determination, or GCD), have come to light in recent years in a variety of species (10, 24) (Table 2).

Although the ancestral state is assumed to be environmental caste determination, independent origins of GCD in ant, bee, and termite lineages suggest it has evolved multiple times in eusocial insects and may not be as rare or exceptional as previously thought (10, 67, 84). This leads to interesting evolutionary questions about the conditions under which GCD evolved. One explanation is frequency-dependent selection, whereby so-called selfish queen alleles could be maintained in populations if they are rare or only weakly influence queen determination. There is some evidence for this (56, 93), with some exceptions (135). GCD also appears to be more prevalent in cases of hybridization between two genetically distinct populations (126).

Social Chromosomes

Another major feature of social insect colony organization is number of reproductives. In *Solenopsis invicta*, monogynous (single-queen) and polygynous (multiple-queen) colony organization is linked to differences in queen size and worker behavior (112). Monogyny is associated with the *B* allele of the *Gp-9* locus; homozygous *BB* workers will not tolerate any other queens regardless of genotype (75). The *Gp-9* locus includes a gene coding for an odorant-binding protein (75); thus, the different alleles likely affect production and perception of queen recognition pheromones (140).

The sequencing of the *S. invicta* genome (163) contributed to the discovery of a suite of linked genes in an area of low recombination around the *Gp-9* locus. Subsequent studies demonstrated that this entire region segregates with the monogyne-polygyne social form, and in essence behaves like a separate, Y-like chromosome, or so-called social chromosome (142). This set of linked genes appears to have coordinated effects on multiple social traits, including queen pheromones, worker odor perception, queen weight, and tolerance and presence of multiple queens in the colony. Intriguingly, another social chromosome was discovered in the ant *Formica selysi* (104), also associated with monogyne-polygyne social forms. Social chromosomes may be more common than previously thought in social insects, influencing the evolution of coordinated suites of complex physiological and behavioral traits. Theoretical studies suggest suppression of recombination may be an important molecular mechanism in “facilitating coordinated shifts in coadapted traits” (104).

Rate of Protein Evolution

The protein evolution hypothesis posits that rapid evolution of specific genes or gene families led to changes in protein function and the evolution of social phenotypes (57). If some genes that were initially expressed in all solitary living individuals—such as those that control foraging or reproduction—are instead differentially expressed in incipient castes, then they may be released from pleiotropic constraints, facilitating adaptive evolution and further elaboration of those castes (40). Evidence for this hypothesis has been observed across solitary and eusocial lineages with positive selection in genes/families relating to signal transduction, development, and metabolism (65, 124, 162).

One genomic property that has the potential to affect rates of DNA sequence and protein evolution is recombination rate. Advanced eusocial insects and honey bees in particular have remarkably high rates of recombination across the genome, particularly in guanine-cytosine (GC)-rich regions (113, 154). GC-rich regions of the genome contain more recombination motifs, increasing the likelihood of increased linkage disequilibrium, which can produce accelerated recombination regions (18). The evolution of sociality greatly reduces effective population sizes (33), and this is expected to increase linkage disequilibrium and the frequency of deleterious mutations due to drift. If early insect societies suffer from small effective population sizes, then, secondarily, high recombination rates might evolve in later stages of social evolution (66) to reduce linkage disequilibrium (154) and/or increase worker genotypic diversity (126). These features of social insects have been suggested to contribute to high rates of DNA sequence evolution, changes in protein-coding sequences, and even the birth of new genes, perhaps facilitating the drastic phenotypic evolution that has accompanied the evolution of eusociality (66).

Novel Genes

An emerging hypothesis posits that novel genes are important for the evolution of novel social phenotypes (50, 63, 130). Novel genes are defined as previously undescribed genes that have no significant homology with known sequences. Novel genes may arise via rapid sequence evolution leading to the loss of detectable homology or via transposable element insertion, or they may be “born” through spontaneous mutation (130). It is important to note that there are innate problems with studying novel genes, because they are defined on the basis of negative data (i.e., the absence of homologous sequences). Our current knowledge of insect genomes is still highly fragmentary; thus, current assessments of novel genes will need to be reassessed as new genomic resources and bioinformatic tools for gene prediction and homology detection are developed (68).

Novel genes have been found in each new social insect genome (65, 100, 128, 148) and may make up 10–30% of the predicted genes in a given genome (159). In a comparison of seven ant genomes, each species was found to possess a large number of unique, species-specific genes, with evidence of a rapid gain of novel genes during evolution, especially in leafcutter ants. It was thus suggested that novel genes play a role in the evolution of derived, lineage-specific traits such as fungus farming (123).

Others have suggested novel genes may be also important for fundamental social traits, including the evolution of castes. Genes that are taxonomically restricted to Hymenoptera, bees, and the genus *Apis* are more likely to be overexpressed in honey bee workers (63) and show evidence of positive selection (50), suggesting novel genes may play an important role in caste differences. In the paper wasps *Polistes canadensis* (39) and *P. dominula* (128), there is an overabundance of novel transcripts that show caste differential expression. In contrast, genus-specific transcripts were

Novel genes:

genes with no known homology to previously described genes; when considered in a comparative context, genes may be novel to a specific group of taxa and are often called taxonomically restricted genes

significantly less likely to be caste related in *P. metricus* (15). In fire ants (*S. invicta*), colony social organization (queen founding strategy) also does not appear to be associated with the expression of novel genes (87).

There has been some inconsistency in the reported associations between the expression of novel genes and social traits. We suggest that some of this inconsistency may be due to variation in the importance of novel genes for different types of behavior, in specific life stages, or at different levels of sociality. Studies in honey bees paved the way, suggesting novel genes are important in advanced eusocial species (50, 63), and there is now some support for this idea from primitively social species (39, 128). However, there have been no studies examining the role of novel genes in early stages of social evolution.

Structure of Gene Networks

To understand the evolution of complex traits, such as social castes, requires insights beyond analyses of single genes to integrated analyses of gene regulatory networks. Research on gene regulatory networks incorporating transcription factors was pioneered in honeybees and ants (6, 29, 69, 117).

Recent studies of social insects have posited that genes at the core of a regulatory network are likely to be more evolutionarily constrained than genes at the periphery. Functional changes in genes that are highly connected or central to a regulatory network are likely to disrupt many biological processes (26). Support for this comes from analysis of a honey bee transcriptional regulatory network characterizing behavioral traits (90). Highly connected, core protein-coding genes (such as transcription factors) should be more conserved in comparison to peripherally located genes (90). Moreover, genes expressed differentially among castes (50, 57, 66) and in specialized tissues including sting and hypopharyngeal glands in honey bee workers (62) have high rates of molecular evolution, suggesting peripheral genes could be important in the advent of behavioral novelty.

GENE REGULATION IN SOCIAL EVOLUTION

The previous section focused on DNA sequence and genome structural differences and their potential role in social evolution, but there has been an equally strong emphasis on the role of gene expression, gene regulation, and, more recently, epigenetics on the expression and evolution of social traits in insect societies. Below, we summarize some of the ideas and evidence for changes in gene expression and its regulation as drivers of social evolution.

Gene Expression and Solitary Ground Plans

Hypotheses focusing on the earliest origins of sociality predict that transitions from solitary to incipiently social societies involve changes in the timing of gene expression. All individuals remain totipotent into adulthood and throughout most of their lives and are capable of performing reproductive and foraging tasks (150). At the origin of sociality, changes in gene expression might start off as being environmentally responsive and stem from preexisting developmental plasticity (151).

The ovarian ground plan hypothesis posits that an uncoupling of solitary reproductive and foraging behaviors ultimately produced eusocial queen and worker castes (150). Gene networks related to reproductive and foraging behavior in solitary insects are predicted to have been co-opted to regulate reproductive queen-like and foraging worker-like traits during the transition

from solitary to caste-containing societies. Tests of this hypothesis using genetic data come mainly from advanced eusocial taxa (4, 5, 46, 97).

The maternal heterochrony hypothesis predicts that worker-like sibling care behaviors are regulated by patterns of gene expression similar to those found in subsocial maternal care behavior (81). Therefore, reproductive division of labor may not require the decoupling of foraging and reproductive regulatory pathways but rather a reorganization of the timing of offspring-care gene expression. Support for this hypothesis comes from empirical transcriptomic studies on advanced eusocial bumble bees (161), primitively social wasps (139), and incipiently social bees (106).

Genetic Toolkits

Examinations of insect social evolution from an evolutionary developmental biology (evo-devo) perspective led to the proposal that castes are derived from new arrangements of solitary behavioral and physiological modules (5, 149, 150) and, along with these, deeply conserved genetic modules (reviewed in 99, 136). A general hypothesis for convergent evolution of eusociality is that there is a shared toolkit of molecular and physiological processes across several independently evolved social insect lineages (136, 138). Because queen and worker castes can be produced from the same genome, the genetic toolkit underlying convergent social caste phenotypes depends on the differential expression of common genes and/or pathways.

In the study of eusociality, a few previous studies on bees and wasps suggested some overlap in gene expression patterns related to social behavior across lineages. Studies comparing *P. metricus* wasps and honey bees highlighted some common patterns of gene expression related to the regulation of foraging/provisioning behavior (138) and aggressive behavior (137). However, the extent of overlap across species in these studies was relatively small, and some behaviors (e.g., reproductive behaviors) were associated with nonshared gene expression patterns (138). Instead, changes in the modulation of key pathways and biological functions (e.g., related to metabolism or nutrient signaling) may be more important than shared individual genes (15, 16). In a similar vein, conserved coexpressed gene modules were associated with ant caste differences, as well as several other social traits, across more than a dozen different ant species (92). These studies suggest there may be key gene networks related to social evolution, but the specific genes involved and the direction of their expression may be more evolutionarily labile (15).

There may even be deeper similarities in the mechanisms that regulate social traits across Hymenoptera and Isoptera. In the termite *Cryptotermes secundus*, differential expression of several genes between workers and reproductives include those coding for juvenile hormone (JH) esterase, vitellogenin, and a cytochrome P450 (145). In *Reticulitermes flavipes*, there is also a causal association between hexamerin expression, JH levels, and development of reproductives versus workers (115). Genes related to metabolism, oxidation reduction, JH signaling, and storage proteins (such as vitellogenin and hexamerin) are also commonly related to caste differentiation in Hymenoptera (reviewed in 136), suggesting functions related to reproduction and metabolism have been utilized multiple times during social evolution to regulate caste differentiation, as part of a core, shared toolkit for fundamental social traits.

cis-Regulatory Evolution

Changes in *cis* gene regulation, including the evolution of transcription factors and transcription factor-binding sites located near (i.e., *cis* to) target genes, have been suggested to be prime movers in phenotypic evolution (160). It has also been suggested that changes in *cis* regulation may also

Evolutionary developmental biology: a comparative approach in biology examining developmental processes across different organisms to determine how they evolved

***cis* gene regulation:** regulation of gene expression by transcription factors and transcription factor-binding sites near target genes

Histone acetylation:

an essential part of gene regulation in which the binding of DNA wrapped around histone cores is regulated through enzymatic addition or removal of acetyl groups on histones, with effects on chromatin structure and gene expression

be one of the main drivers of social evolution in insects (110, 164). Methods for identifying and studying *cis*-regulatory elements, including promoters, enhancers, and silencers and their targets, have rapidly improved in recent years, including advances in predicting *cis*-regulatory motifs as well as their associated targets (6, 123).

Numerous *cis*-regulatory motifs associated with major transcription factors involved in olfaction, neural development, and behavior in *Drosophila* are associated with brain gene-expression differences in nursing and foraging worker honey bees, suggesting deep conservation of *cis*-regulatory motifs related to behavior in insects (125). Some of these *cis*-regulatory motifs are associated with a common set of transcription factors responding to diverse social environmental and internal physiological factors that regulate honey bee behavioral maturation (9). Five major transcription factors, including the deeply conserved *egr* and *pax6*, are associated with *cis*-regulatory motifs in a large proportion of genes that show expression patterns associated with foraging (69). Experimental studies causally implicate one major transcription factor, *ultraspiracle*, in the regulation of behavioral maturation and downstream changes in brain gene expression (9).

These pioneering studies in honey bees raise the interesting question of whether the same deeply conserved transcription factors and associated *cis*-regulatory elements are associated with social behavior across diverse lineages of social insects, as predicted by the *cis*-regulation view of phenotypic evolution. There has been less work in this area outside of honey bees; however, a comparative study examining ant genomes uncovered a large number of conserved *cis*- and *trans*-regulatory motifs across seven ant species, with evidence of significant evolutionary changes in the *cis*-regulatory motifs of over 2,000 genes.

Epigenetic Modifications

There has been great recent interest in the role of two different forms of epigenetic modifications in gene regulation and evolution of sociality in insects, DNA methylation and histone acetylation (89, 147). Initial studies suggested DNA methylation was ubiquitous within the social Hymenoptera (146), which stood in stark contrast to the patchy and labile patterns of DNA methylation in other insects such as flies and beetles (45). A flurry of research activity on DNA methylation in honey bees suggests that differential DNA methylation is related to queen-worker caste differences (86). Furthermore, experimental knockdown of expression of one of the core methylation genes, *DNMT3* (*DNA methyltransferase 3*), led to changes in alternative splicing of numerous genes (79) and to differences in caste-related phenotypes (77). DNA methylation may also regulate behavioral plasticity within the honey bee worker caste, as there are differences in global methylation patterns between nurses and foragers (51), and pharmacological inhibition of DNA methylation may affect learning and memory (85).

DNA methylation was posited to be important for the evolution of caste differences (147) because epigenetic modifications may increase the regulatory capacity of the genome and allow for greater phenotypic plasticity (89). Comparisons of multiple bee genomes hinted that increased genome-wide DNA methylation is associated with increasing social complexity (65). However, outside of bees, there is surprising evolutionary lability in DNA methylation systems. There has been a loss of the *de novo* methylation enzyme DNMT3 in the vespid wasp lineage (100, 128), with a nearly complete reduction of cytosine DNA methylation in the primitively social *P. dominula* (128). In ants, there may be some differences in DNA methylation patterns between queens and workers (20), but the association between DNA methylation and caste differences appears to be weak and likely not causal (78). A more conservative analysis by Libbrecht et al. (78) suggests most social insect DNA methylation is highly stable and not related to dynamic expression, and the authors questioned DNA methylation's importance in caste plasticity. At this time, there is a

notable lack of consensus across researchers and across species related to the importance of DNA methylation in caste determination and social evolution. This reflects how little we currently understand about the function and significance of DNA methylation in social insects, leaving ample opportunities for future research in this area.

There has been a recent focus on other epigenetic mechanisms, such as histone acetylation, in the regulation of social traits and their evolution in insects. Studies in the carpenter ant *Camponotus floridanus* uncovered differences in the acetylation of K27 residues on histone H3 (19, 122), with pronounced differences between castes related to sequence motifs of transcription factors, and genes related to development and neural function. Histone acetylation is also likely to play a role in the regulation of foraging and scouting behavior in major and minor workers of this species. Experimental manipulations of histone activity suggested hundreds of genes linked to hyperacetylated histones are related to scouting behavior and are associated with the action of histone deacetylases and the major histone acetyltransferase gene CBP (122).

Noncoding microRNAs (miRNAs) are known to be involved in the regulation of insect development and metabolism (11) and are typically thought to suppress protein production via binding to complementary mRNA strands and blocking translation. miRNAs have been found in the genomes of honey bees (144), other bees (65), ants (20), wasps (128), and termites (134). Differential expression of miRNAs has been found between the honey bee queen and worker caste, and miRNAs may be active components of royal jelly (30, 49). There are also differences in miRNA expression between honey bee worker behavioral castes (13, 83), suggesting miRNA profiles change during development. Conserved miRNAs were also found across seven species of ants, with a few also showing caste differential expression in *C. floridanus* (124). The extent of miRNA contribution to the regulation of social traits is not yet fully explored across species.

Genomic Imprinting and Intragenomic Conflict

Parent-of-origin effects on gene expression based on epigenetic modifications, or genomic imprinting, have been of great interest in evolutionary biology because they set up the potential for intragenomic conflict (155). In such cases, biased expression of father-derived alleles (patrigenes) may compete with expression of mother-derived alleles (matrigenes), such that patrigenes should promote phenotypes that overuse maternal resources, whereas matrigenes should result in conserving maternal resources. Queller (105) extended the theory of genomic imprinting to social insects, making predictions about how relatedness asymmetries (due to haplodiploidy) and social living could lead to parent-of-origin effects on social traits.

In social interactions between two full-sister hymenopterans, patrigenes should promote altruistic behavior (favoring passing on of the same patrigenes), whereas matrigenes should promote selfishness (105). The prediction is reversed in social systems with multiple paternity where sisters have different fathers, in which caste patrigenes should favor selfishness. Crossbreeding studies between two strains of honey bees found evidence of a strong paternal effect on worker fertility (96). This agrees with the prediction from intragenomic conflict theory that in situations of multiple paternity (honey bees are highly polyandrous), paternal alleles should favor selfishness (personal reproduction). On the molecular level, many genes in the honey bee genome show parent-of-origin effects on gene expression (72). Furthermore, patrigene expression is biased in reproductive tissues, and the patrigene bias is especially pronounced in workers with activated ovaries in response to queenless conditions (41).

These data hint at the potential for imprinting to play a role in genome evolution in social insects. Kronauer (76) warned that such predictions must also consider the effect of each gene on

microRNAs: small noncoding RNA molecules that function in posttranslational gene expression regulation and RNA silencing

Genomic imprinting: an epigenetic process by which genes are expressed (or “imprinted”) with parent-of-origin specificity. Father-derived alleles are also termed patrigenes, and matrigenes are maternal-derived alleles

Haplodiploidy: a sex determination system in which males are haploid and develop from unfertilized eggs whereas females are diploid, developing from fertilized eggs

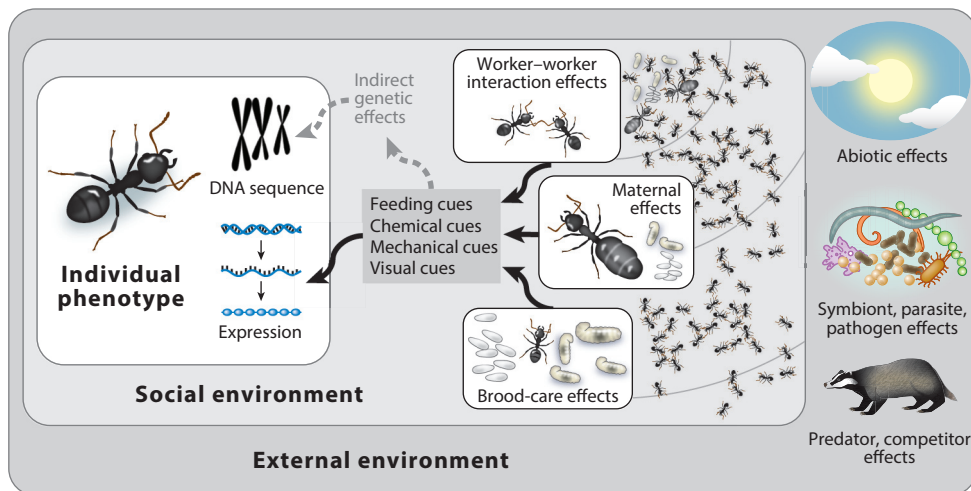


Figure 2

Environmental drivers of social insect gene expression and genome evolution. The ecological evolutionary developmental biology (eco-evo-devo) synthesis predicts that multiple factors all mediate molecular evolution. Social insects are affected by other individuals of the same species in the colony (social environment) and myriad additional factors, including symbionts, parasites, pathogens, predators, competitors, and abiotic effects (external environment). These factors can feed back on gene expression patterns and, via indirect genetic effects, also impact DNA sequence evolution.

caste and role of the individual and that initial predictions may be complicated by the fact that many genes will be differentially expressed and have distinct roles in different castes. There are many additional predictions to be tested in social insects, and with the advent of many advances in social insect epigenetics, this is a rapidly expanding area for future research.

ENVIRONMENTAL EFFECTS ON SOCIAL INSECT GENOMES

Genes and molecular mechanisms should not be seen as directly responsible for insect sociality; rather, genes “create a framework within which the environment acts to shape the behavior of an individual” (22, p. 68). In this section, we summarize the environmental drivers of insect social organization and the evidence that they directly or indirectly influence the activity and the evolution of social insect genomes (Figure 2).

The Primacy of the Social Environment

The social environment, both maternal and sib-social, can strongly influence the pheromonal, nutritional, and physical environment during social insect development (61). These influences can occur extremely early in development and include differential maternal investment in eggs (118, 152) and maternal and sib-social effects on early instar larvae (23), but relatively little is known about gene expression changes during very early stages of development (64, 91, 98, 134). Large changes associated with adult social environment are notably observed in regulation of gene expression (87, 106, 137, 161) and may also result in epigenetic modifications (51). Changes

in gene expression and epigenetic states can be reversible based on the social environment, as observed in nurse-forager transitions in honey bee workers (51, 153).

Social interactions can also indirectly promote higher rates of DNA sequence evolution. Maternal- and sib-effect genes are expressed in mothers and siblings, respectively, but have phenotypic effects on other individuals. Via indirect genetic effects, such genes are predicted to experience weaker selection and contain higher levels of polymorphism relative to genes with direct fitness effects (82). In accordance with this prediction, genes expressed in tissues specialized for social functions in advanced eusocial honey bees have higher rates of molecular evolution compared to genes expressed in conserved tissues found in all insects (62).

What are the specific social factors that influence social insect genomes? One important driver of caste, behavior, and gene expression is nutrition, which is a social factor because food is provided/controlled by other members of the colony. Young honey bee larvae that are fed royal jelly (instead of a less-rich food source) experience changes in hormone titers and large-scale downstream changes in gene expression that lead to divergent queen and worker developmental trajectories (38, 47). Food quantity/quality can also affect adult worker honey bee division of labor for foraging tasks, and this is associated with numerous changes in brain and fat body gene expression (7, 8). There are also known associations between nutrition and caste-related physiology, behavior, and development in ants, wasps, and termites (27, 35, 73). In *R. flavipes* termites, the accumulation of hexameric storage proteins depends on nutritional status (115) and soldier development is associated with changes in the expression of numerous genes (116), including a causal influence of hexamerins (165).

Another source of social information is chemical cues from conspecifics, including cuticular hydrocarbons and pheromones. In *C. secundus* termites, expression of a gene involved in chemical communication (beta-glycosidase) differentiates typical workers from reproductive workers (145), and individuals with disruption of this gene are treated aggressively by workers, likely owing to a change in chemical profiles (74). In honey bees, there are large-scale changes in brain gene expression of workers exposed to queen pheromone (48), brood pheromone (2), and alarm pheromone (3). Queen pheromone and alarm pheromone induce changes in the expression of transcription factors (e.g., *kruppel homolog 1* and *c-jun*) that may affect large-scale downstream changes in gene expression (48). The genomes of social insects are also rich in odorant and pheromone receptors and binding proteins (148), and there is evidence of significant protein sequence evolution in these gene families in bees (162).

Social insects also use auditory, mechanical, and visual information for communication. The honey bee dance language uses sound and mechanical signals to communicate the location and profitability of food sources, and there are distinct patterns of brain gene expression characterizing dancing bees from dance followers (120). Mechanical cues may also be involved in the development of reproductive and nonreproductive caste differences in ants and wasps (reviewed in 60). In *P. fuscatus*, maternally produced vibrations during development bias larvae to possess worker-like physiological traits as adults (131). Visual cues are also important in individual recognition in some *Polistes* wasps, and this ability is associated with brain expression of genes related to calcium signaling (17).

The complex social environment of social insects suggests advanced sociality may be associated with increasing neural complexity. This idea, termed the social brain hypothesis, posits that the cognitive demands of social living select for enhanced function, connectivity, and volume of specific brain regions (80). Although the idea has not received strong support from neuroanatomy, studies of molecular evolution in bees suggest positive selection on genes related to synaptic transmission, learning/memory, and neural development in advanced eusocial species (65).

Indirect genetic effects:

when a gene in one organism/individual exerts a phenotypic influence indirectly through affecting traits in another; genes affecting traits involved in sibling and maternal care have sibling and maternal effects, respectively

Extended phenotype: the idea that the effect of an organism's genes extends beyond its own body to affect the environment and other organisms' phenotypes

Parasites, Pathogens, Symbionts, and Microbiomes

Parasites, pathogens, symbionts, and beneficial microbiota can be powerful drivers of phenotypic and genetic evolution. The extended phenotype idea posits that via manipulation of the host environment, genes within the genomes of parasites, pathogens, or symbionts affect the host phenotype (55). Thus, in considering the evolution of insect sociality and social insect genomes, we must also consider the evolution of their microfauna. Some of the most striking examples of coevolution between social insects and microfauna are in the fungus-growing ants and termites and their accompanying bacterial communities (94). The sequencing of the genomes of the leafcutter ants *Atta cephalotes* and *Acromyrmex echinator* (95) revealed a reduced complement of genes related to nutrient acquisition, perhaps a result of the ants' obligate dependence on the fungus for food (129).

Because of central place nests, high densities of individuals, and high rates of physical interaction between individuals, social insects have been suggested to be especially prone to parasite and pathogen infection (158). Despite this, sequencing of the honey bee and other bee genomes revealed the presence of relatively few, or at least not a clearly expanded, repertoire of innate immune genes (114, 148), perhaps because special mechanisms of social immunity, such as allogrooming, culling the sick, and social fever, have evolved to combat pathogens. Numerous studies have shown large and profound effects of pathogenic mites, bacteria, fungi, and viruses on gene expression in several tissues in honey bees (28, 42, 119). Beyond pathogenesis, there are also striking examples in which parasites show evidence of manipulating the social insect host phenotypes to their advantage. For example, *Cordyceps* fungi cause large changes in ant host brains and gene expression, culminating in aberrant leaf-biting behavior that serves to spread fungal spores (36). *P. dominula* wasps are hosts to parasitoid strepsipterans that lead to aberrant nest-abandoning behavior that may facilitate parasite mating (12), and this has the potential to be associated with shifts in the expression of caste-related genes. Clearly, social insect phenotypes and genome evolution are not driven solely by interactions with conspecifics—both beneficial and harmful parasites and pathogens can exert powerful effects on social insect genomes, gene expression, and their evolution.

Abiotic Factors

The abiotic environment is likely to be an important driver of cooperative behavior in insects, particularly factors such as temperature and climate. However, the role of ecological factors in social evolution has been studied very little on the molecular level. General patterns of the geographical distribution of species across bees and wasps indicate that higher forms of sociality (e.g., large colony size, perennial colonies, swarm founding, and morphological caste formation) are more likely to occur in tropical environments compared to temperate environments (103). It has been suggested that reproductive diapause and a bivoltine life cycle (adaptations to temperate climates) are important preadaptations for caste evolution in wasps (59). In addition, social transitions in halictid bees, which have gained and lost eusociality multiple times in the past few million years (59), are thought to be related to climatic warming periods, and altitude and season length are related to solitary versus social nesting populations within a facultatively social species (71). In a recent study within the primitively social wasp genus *Polistes*, several abiotic factors such as temperature variability, temperature, and rainfall were associated with both the presence/absence of cooperative nest founding and the number of cooperating foundresses within these associations (121). Thus, abiotic factors in the environment are likely to be important selective agents for cooperative behavior, and there are likely to be accompanying evolutionary changes in genetic mechanisms affecting temperature response and/or diapause during social transitions.

SYNTHESIS AND EVOLUTIONARY FRAMEWORKS

In the above sections, we reviewed a wide variety of different molecular mechanisms and evidence for their roles in the regulation and evolution of insect societies. The diversity of different genetic mechanisms is bewildering and begs the question of whether there are any patterns or underlying genetic themes in eusocial evolution. It is tempting to search for a unifying theory; can we identify patterns of genomic evolution that have been repeatable across the diverse and convergently evolving social insect lineages? Each lineage has its own unique evolutionary history and set of life history traits; thus, will it prove to be impossible to derive common patterns from these diverse organisms? We do not yet have answers to these questions, but below we outline two possible frameworks for beginning the search for unifying themes underlying the molecular evolution of eusociality.

Social Ladder Framework

Recently we proposed a broad model, the social ladder hypothesis, which posits that different combinations of molecular mechanisms might be acting at each stage in social evolution (109). We emphasized that understanding the evolution of eusociality cannot be explored as a single transition. Beyond the necessary preconditions, including parental care and defensible nests, many incremental steps are involved in the evolution of eusociality and various stepwise transitions have been proposed (37). In examining the molecular evolution of eusociality, it is critical to consider the full social spectrum from the earliest origins of cooperative breeding to the subsequent elaboration of group-level traits in highly eusocial colonies (54, 58). Previous authors have been careful to clarify that stepwise transitions from solitary to eusocial colony organization are by no means preordained and each stage has its own adaptive value (37). It is noteworthy that advanced eusociality is not an ultimate evolutionary endpoint because multiple reversions from social to solitary life are known across incipiently and primitively social groups (108, 143).

The social ladder framework makes predictions about the types of genetic changes associated with each stage in social evolution. Early in social evolution, regulatory genomic changes, such as shifts in the timing and location of expression of conserved genes (akin to the ovarian ground plan and maternal heterochrony hypotheses), are predicted to be the primary drivers of social phenotypes. This is based on the idea that underlying phenotypic plasticity (and mechanisms centering on gene expression and epigenetics) can serve as the fuel for initial stages of social evolution. Then, in the intermediate stages of social evolution from incipiently to primitively social, roles become less flexible and more fixed (e.g., more stable caste differences). This would be associated with larger and more permanent caste biases in expression and more fixed genomic changes, including both regulatory and protein coding–sequence changes. As queen and worker phenotypes diverge (and genes take on caste-specific roles), this can open the door for more rapid and dramatic changes in coding sequences. Finally, in later stages of social evolution, colony-level selection can be a strong driver of more dramatic changes in social insect genomic composition.

Specific predictions of the social ladder framework include (*a*) changes in gene expression and epigenetic changes will be important during early, intermediate, and late stages of social evolution; (*b*) changes in protein-coding sequences will be important during intermediate and late stages of social evolution; and (*c*) large genomic changes, such as the appearance of novel genes, gene family expansion/contraction, and changes in genome structure (e.g., social chromosomes), will be most important during later stages of social evolution (109).

In **Table 2** we provide a preliminary summary of the types of molecular mechanisms associated with different social traits and where they fall along the so-called social ladder. In general, the data thus far support some of the general predictions of the social ladder hypothesis. However,

Genetic assimilation:

the process by which an environmentally induced phenotypic response becomes genetically fixed through a persistent selective environment; after fixation, the originally environmentally induced phenotype persists in the absence of the initial inducing environmental stimulus

there are still many gaps in our knowledge of the genetic regulation of sociality in insects, with especially sparse data for incipiently social species and solitary outgroups. In addition, there is the problem of ascertainment bias—for example, bias toward exploring gene expression in early social transitions and bias toward protein evolution and novel genes in later social transitions. Thus, the time is right for studies that comprehensively investigate multiple mechanisms at multiple levels of sociality, especially in groups such as vespid wasps and xylocopine bees, which encompass the full range of sociality within a single monophyletic lineage (**Figure 1**).

Eco-Evo-Devo Framework

The extended evolutionary synthesis has focused on integrating an appreciation of development (evo-devo), plasticity, and genomic flexibility into our understanding of evolution (102). The emerging field of ecological evolutionary developmental biology (eco-evo-devo) is further integrating ecological relationships, emphasizing the important role of the environment as an inducer of phenotypic (and thus evolutionary) change (1). Eco-evo-devo stresses the role of plasticity as an evolutionary prime mover. The importance of phenotypic (both developmental and behavioral) plasticity as important factors in the success and evolution of social insects has long been recognized (149). Eco-evo-devo also stresses the importance of ecological interactions, considering each organism as a holobiont that evolves as an integrated part of a complex web of interactions including symbionts, microbiomes, pathogens, and parasites (44). As discussed above, social insects arguably represent one of the most interaction-rich biological systems because of their susceptibility to parasites and pathogens, as well as their tightly coevolved mutualistic relationships with other micro- and macro-organisms (34). Thus, we suggest applying eco-evo-devo ideas can provide a fruitful framework for studying molecular evolution in insect societies.

An understudied mechanism forming a key part of eco-evo-devo is the idea of genetic assimilation. Waddington (141, p. 289) defined genetic assimilation as a process “by which a phenotypic character, which initially is produced only in response to some environmental influence, becomes, through a process of selection, taken over by the genotype, so that it is formed even in the absence of the environmental influence which had at first been necessary.” If behavior is the first response to changes in the environment, then initially plastic behavior has the potential to subsequently become encoded via genetic assimilation (see **Figure 3**) (14, 132). Phenotypic plasticity in reproductive behavior, parental care, and foraging in solitary and subsocial species could provide the raw materials on which selection can act (151). If these characteristics become epigenetically inherited, then this could produce the division of labor seen in incipiently and primitively social insects. Subsequently, this could lead to the evolution of novel phenotypes and the canalization of developmental pathways as observed in advanced eusocial species (101). Although there is no direct evidence of genetic assimilation in eusocial insects, a transcriptomic comparison in honey bees suggested many of the same genes are expressed during aggressive responses in real time (response to alarm pheromone), developmental time (older soldier bee specialists compared to young bees), and evolutionary time (docile and aggressive populations) (3). Thus, it is possible that a process of genetic assimilation resulted in environmentally induced changes in aggression-related gene expression becoming fixed in aggressive populations (**Figure 3**).

The eco-evo-devo framework can be used to make predictions about the types of mechanisms expected to be prime movers in social evolution. These include changes in regulation of conserved genes, epigenetics, and selection on hub genes in gene networks that may have cascading effects on numerous downstream genes during development. Eco-evo-devo provides insights into the types of genes most likely to be associated with evolutionary change during social transitions. We suggest these would include genes such as heat shock proteins (molecular chaperones related

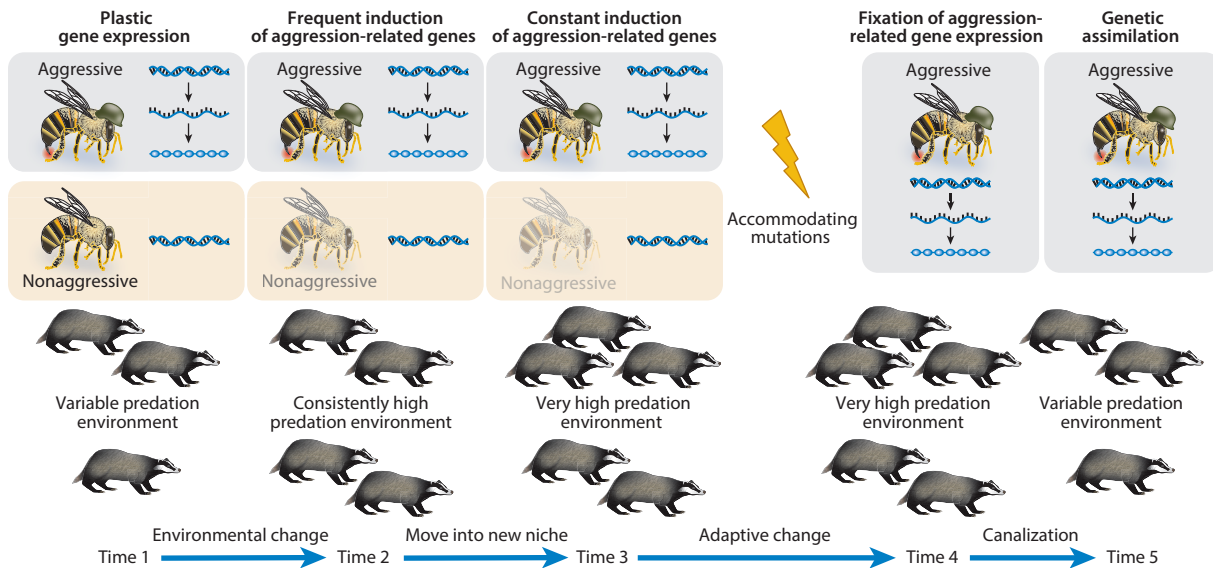


Figure 3

Scenario of genetic assimilation, as applied to the evolution of aggression in honey bees. Initially, individual phenotypic plasticity provides an adaptive response to variable environmental stimuli—for example, aggressive response to predation pressure (time 1). Subsequently, with an environmental change (time 2), such as increased predation pressure, the gene expression pattern inducing the aggressive response is more often exhibited compared to the nonaggressive response. This may allow aggressive colonies to move into previously unoccupied niches in the environment (time 3), such as very high predation environments. Over time, environmentally induced responses in gene expression and aggressive phenotype can become fixed differences as a result of the accumulation of accommodating mutations (time 4). The response then becomes canalized, resulting in a loss of plasticity, and individuals are fixed for the aggressive phenotype, and associated gene expression, even in the absence of the high predation related environmental stimulus (time 5).

to abiotic stress and environmental change), genes related to immunity that are coevolving with major pathogens and symbionts, and major developmental regulators such as transcription factors, as well as environmentally responsive genes such as those related to diapause and nutritional stress.

CONCLUSIONS

There has been substantial progress in uncovering molecular mechanisms associated with the evolution of insect sociality, revealing diverse sequence-based and expression-based evolutionary changes associated with social evolution. Looking to the future, an appreciation of both the diversity of genetic mechanisms and the diversity of social forms is necessary to build a more comprehensive understanding of the molecular evolution of sociality. Examining advanced eusocial species to ask what genes and genetic changes underlie their complex phenotypes will reveal only part of the multistep social evolutionary process. Likewise, traditional top-down approaches examining DNA sequence changes associated with behavior will not fully reveal the role of ecology and behavior in genetic changes. If behavioral plasticity allows solitary and social insects to enter new niches, leading to subsequent genetic assimilation, then these traditional examinations and experiments may miss key aspects of the evolutionary process. Consequently, bottom-up examinations of phenotypic plasticity and epigenetic regulation are untapped and potentially illuminating lines of research. Such approaches may be applied to early stages of social evolution, where plasticity

has already been proposed to be important in the origins of castes, as well as to the evolution of more derived eusocial traits in later stages of social evolution.

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