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Endocrine uncoupling of the trade-off between reproduction and somatic maintenance in eusocial insects

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In most animals reproduction trades off with somatic maintenance and survival. Physiologically this trade-off is mediated by hormones with opposite effects on reproduction and maintenance. In many insects, this regulation is achieved by an endocrine network that integrates insulin-like/IGF-1 signaling (IIS), juvenile hormone (JH), and the yolk precursor vitellogenin (Vg) (or, more generally, yolk proteins [YPs]). Downregulation of this network promotes maintenance and survival at the expense of reproduction. Remarkably, however, queens of highly eusocial social insects exhibit *both* enormous reproductive output *and* longevity, thus escaping the trade-off. Here we argue — based on recent evidence — that the proximate reason for why eusocial insects can decouple this trade-off is that they have evolved a different 'wiring' of the IIS-JH-Vg/YP circuit.

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> ''Hormones are natural candidates for physiological mechanisms that can give rise to antagonistic pleiotropy... When, for example, hormones mobilize the organism for reproduction, the transfer of resources from somatic functions to reproductive functions can be expected to produce trade-offs between the corresponding fitness components, survival, and fecundity, respectively.''
>
> Finch and Rose (1995) [17]

Introduction

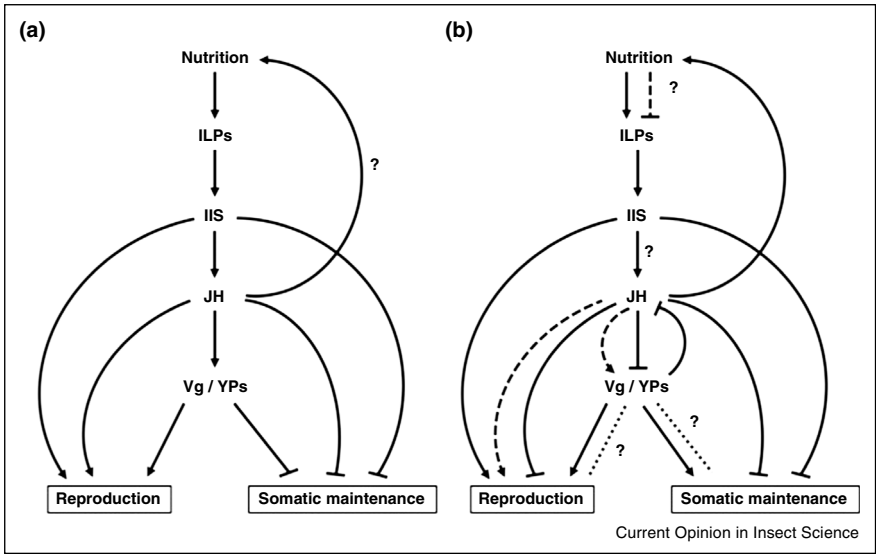
In many organisms one observes a negative relationship (a 'trade-off') between reproduction versus somatic maintenance and survival ability; increased reproduction thus exacts costs in terms of reduced maintenance (e.g., stress resistance, immunity) and lowered survival [1,2,3,4,5]. This trade-off has been well documented at the phenotypic, physiological or quantitative genetic level in numerous species and represents a major constraint upon physiology and the evolution of life histories [2,3,4,5,6,7].

A traditional population genetic explanation for such trade-offs is the existence of alleles with antagonistic pleiotropic effects upon fitness components (life history traits), for example alleles that promote growth and/or reproduction at the expense of somatic maintenance and survival; such alleles contribute to negative genetic correlations between reproductive and maintenance traits [6,7]. At the physiological level, the classical interpretation of the reproduction-maintenance trade-off is that the energetically costly process of reproduction 'competes' with the energetic demands of somatic maintenance and survival [2,3,4,5,8]. These interpretations — genetic versus physiological — are obviously not mutually exclusive [4,5,7].

Although a large body of literature supports the notion of energy or resource allocation trade-offs [2,3,4,5,8], recent evidence suggests that under some circumstances the fecundity/longevity trade-off can be 'decoupled' or 'broken' [3,4,5,9] (Here we refer to this trade-off, more generally, as the 'reproduction-maintenance' trade-off since survival/longevity are a function of somatic maintenance processes, including repair, stress resistance, immunity, etc.). Most examples of such a 'decoupling' come from laboratory studies of large-effect mutants or transgenes in model organisms (e.g., *Caenorhabditis elegans*, *Drosophila melanogaster*); however, in at least some of these cases, the ''breaking'' of the trade-off is likely to be artifactual or illusory [4]. For example, certain long-lived *C. elegans* mutants of the insulin-like receptor gene *daf-2* do not exhibit any measurable fitness costs (e.g., in terms of fertility), but lose out when competed against wildtype worms [4]. The best evidence for a real, naturally occurring uncoupling of the reproduction-maintenance trade-off is provided by eusocial insects (ants, termites, bees, wasps): in many highly eusocial insect species, queens can achieve enormous reproductive output while at the same time being extraordinarily long-lived [10,11,12,13] (Figure 1).

Here we discuss possible proximate explanations for why queens in highly eusocial insects, in contrast to other insects, might be able of 'decoupling' the trade-off

Figure 1



Model of the endocrine regulation of the reproduction-maintenance trade-off in **(a)** non-social insects versus **(b)** highly eusocial insects. Arrows indicate activation; stop bars represent repression; and dotted lines denote the absence of an effect. Solid versus dashed lines represent regulatory alternatives; question marks denote unknown or poorly understood relationships. **(a)** In most non-social insects, high nutritional input stimulates the production of insulin-like peptides (ILPs). ILPs activate insulin/insulin-like growth factor signaling (IIS), which in turn activates the production of juvenile hormone (JH). IIS and JH stimulate reproduction at the expense of maintenance, either interdependently and/or independently. JH activates the production of vitellogenin (Vg) and/or yolk protein (YP). Vg/YP promotes reproduction at the expense of maintenance. **(b)** In highly eusocial insects, high nutritional input is thought to stimulate ILP production, but in honey bees and potentially also other species this relationship might be reversed. ILPs activate IIS, and in several species low IIS is associated with long queen lifespan, as expected based on non-social insects. IIS likely activates JH production, but this still remains poorly understood. Depending on the species, JH either retains its ancestral gonadotropic function or its function has been altered (e.g., JH reduces reproduction); yet, in all cases we have reviewed JH seems to negatively impact somatic maintenance in eusocial insects. In some species, JH either promotes Vg/YP production, inhibits it (e.g., in honey bees JH and Vg are involved in a double-repressor loop), or might be decoupled from promoting Vg/YP synthesis. Again depending on the taxon, Vg/YP can either promote reproduction or not. At least in honey bees, Vg/YP seem to promote somatic maintenance and long life; in several species, Vg/YP has been co-opted for different non-classical functions, including in social behavior, caste determination and polyphenism. Thus, especially in eusocial insects, the 'wiring' of the JH-Vg/YP part of the network seems to be evolutionarily highly 'flexible' or 'labile'; the evidence at hand suggests that modifications of this part of the circuitry can make a significant contribution to the uncoupling of the reproduction-maintenance trade-off in highly eusocial insects.

between reproduction versus maintenance and survival. Based on recent evidence from honey bees and ants [14,15••,16] we argue that this is likely due to a different 'wiring', i.e. changes in the regulatory architecture, of the endocrine network that underlies the physiological regulation of the reproduction-maintenance trade-off. We conclude that a better understanding of proximate mechanisms might make an important contribution to our understanding of ultimate causation in life history evolution [5,17,18,19•,20,21,22,23,24,25,26,27,28,29•].

Endocrine regulation of the reproduction-maintenance trade-off

Numerous studies in many species indicate that at the physiological level various hormones can have opposite regulatory effects on growth and reproduction versus maintenance and survival; such hormones might thus represent endocrine key mediators of the reproduction-maintenance trade-off [5,17,18,19•,20,21,22,23,24,25,26,27,28]. Although the molecular details can differ substantially among taxa, in many species the reproduction-maintenance trade-off seems to be governed by a neuroendocrine-reproductive 'axis' (or probably more accurately — due to feedforward and feedback loops — a 'network') [5,18,19•,20,21,25,29•,30].

In the nematode *C. elegans*, various insects including *Drosophila*, and the mouse *Mus musculus*, environmental cues and dietary inputs are integrated by the central nervous system (CNS) and relayed by endocrine signals which activate a 'pro-reproductive, pro-aging mode'; conversely, downregulation of this circuitry switches the system to a 'pro-maintenance, pro-survival mode' at the expense of growth and/or reproduction [18,19•,25,29•,30]. Across species the most evolutionarily conserved components of this network seem to be those involved in insulin/IGF-like signaling (IIS); across several model and non-model organisms downregulation of IIS is associated with extended lifespan and increased stress resistance but reduced growth and/or reproduction [18,19•,20,21,24,29•,30].

In rodents and other mammals, for example, the hypothalamic–pituitary–gonadal (HPG) and somatotropic (growth hormone [GH] — insulin-like growth factor 1 [IGF-1]) signaling axes have emerged as major mediators of the trade-off between growth and reproduction versus maintenance and survival [19•]. Interestingly, in *Drosophila* and other insects a functionally parallel endocrine axis integrates signals between the brain, endocrine glands attached to the brain (the *corpora allata* and *corpora cardiaca*; equivalent to the hypothalamus/pituitary), the fat body (equivalent to mammalian liver and adipose), and the gonads. This system integrates IIS, lipophilic hormones downstream of IIS which act as gonadotropins (mainly juvenile hormone [JH], but also 20-hydroxyecdysone [20E]), and the yolk precursor vitellogenin (Vg) or yolk proteins [YPs] [18,20,22,23,24,25,26,27,29•,30,31•]. Likewise, a functionally parallel signaling axis in *C. elegans* connects neuroendocrine signals including IIS and TGFβ signals with steroid hormones (dafachronic acids) and — as of yet unidentified — gonadal signals [18,21,29•,30].

The IIS-JH-Vg/YP signaling network in non-social insects

To understand the possible proximate reasons for why the reproduction-maintenance trade-off can be uncoupled in eusocial insects [14,15••,16], we must first discuss some details of the IIS-JH-Vg/YP axis in non-social insects and other invertebrates.

At the level of IIS, many experiments using mutants and transgenes in *C. elegans* and *Drosophila* have shown that downregulation of IIS pathway components extends lifespan and increases stress resistance [18,20,21]. These changes are often accompanied by reduced growth and/or decreased fertility, even though in some cases the lifespan-extending effects can be genetically separated from the negative effects on growth and/or reproduction [18,20,21]. Similarly, ablation of the insulin-producing cells (IPCs) in the *pars intercerebralis* of the CNS in *D. melanogaster* and the linden bug *Pyrrhocoris apterus* extends lifespan at the expense of fecundity [20,24].

In response to IIS the *corpora allata* (CA) glands (or the single *corpus allatum* of *D. melanogaster*) behind the brain produce JH, a highly 'pleiotropic' sesquiterpenoid with effects on development, metamorphosis, reproductive maturation, fecundity, stress resistance, immunity and lifespan [17,18,20,25]. Several levels of evidence indicate that JH is a major 'pro-aging' gonadotropin that mediates the reproduction-maintenance trade-off. First, long-lived, sterile *D. melanogaster* mutants of the insulin-like receptor *InR* (the fly homolog of *C. elegans daf-2*) are JH-deficient, and treatment of these mutants with a JH analog (JHa) restores (shorter) wildtype lifespan and partly rescues the fertility defect [18,22,25]. Second, surgical or transgenic ablation of the CA glands in grasshoppers (*Anacridium*, *Schistocerca*, *Locusta*), the monarch butterfly (*Danaus plexippus*), the linden bug and fruit flies extends lifespan and promotes somatic maintenance at the cost of reduced fertility [22,23,24,25,31•]. Third, treatment of wildtype *D. melanogaster* with JHa promotes fecundity but shortens lifespan and increases oxidative stress [25,26]. Fourth, JH is a potent suppressor of innate immunity in *Drosophila* and other insects [16,25,32].

One of the principal gonadotropic functions of JH is to regulate the production of vitellogenin (Vg), an egg yolk precursor protein, and of YPs [14,25,33,34,35•]. Owing to their important role in lipid storage and transport, it has been hypothesized that Vgs and YPs might play an important role in lifespan regulation [36]. In support of this notion, the *C. elegans* Vg genes *vit-2* and *vit-5* are regulated by IIS, and RNAi against these genes promotes longevity [37]. Similarly, RNAi against *Vg* in the lubber grasshopper (*Romalea microptera*) causes ovarian growth arrest and extends lifespan [38••]. Although the *Drosophila* YP genes *yp1*, *yp2*, and *yp3* are not direct sequence homologs of the *vitellogenin* (*Vg*) genes of other insects, *Drosophila* YPs are thought to play the same storage protein role as Vgs [33,39••,40]; *yp* mutations affect ovariole number and fertility, and expression of YPs is negatively correlated with *Drosophila* lifespan [41]. However, the potential effects of YP RNAi on lifespan in fruit flies have not been investigated yet. Finally, transgenic overexpression of the *Drosophila Vg*-like gene (*CG31150*, also called *cv-d*) and of the (exogenous) honey bee (*Apis mellifera*) *Vg* gene in the fly decreases *Drosophila* lifespan [39••]. Thus, although the mechanistic details remain poorly understood, Vgs/YPs seem to be intimately involved in the reproduction-maintenance trade-off.

Together, the evidence available to date shows that in non-social insects and other invertebrates the IIS - lipophilic hormone (e.g., JH) - Vg/YP signaling network has pervasive — likely evolutionarily conserved — pro-reproductive and pro-aging effects. Downregulation of this network, for example in response to (depending on the species) low nutrient availability or other environmental changes (e.g., temperature, photoperiod), switches the physiological state of the organism to a pro-maintenance, pro-survival 'mode' at the expense of growth and/or reproduction [29•]. How then — given that the queens of highly eusocial insect species have managed to escape the reproduction-maintenance trade-off — is this endocrine circuitry 'wired' in these insects?

Modified regulation of the reproduction-maintenance trade-off in highly eusocial insects

Based on three recent studies in honey bees and ants, by Corona *et al.* [14], von Wyschetzki *et al.* [15••], and Pamminger *et al.* [16], a picture is beginning to emerge which suggests that the reproduction-maintenance

trade-off can be decoupled by changes in the regulatory architecture of the IIS-JH-Vg/YP network.

In honey bees, in contrast to most insects, JH and Vg titers are not positively but inversely correlated. In workers, there is a negative ('double repressor') feedback loop between JH and Vg whereby Vg is high and JH is low in stress-resistant nurse bees, whereas JH is high and Vg low in the more stress-susceptible forager bees: increased JH levels and decreased Vg titers cause nurse bees (in the hive, characterized by high pollen intake, corpulent bodies, high stress resistance) to transition to become forager bees (characterized by high nectar intake, lean bodies, low stress resistance) [29•,42] (also see Rueppell *et al.*, in this issue). The correlation between high JH titers and increased stress susceptibility in worker bees is consistent with findings from non-social insects, suggesting that JH acts as a 'pro-stress', 'pro-aging' hormone (see above). In contrast, Vg appears to promote somatic maintenance and survival, unlike the hypothesized 'pro-aging' role of Vgs/YPs in non-social insects: indeed, *Vg* RNAi knockdown assays in the honey bee demonstrate that Vg acts as a major antioxidant, protecting workers against oxidative stress-induced mortality [29•,43,44].

The above findings have led to the suggestion that Vg might also be involved in regulating queen lifespan [29•,43,44]. Consistent with this notion, queens show an age-dependent drop in JH, accompanied by an increase in Vg levels, and are more resistant to oxidative stress than workers [14]. (Two noteworthy side comments in this context are: (i) in contrast to old queens, JH is elevated in young queens, and this is associated with mating flight activity; after the mating flights, they only fly again when they leave together with the swarm; shortly before swarming, Vg levels are decreased and oogenesis is reduced; and (ii) increased JH levels are also seen in drones before they leave the hive to form drone aggregations, and JH titers in drones parallel the levels of Vg; titers of Vg are low, however, and its functional role in drones remains unclear [45,46].) Old queens relative to old workers also exhibit downregulation of an insulin-like peptide (ILP) and two insulin receptors, which might perhaps be in line with the pro-survival effects of reduced IIS observed in other species [14]. This downregulation might be due to low JH titers in older queens since treatment of queens with JHa increases ILP expression [14]. A similar JH-ILP feedback is observed in CA-ablated flies which show downregulation of ILP6 (however, in contrast to other ILPs, ILP6 promotes rather than decreases lifespan), indicating that JH promotes ILP6 expression [31•].

Given the existence of a JH-Vg double-repressor feedback loop in workers and the fact that Vg synthesis can occur independent of JH in honey bees, a fundamental question thus concerns evolutionary differences among insects in the 'coupling strength' between JH as a gonadotropic hormone and the synthesis of Vg, which is typically taken as a general proxy for female fecundity and fertility. A key difference between highly eusocial and non-social insects is that the latter, especially species that live relatively long, exhibit (often diet-dependent) reproductive cycles whose initiation requires a gonadotropic signal (typically JH, but in some dipterans also ecdysone) which induces Vg/YP production in the fat body. In marked contrast, Vg production and egg laying is continuous in the queens of highly eusocial bees, wasps, and ants, so that the reproductive process — once it has been triggered — can essentially run constitutively during an individual's reproductive lifespan. In the honey bee, for example, JH still plays a gonadotropic role, but this function has been shifted from the adult to the pharate adult stage, i.e. the time shortly before the queen sheds the pupal cuticle and emerges from the brood cell: during the pharate stage, JH titers increase in queens and application of JH induces Vg synthesis [47,48]. It is thus tempting to speculate that during the evolution of advanced insect eusociality the gonadotropic function of JH in queens might have undergone a heterochronic shift and that this shift might have removed evolutionary constraints on the JH-Vg/YP network, thereby 'freeing' JH and/or Vg/YP to take on other functional roles (e.g., flight, oxidative stress resistance, etc.). While such a scenario is not yet well supported by evidence, its plausibility is strengthened by the fact that in lepidopterans the coupling strength of JH and ecdysone to Vg varies among species depending on their particular life history [49].

Based on these findings, Corona *et al.* [14] have proposed a model that might explain the uncoupling of the reproduction-maintenance trade-off in honey bees. Together with work by Gro Amdam's group [43,44], their model makes the following assertions [14]: (a) as in other species, downregulation of IIS has a pro-longevity effect in bees, but the typical relationship between nutrition (which normally promotes IIS) and IIS is reversed so that the high nutritional status of queens inhibits ILP production and/or secretion; (b) in contrast to most other insects, the typical gonadotropic function of JH has been altered in bees: the typical, positive JH-Vg coupling has been shifted to the pharate adult stage, whereas in adult (non-pharate) queens Vg synthesis can run largely independently of JH input, and high JH can even repress vitellogenesis and act as a suppressor of Vg; (c) Vg plays a major role as a pro-maintenance antioxidant; and (d) the relationship between JH and IIS is mediated by Vg which might now act as a central endocrine signaling molecule rather than a 'simple' yolk protein precursor. This being said, a major caveat is that nothing is known yet about the putative role of Vg as a signaling molecule: this clearly requires in-depth future investigation.

Hence, there are at least three aspects of the IIS-JH-Vg/YP network that are different in the honey bee as compared to non-social insects: the disconnect between high

nutrition and IIS; the altered gonadotropic role of JH; and the pro-survival (rather than pro-aging) function of Vg (or of YPs in general). Indeed, it has been found that *Vg* RNAi decreases bee worker lifespan [44], and the data from queens [14] are consistent with a lifespan-promoting effects of Vg as well.

A second recent study reporting an alternative regulation of the reproduction-maintenance trade-off is due to von Wyschetzki *et al.* [15••] (also see Oettler and Schrempf, in this issue). In this paper, the authors examine whole-body transcriptomes of differently aged queens of the ant *Cardiocondyla obscurior*. By comparing gene expression patterns in the ant to age-related expression changes in *D. melanogaster* they find major similarities in age-dependent transcription between these species. However, for many transcripts the age-dependent expression patterns go in opposite directions between ants and flies: as compared to young queens, old queens upregulate reproductive genes but downregulate metabolic genes, whereas the opposite pattern is seen in females flies [15••]. In terms of an involvement of IIS and JH signaling, the authors detected differential expression of *Nlaz* (a homolog of vertebrate apolipoprotein D [APOD]), which has previously been shown to affect *Drosophila* lifespan; *Adenylyl cyclase 76E* (*Ac76E*), which represents a direct transcriptional target of the major IIS (forkhead Box O) transcription factor *foxo* and which has been shown to affect JH production; and of a putative JH binding protein (homolog of *Drosophila* CG34316).

In contrast to the paper by Corona *et al.* [14], however, this study does not find evidence for a major role of Vg in regulating fecundity or longevity in *C. obscurior*: the ortholog of the honey bee 'vitellogenin-like' gene GB52464 was moderately downregulated in older mated queens. Similarly, the authors observed upregulation of *InR* in older, more fertile queens [15••], which might be seen as being inconsistent with the model proposed for the honey bee queen, positing a downregulation of IIS [14]. On the other hand, the upregulation of *InR* could actually be *consistent with downregulation of IIS*: in *Drosophila*, downregulation of IIS causes increased activity of *foxo* which in turn causes the transcriptional upregulation of INR protein at the cell membrane [50]. It therefore remains unclear whether these findings (especially with regard to Vg) possibly mean that different eusocial insects might have evolved alternative ways of uncoupling the reproduction-maintenance trade-off (also see below).

In the third study, Pamminger *et al.* [16] show that long-lived queens of the ant *Lasius niger* likely defy the reproduction — immunity trade-off by decoupling the gonadotropic versus immunosuppressive effects of JH. The authors find that — in contrast to its typical in pro-reproductive effects in most other insects — JHa treatment decreases fecundity, increases the number of non-vitellogenic oocytes, and reduces investment in maternal care [16]. In contrast, and similar to other insects, JHa decreases the activity of the immune effectors phenoloxidase (PO) and prephenoloxidase (PPO) and reduces survival upon pathogen exposure. This alteration of the role of JH with regard to reproduction is similar to that reported for honey bees [14], suggesting that modifications (e.g., separation) of JH functions might contribute to the uncoupling of the reproduction-maintenance trade-off in important ways. Thus, by releasing JH from its pro-reproductive role, *L. niger* queens might be able to avoid the immuno-suppressive effects of JH. However, a major caveat is that the authors did not quantify JH titers and measure whether and how JHa treatment affects JH signaling in this system. For example, JHa application can have unintended pharmacological side-effects when its dosage is too high, and it is thus important to perform dose-response experiments within the normal physiological range.

As the authors discuss, their model of altered or 'separable' JH functions might be plausible when considering a broader phylogenetic view: in bumblebees, wasps and primitively eusocial bees, which are typically characterized by high reproductive output, elevated JH titers, and relatively short queen lifespans, JH acts as a 'classical' gonadotropin (as in most other, non-social insects) [51,52], while in ants of the genus *Diacamma* reproduction is associated with both low JH and increased lifespan [53,54]. Yet, as Pamminger *et al.* [16] note, JH *does function* as a gonadotropin with stimulatory effects on Vg expression in relatively long-lived queens of the fire ant *Solenopsis invicta* [51,52]. Similarly, JHa treatment stimulates *Vg1* and *Vg2* gene expression in queens of the seed harvester ant (*Pogonomyrmex rugosus*) [35•], a genus that typically exhibits long queen lifespans. Thus, whether *Solenopsis* and *Pogonomyrmex* ants (or different eusocial insects more generally) have evolved different solutions to the problem of uncoupling the reproduction-maintenance trade-off remains unclear but seems likely [16].

These considerations, and our above discussion of the timing shift of the gonadotropic function in honey bee queens, highlight the importance of analyzing the evolution of the IIS-JH-Vg/YP network from a proper phylogenetic point of view. For example, a major point in this context is the distinction between primitively and highly eusocial insects (i.e., primitively eusocial bees and wasps versus highly eusocial bees and ants): in contrast to primitively eusocial insects, highly eusocial bees and ants are characterized by the fixation of caste fate during postembryonic development, i.e. what Wilson and Hölldobler [55] have called the 'point of no return' in the evolution of Hymenopteran eusociality (for a recent review of the endocrine mechanisms underpinning caste differentiation see [56]). It is thus an attractive possibility that the irreversible transition to fixed caste phenotypes

might have removed constraints on the IIS-JH-Vg/Yp regulatory network, thereby allowing for the 'uncoupling' of the reproduction-maintenance trade-off. Another important point is that most primitively eusocial Hymenoptera, especially those from temperate climates, have annual colonies, with the queen dying at the end of the season and thus not living longer than the workers; in contrast, highly eusocial species have perennial iteroparous colonies. In the future it will clearly be crucial to conduct broad-scale comparative studies across non-social, primitively eusocial, and highly eusocial insects to gain an improved understanding of the uncoupling of the reproduction-maintenance trade-off in eusocial insects and beyond.

> ''Our hope that a few pathways will be shown to mediate life history variation in most animals should also be tempered by the realization that the causes of variation in traits such as growth rate, fertility, and survival are often more complex than the causation of traits such as digit number, limb components, and body axes. . .That does not mean that. . . IIS is not important in mediating trade-offs. . .It very probably plays a key role. But it does mean that dissecting the causes influencing such traits is a major experimental challenge.''
>
> Stearns (2011) [57]

Conclusions

Several recent studies suggest that we might be able to begin to understand the proximate reasons for why highly eusocial insects have managed to defy the reproduction-maintenance trade-off. These studies indicate that the functions of endocrine regulators of this trade-off have been altered in honey bees and several ants as compared to non-social insects. At the same time, the picture emerging from these studies indicates that different eusocial insects might have evolved distinct proximate solutions to the problem of decoupling the trade-off. For instance, the various functions of JH are unlikely to be conserved among eusocial insects and, to quote Pamminger *et al.* [16], JH 'can act as a flexible tool in regulating key systemic processes in different genera'. A similar argument can be made for vitellogenin whose traditional function in reproduction seems to have been 'remodeled' in different eusocial insects, including roles in social organization, behavior, stress resistance, and lifespan [58••]. Given the complexities of endocrine physiology, this might be a sobering take-home message [57], but it is certainly noteworthy that a growing number of studies identifies the same key players to be involved in the physiological regulation of social insect life histories (including caste determination and polyphenism) and the uncoupling of the reproduction-maintenance trade-off. Obviously, it is still early days for investigations into the mechanisms underlying trade-offs [5]; we remain convinced that future studies, such as the ones we have discussed here [14,15••,16], hold great promise for illuminating the uncoupling of the reproduction-maintenance trade-off in eusocial insects. There is a major need for more comparative studies of life history physiology across species, and for more dialog between life history theorists and physiologists [3,5,57].

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