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REVIEW

Social context, stress, and plasticity of aging

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Summary

Positive social contact is an important factor in healthy aging, but our understanding of how social interactions influence senescence is incomplete. As life expectancy continues to increase because of reduced death rates among elderly, the beneficial role of social relationships is emerging as a cross-cutting theme in research on aging and healthspan. There is a need to improve knowledge on how behavior shapes, and is shaped by, the social environment, as well as needs to identify and study biological mechanisms that can translate differences in the social aspects of behavioral efforts, relationships, and stress reactivity (the general physiological and behavioral response-pattern to harmful, dangerous or unpleasant situations) into variation in aging. Honey bees (*Apis mellifera*) provide a genetic model in sociobiology, behavioral neuroscience, and gerontology that is uniquely sensitive to social exchange. Different behavioral contact between these social insects can shorten or extend lifespan more than 10-fold, and some aspects of their senescence are reversed by social cues that trigger aged individuals to express youthful repertoires of behavior. Here, I summarize how variation in social interactions contributes to this plasticity of aging and explain how beneficial and detrimental roles of social relationships can be traced from environmental and biological effects on honey bee physiology and behavior, to the expression of recovery-related plasticity, stress reactivity, and survival during old age. This system provides intriguing opportunities for research on aging.

Key words: aging reversal; honey bee; insulin-like peptides; recovery-related plasticity; social contact; stress reactivity.

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Introduction

Positive social relationships improve health and longevity and reduce the risk of frailty and cognitive decline (Tucker *et al.*, 1999; Holtzman *et al.*, 2004; Thanakwang, 2009). Negative inter-individual interactions and social stress, reciprocally, are well-known risks in the aging process (Rook, 2000; Bisschop *et al.*, 2003). Social relationships emerge from active behavioral efforts and responses of individuals, but our understanding of causal routes that connect social exchange and behavior to physical and mental health, cognitive performance, stress resilience (ability to restore physiological and behavioral systems during or after stress), and survival is incomplete (Kudielka *et al.*, 2000; Hart *et al.*, 2003; Ramsden, 2007). At the same time, death rates among elderly continue to decline without a corresponding increase in disease-free life expectancy (Robine & Jagger, 2005). This challenge calls for research to improve knowledge on social-environmental influences that shape behavior as well as for studies to identify biological mechanisms that can connect different social contexts and stressors to variation in life outcomes during old age (Rook, 2000; Ruan & Wu, 2008; Rohr & Lang, 2009; Charles & Carstensen, 2010).

The fruit fly *Drosophila melanogaster* provides a simple genetic system for studying inter-individual interactions (Svetec & Ferveur, 2005; Lazareva *et al.*, 2007) and longevity (Zwaan *et al.*, 1995; Tatar *et al.*, 2001). Recent work takes advantage of these assets and exemplifies that social interactions can influence fly longevity. Ruan & Wu (2008) cohoused short-lived fly mutants for the *Sod* gene, which encodes the antioxidant enzyme Cu/Zn superoxide dismutase, with one or several young wild-type 'helper' (companion) flies. This group setting increased motor ability, stress resistance (ability to maintain physiological and behavioral stability during and after stress), and lifespan in the mutant flies, while cohousing with physically impaired wild-type helpers, or with other short-lived *Sod* mutants, did not give similar positive results. It seems that *Sod* mutant flies are sensitive to social contact and useful for identifying factors that can mediate beneficial effects of social interactions (Ruan & Wu, 2008).

In the laboratory, the survival of *Sod* mutant flies can double in response to cohousing with helpers. In comparison, honey bees (*Apis mellifera*) can accelerate, postpone, or reverse aspects of senescence to change lifespan more than 10-fold in response different social contact (Maurizio, 1950; Seehuus *et al.*, 2006a; Behrends *et al.*, 2007). In this review, I explain how honey bee survival is so strongly influenced by social relationships and propose that the social sensitivity, rich behavioral repertoire, and large-sized organs and tissue-systems of this insect present new possibilities

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for modeling physical, physiological, and cognitive effects of social contact during aging.

Reproduction vs. caregiving – the life-histories of social insects

'What is so different about an individual social insect?' – a question I receive regularly. The uniqueness of social insects is apparent from their highly organized societies, with elaborate nest architectures, structured caste systems, and effective strategies of foraging and defense (Hölldobler & Wilson, 2008). However, sophisticated social arrangements do not necessarily convey how the life-history of an individual social insect is different from that of, say, a fly.

The elemental differences between a single social insect, like a honey bee, and an individual solitary insect, like a fruit fly, reside in the animals' reproductive physiology and caregiving behavior. The vast majority of individual social insects has largely inactive, reduced or missing reproductive organs, and never leaves the natal nest location to reproduce. In that way, their biology excludes life-history elements that are broadly present in animals including *Drosophila*: dispersal, sexual maturation, courtship, mating, and egg-laying. Adulthood, instead, is devoted to caregiving directed toward conspecifics, usually younger siblings. These alloparental caregivers, or helpers, are called 'workers'. The specialized life-history case of workers may provide unique insight into the evolvability of aging, as it exemplifies how selection on advanced sociality and kinship care can impact mechanisms of senescence (Seehuus *et al.*, 2006b). While being similar genetically, workers show phenotypic plasticity in terms of morphology, physiology, and social behavior. Workers develop from eggs laid by reproductives – a social minority with greatly enhanced fertility and little or no expression of caregiving behavior (see (Hölldobler & Wilson, 2008) for a review).

Honey bee colonies are headed by a single reproductive, the queen (Winston, 1987). The workers, usually 10 000–40 000 in total, are also female. A few hundred males occur seasonally, see (Rueppell *et al.*, 2005) for a summary on male life-history. A mated queen can lay up to 2000 eggs daily, while her worker daughters provide for the society. Their nest consists of vertical wax-sheets where brood (eggs, larvae, and pupae) and callow adults inhabit the protected center. The young are net receivers of resources from mature workers that engage in a large number of caregiving activities; cleaning, nursing, warming, cooling, nest construction, foraging, and defense.

Female ontogeny, plasticity, and caste structure in honey bees

The major source of inter-individual variation in honey bee lifespan is differences in worker social behavior. Differences in this behavior have genetic and maturational components, but are conditional on social context, physiology, and the behavioral history of each bee. Previous studies explain 2–16% of individual behavior with genotype, leaving substantial room for the social environment to modulate behavior and aging (see (Ihle *et al.*, 2010) and references therein).

Mature workers first pick up within-nest tasks, like cleaning and nursing. After 2–3 weeks, they shift to outside activities that involve foraging for nectar (carbohydrates), pollen (protein, lipids), propolis (anti-microbial material), or water (Seeley, 1982). Workers can labor for months in the nest, but seldom survive more than 2 weeks as foragers (Dukas, 2008). Once expressed, foraging behavior is permanent as long as replacement helpers are born in the central nest and initiate cleaning and nursing activities there (Seeley, 1982; Robinson *et al.*, 1992). This ontogeny generates a spatiotemporal, age-related division of labor between young caregivers that work inside the nest as 'nurses' and the older foragers that provision the society with resources from the external environment.

The ontogeny of worker bees is characterized by huge flexibility (Fig. 1). Division of labor, therefore, is not rigid but a dynamic social arrangement built on the modules of nursing and foraging (Miojevic, 1940; Robinson *et al.*, 1992; Huang & Robinson, 1996). Behavioral progression is accelerated, delayed, or reversed by changes in the social context that affect the frequency or form of interactions between the workers. Thus, a bee's response to social contact can be revealed by her progression or regression from nursing to foraging – the final behavioral state that constrains survival by conferring high levels of damage and mortality risk (Finch, 1990). The resulting plasticity of lifespan is a model for transitions in life-history (Elekonich & Roberts, 2005) and a focal point in research on honey bee aging (see (Münch & Amdam, 2010) and citations therein).

Queen longevity also receives attention (Corona *et al.*, 2007; Haddad *et al.*, 2007; Remolina & Hughes, 2008). Queens are long-lived (up to about 5 years) but delicate and show less phenotypic plasticity than workers (Page & Peng, 2001). Queens require constant feeding and grooming, and their behavior is rigid and reduced to revolve around egg-laying. Aging is also difficult to quantify. Queens survive at the mercy of society, as the majority is killed and replaced within 2 years (Page & Peng, 2001). Replacement, thereby, usually occurs before queens reach their full potential in lifespan and likely also prior to aging (Al-Lawati & Bienefeld, 2009). Therefore, workers are the case in point for my review.

Social relationships, behavior, and survival

Interactions between nurses and foragers are mutually reinforcing (Amdam & Omholt, 2003). Changes in demography that alter the ratio of nurses to foragers, consequently, destabilize behavioral commitments and release plasticity. If foragers are removed (Fig. 1B), some nurses respond with precocious foraging (Huang & Robinson, 1996). If nurses are removed (Fig. 1C), some foragers respond with reversal (Robinson *et al.*, 1992; Huang & Robinson, 1996).

Foragers slow the release of foraging behavior in nurses by direct contact (Pankiw, 2004). A contact cue is ethyl oleate, which also is present in a larval chemical blend (brood

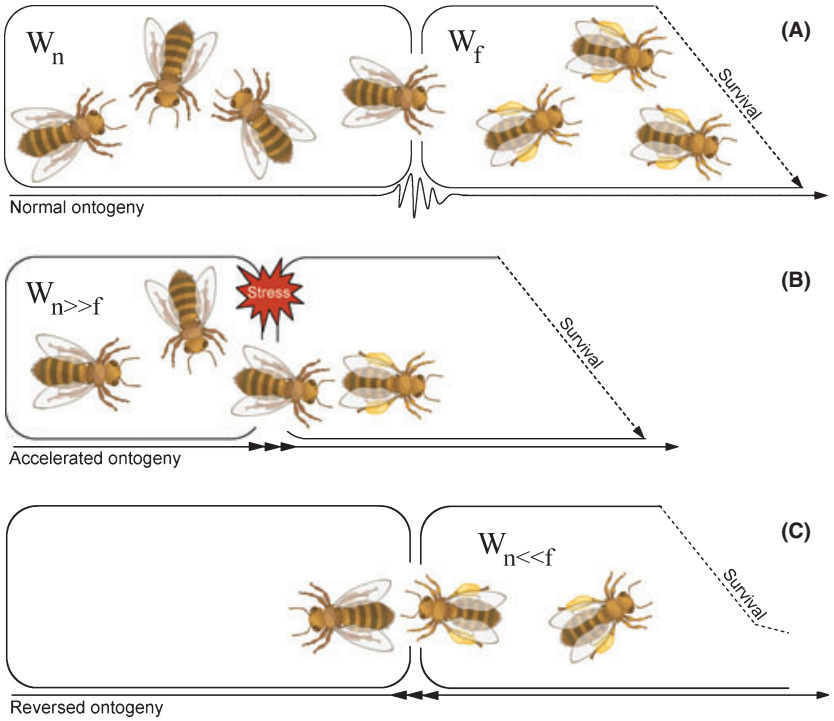

Fig. 1 Honey bee worker ontogeny and flexibility of social behavior. Adult workers conduct a variety of social tasks that are broadly divided into within-nest nursing activities (Worker nurse, W_n) and outside-nest foraging labor (Worker forager, W_f, worker symbols with lumps of yellow pollen on hind legs). (A) Workers usually progress through tasks in an age-associated sequence, such that the nurse-stage precedes that of foraging (left to right). The shift between the two behavioral modules generally occurs when bees are 2–3 weeks old, but inter-individual variation is considerable; indicated by a folding of the time-line, range is often 1–8 weeks (Amdam & Omholt, 2003). Total lifespan correlates with the bees' age at foraging onset because foraging reduces life expectancy (dashed arrow indicate survival). (B) Forager signals slow the behavioral progression of nurse bees, and ontogeny is accelerated if foragers are removed from a colony. Similar acceleration is seen after stress (red stress symbol). (C) Shortage of nurse bees causes some foragers to reverse ontogeny and return to nursing tasks.

pheromone) that can encourage nursing (Le Conte *et al.*, 1994; Leoncini *et al.*, 2004). Queen mandibular pheromone has some similar effects on worker care behavior and acts on dopamine pathways to change nervous system processes and on peripheral tissues to increase worker adiposity (Beggs *et al.*, 2007; Fischer & Grozinger, 2008). In summary, compounds from foragers, larvae, and queen can act on the nurse bee brain and nutrient stores to slow ontogeny and, thus, increase survival.

Less is known on how nursing reinforces foraging behavior, but regulation of social feeding can play a role. Nurse bees control the foragers' intake of proteins and lipids (Crailsheim, 1990). In insects, intrinsic nutrient status is monitored by brain and fat body (functionally homologous to vertebrate liver and white fat), and this sensing is a driver of life-history plasticity and behavior in many taxa (reviewed by Tatar *et al.*, 2003; Kenyon, 2005; Wang *et al.*, 2010). Increased signaling via nutrient sensing pathways is involved during a bee's shift to foraging behavior (Ament *et al.*, 2008) and reduced signaling by the same pathways may aid reversal.

Social stress, stress reactivity, and survival

Social isolation releases a stress response in worker bees, including increased levels of juvenile hormone (JH, Huang & Robinson, 1992; Pankiw & Page, 2003; Lin *et al.*, 2004). JH is synthesized by the *corpora allata* glands behind the brain, and it is central to insect larval transitions and adult reproduction and longevity regulation in addition to its role in the stress response (Gruntenko *et al.*, 2000; Tauchman *et al.*, 2007). Different stress regimens elicit different responses, but many stressors elevate JH in insects (reviewed by Gruntenko *et al.*, 2003). JH and biogenic amine signaling (dopamine, octopamine) during stress correlate with reduced whole-body levels of glucose, glycogen, and fat in *Drosophila* – concordant with changes in energy metabolism (reviewed by Vermeulen & Loeschcke, 2007). This reactivity helps insects endure stress. And, although connections of JH, stress sensitivity (inability to maintain physiological and behavioral stability during stress), and survival are complex (e.g., conditional on sex, life-stage, nutrition, and fertility Flatt *et al.*, 2005), flies with impaired JH sensitivity can show low reactivity and reduced survival with stress (Gruntenko *et al.*, 2000).

In worker bees, natural caregiver roles also correlate with variation in JH and levels of biogenic amines in the brain (primarily octopamine and serotonin, Wagener-Hulme *et al.*, 1999). Signaling is typically lower in nurse bees and higher in foragers, most consistently for JH and octopamine, and corresponds with changes in energy metabolism and whole-body nutrient stores, as in *Drosophila* (Toth & Robinson, 2005; Ament *et al.*, 2008). Treatment with JH, JH analog, or octopamine elicits foraging behavior (Jaycox *et al.*, 1974; Robinson, 1987; Schultz &

Robinson, 2001; Pankiw & Page, 2003). Diverse social stressors, such as colony disturbances, disease, and starvation, can elevate JH, octopamine, and serotonin signaling in workers and trigger foraging behavior (Harris & Woodring, 1992; Kaatz *et al.*, 1994; Schultz *et al.*, 1998). Honey bee genotypes with low JH reactivity, furthermore, show reduced stress reactivity, increased stress susceptibility, and a slow ontogeny with late onset of foraging (Amdam *et al.*, 2007; Ihle *et al.*, 2010). Thus, perhaps contrasting more complex connections in flies, these results support a clear link between JH, the stress response, the release of foraging behavior, and survival in honey bees (Fig. 1B).

JH, however, is not required for workers to forage (Sullivan *et al.*, 2003). Some forages have low JH titers (Huang & Robinson, 1995), and removal of *corpora allata* (eliminating the glands producing JH) does not inhibit bees from foraging tasks (Sullivan *et al.*, 2000, 2003). Nonetheless, JH can be one releaser of foraging behavior, such that nurse bees that experience social, physical, nutritional, or immune stress are more likely to abandon their tasks and initiate foraging. Stress reactivity, thereby, is life-shortening in honey bees because the nurse-to-forager transition increases worker mortality (Dukas, 2008).

Behavior and aging

Nurse bees and foragers show age-associated functional decline, but the progression of senescence is faster in foragers and influences more faculties.

Overaged nurses (30–50 days old) are more sensitive than younger bees to starvation, heat, and oxidative stress and also show reduced capacity to endure foraging (Remolina *et al.*, 2007; Rueppell *et al.*, 2007b). This drop in resilience points to senescence, but is also consistent with the connection between stress reactivity and foraging behavior (Fig. 1B). A residual population of overaged nurses can be enriched in individuals with low stress reactivity because such bees are less likely to respond to lifetime social, physical, nutritional, and immune challenges with foraging. Low stress reactivity can confer high stress susceptibility (Gruntenko *et al.*, 2000) and give the overall impression that stress resilience drops as nurse-age increases. The proposition that 30- to 50-day-old nurses are not senescent is supported by their intact ability to care for larvae (Miojevic, 1940; Haydak, 1963). Also, when challenged in sensory sensitivity-assays, in tests of associative (Pavlovian) learning and memory, and in studies of walking velocity, workers up to 55 days old do not show functional decline (Behrends *et al.*, 2007; Rueppell *et al.*, 2007a; Scheiner & Amdam, 2009).

In foragers, mortality is about 20% until 10 days after foraging onset and then increases steeply to almost 100% after 18 days of activity (Dukas, 2008). Foragers are depleted of stored lipids and proteins (Toth & Robinson, 2005), and peak kinematic performance declines toward the end of their lifespan (Vance *et al.*, 2009). Their immune cells (hemocytes) become pycnotic and apoptose in conjunction with elevated JH titers and the hemocyte nodulation response, a principal defense against bacterial infection, is abolished (Vecchi *et al.*, 1972; Wille & Rutz, 1975; Bedick *et al.*, 2001; Amdam *et al.*, 2005). After more than 15 days of flight, foragers also show reduced associative learning ability and deficit in spatial memory extinction (Behrends *et al.*, 2007; Scheiner & Amdam, 2009; Münch *et al.*, 2010). This functional decline in central processing capacity is paralleled by changes in the brain: oxidative damage to proteins and lipids, protein accumulation, and reduced concentrations of several kinases, synaptic- and neuronal growth-related proteins (Seehuus *et al.*, 2006a; Wolschin *et al.*, 2009; C. Tolfsen, G.V. Amdam, unpublished data). Overall, foragers experience many symptoms of aging similar to those of other animals (Münch & Amdam, 2010).

Vitellogenin, aging reversal, and negligible senescence

Workers that revert from foraging to nursing behavior survive for several weeks (Robinson *et al.*, 1992). Their circulating JH titers and brain octopamine levels decline, and within 8–10 days of reversal hemolymph (blood) levels of vitellogenin can increase to preforaging concentrations (Huang & Robinson, 1996; Schulz & Robinson, 1999; Amdam *et al.*, 2005). Vitellogenin is a multifunctional phospholipoglyco-protein, yolk precursor, and antioxidant in honey bees. It is strongly expressed in nurses, which use constituents of vitellogenin in brood rearing (Amdam *et al.*, 2003). RNA interference-mediated gene knockdown experiments have established that this protein acts as a break on JH and foraging behavior (Fig. 2), enhances immunity, and increases survival in workers (Amdam *et al.*, 2004; Seehuus *et al.*, 2006b; Nelson *et al.*, 2007). The regulation of the *vitellogenin* gene is not fully understood in the bee, but the protein is positively influenced by nutrient availability and hemolymph amino acids, and negatively affected by JH (Fig. 2), stress, and knockdown of the target of rapamycin (*TOR*) gene that is regulator of the *vitellogenin* homologue of mosquitoes (Pinto *et al.*, 2000; Patel *et al.*, 2007; Nilsen *et al.*, 2011). In workers, vitellogenin is primarily synthesized and stored in the trophocyte cells of fat body, where it can be a general signal of nutrient surplus and adiposity (Toth & Robinson, 2005).

In addition to restoration of these and several other aspects of preforaging biochemistry, gene expression, physiology, and behavior, the associative learning performance of reverted bees can improve (Baker *et al.*, 2010). Brain recovery-related plasticity, i.e., the ability to improve central processing capacity after aging, correlates with changed protein levels in the worker brain. Noteworthy are increased amounts of an antioxidant peroxiredoxin and chaperone molecules of the heat shock protein family (Fig. 3). Brain recovery-related plasticity in bees may thus be connected to cellular stress resilience, maintenance, and repair processes (Baker *et al.*, 2010). Such mechanisms can now be related to social factors, as the releasing stimulus for reversal is a change in the social structure of the colony (Fig. 1C).

Social change can also result in workers that achieve extreme lifespans of 250–300 days (Maurizio, 1950). These remarkably long-lived bees are an adaptation to colony survival in temperate

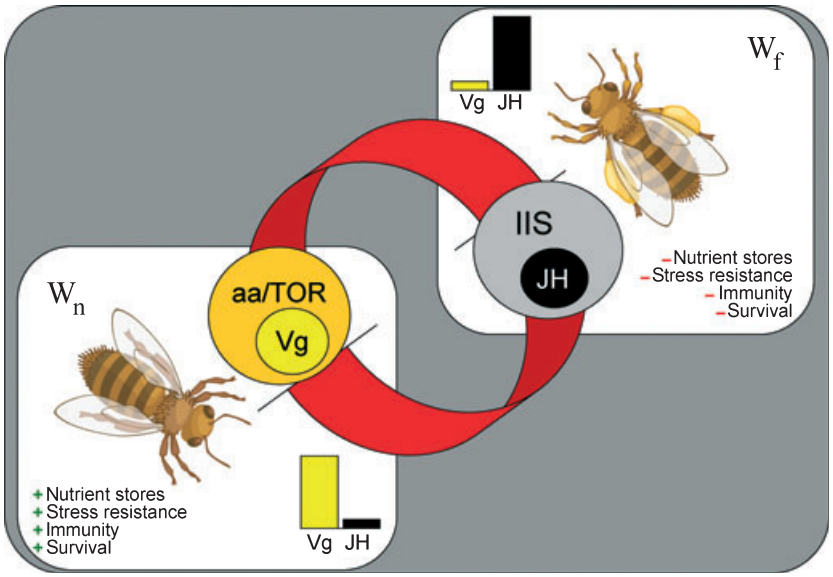

Fig. 2 Central regulators of worker ontogeny and lifespan. In worker nurse bees (W_n), amino acids (aa) and target of rapamycin (TOR) support vitellogenin synthesis (Vg, yellow). Vg, or factors that communicate high intrinsic Vg levels, can repress insulin/insulin-like signals (IIS, gray) upstream of juvenile hormone (JH, black) that typically is elevated in foragers (W_f). High JH levels, conversely, repress Vg and this mutual negative regulation between Vg and JH is indicated by red 'stop' feedback arrows. When nurse bees with natural aa and TOR levels are subjected to Vg knockdown, JH levels increase, Vg is further suppressed, and the bees are more likely to initiate foraging (Guidugli *et al.*, 2005; Nelson *et al.*, 2007). Vg and IIS/JH, respectively, have positive (green+) vs. negative (red–) effects on somatic maintenance. Regulation that involves vitellogenin and IIS/JH, therefore, influences both behavior and survival in bees.

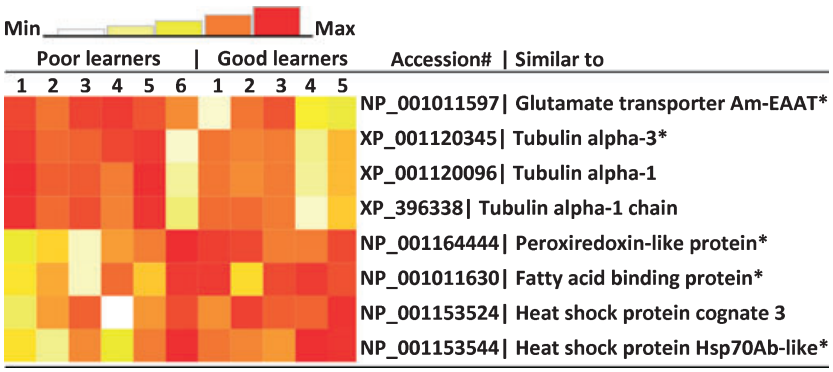

Fig. 3 Protein abundance differences that correlate with brain recovery-related plasticity in worker bees. This heat map displays relative protein amounts quantified by a liquid chromatography and tandem mass spectrometry method (Liu *et al.*, 2004). Abundance increases from white (Min) over yellow to red (Max). Columns correspond to individual central brains and rows to individual predicted proteins. Proteins differed ($P < 0.05$) in a comparison with reverted bees (former foragers, now performing nursing tasks) that failed to improve brain function ('Poor learners') relative to reverted bees that expressed recovery-related plasticity after aging ('Good learners'). Asterisks indicate ≥ 2-fold median differences. Accession #, GenBank (http://www.ncbi.nlm.nih.gov/genbank). A distinct connection between an antioxidant peroxiredoxin, heat shock proteins, and recovery of associative learning ability after aging was validated by control comparisons: In bees that differed in learning but never foraged and senesced, ability was linked to variation in structural proteins and metabolic enzymes. For discussion and details, see Baker *et al.* (2010).

zones and develop when larval pheromones are absent from the colony (Smedal *et al.*, 2009). The phenotype is called *diutinus* or 'winter' bee – the latter because larvae (and other stages of brood) are naturally absent during temperate winter when colonies are unable to acquire resources for growth and reproduction. *Diutinus* bees do not express foraging behavior and are characterized by low JH titers, elevated oxidative stress resilience, and an excessive accumulation of vitellogenin in fat body that is attenuated by brood pheromone (Fluri *et al.*, 1977; Seehuus *et al.*, 2006b; Smedal *et al.*, 2009). However, the workers are not quiescent or in diapause. Their main activities are heating and thermoregulation, which keep the colony core at about 28 °C even when ambient temperatures drop below –20 °C (Omholt, 1987). Senescence is negligible during the *diutinus* life-stage that is unlikely to confer a cost to the subsequent function and survival of the bees: post*diutinus* workers have intact brain function (Behrends & Scheiner, 2010), they segregate into nurses and foragers when colonies commence brood rearing,

and thereafter, normal patterns of nursing, foraging, and mortality unfold (Sekiguchi & Sakagami, 1966; Terada *et al.*, 1975).

Molecular mechanisms connecting social interactions and aging

Connections between social context and honey bee behavioral physiology (Fig. 1-3) translate into plastic patterns of aging as workers respond to social-environmental factors with shifts between behavioral roles. In several studies of worker bees (Seehuus *et al.*, 2006b; Ament *et al.*, 2008; Wang *et al.*, 2010), these patterns have been related to insulin/insulin-like signaling (IIS, Fig. 2); a highly pleiotropic nutrient-sensing pathway that influences diverse processes in animals, such as growth, development, metabolic homoeostasis, fecundity, stress resistance, and aging (see (Broughton & Partridge, 2009) for a review).

In *Drosophila*, impaired IIS reduces JH, inhibits vitellogenesis (yolk production and egg development), protects against oxidative insult and starvation stress, increases disaccharide glucose, glycogen, and lipid levels, and extends lifespan (reviewed by Broughton & Partridge, 2009). Nutrient availability, reciprocally, can elicit IIS and increase JH signaling, which up-regulates vitellogenesis while stress resistance and lifespan are reduced (reviewed by Flatt *et al.*, 2005; Toivonen & Partridge, 2009). JH is also an immuno-suppressant in *Drosophila* (Flatt *et al.*, 2008).

Comparative studies suggest that these negative effects of IIS/JH on adiposity, immunity, and longevity are conserved between the fly and the bee, as is the positive association between nutrient availability and yolk protein synthesis (Remolina & Hughes, 2008). The link between JH and vitellogenin, however, is remodeled in honey bees to form a feedback system (Amdam & Omholt, 2003; Fig. 2), in which the presence of vitellogenin can suppress IIS/JH signals and confer stress resistance, immunity, and survival to the workers and the queen (Guidugli *et al.*, 2005; Seehuus *et al.*, 2006b; Corona *et al.*, 2007). Social and behavioral modulation of the circulating (hemolymph) and stored (fat body) amount of vitellogenin, therefore, correlates with observed patterns of longevity and senescence in workers (Münch & Amdam, 2010).

The causal route from high vitellogenin levels to reduced IIS/JH in worker bees is not fully understood. IIS is generally initiated when insulin or insulin-like peptides (ILP) bind to the insulin receptor (InR), leading to phosphorylation of the membrane-associated insulin receptor substrate (IRS). Honey bees express two ILP in brain and fat body. *ILP1* mRNA levels may increase in worker brain with nutritional stress, JH analog treatment, and foraging (Corona *et al.*, 2007; Ament *et al.*, 2008). In worker fat body, *ILP1* can be specific to oenocyte cells that are active in storing fat (Nilsen *et al.*, 2011). *ILP2* does not respond consistently to the factors that modulate *ILP1* in the worker bees (Corona *et al.*, 2007; Ament *et al.*, 2008) and is transcribed by both oenocytes and trophocytes in fat body (Nilsen *et al.*, 2011). In this tissue, *ILP1* is upregulated by amino acids that enhance the transcription of *vitellogenin* as well. *ILP2* and *vitellogenin* also show strong correlation in worker honey bees, but, while *ILP1* tracks *vitellogenin* almost linearly, *ILP2* exhibits switch-like behavior (Nilsen *et al.*, 2011).

Likely, *ILP1* and *ILP2* genes of the bee are functionally different: *ILP1* can convey the dynamic level of nutrient-sensing by fat body and, in conjunction with increased expression in brain, be active in mobilizing stored resources during metabolic challenges such as foraging or stress. *ILP2* shifts from highly expressed in nurse bee fat body to less expressed in foragers (K.E. Ihle, unpublished data) and also becomes negatively associated with elevated JH levels when *vitellogenin* is knocked down (Nilsen *et al.*, 2011). Its switch-like behavior could communicate shifts in peripheral nutrient surplus and vitellogenin storage to the brain (Nilsen *et al.*, 2011). Building on this speculation, we can explain how increased nutrient availability leads to reduced IIS: ILP1 and ILP2 can be the agonist vs. antagonist of IIS in honey bee brain (Fig. 4), similar, e.g., to the roles of the ILPs INS-7 vs. INS-1 of the nematode worm *Caenorhabditis elegans* (Pierce *et al.*, 2001; Murphy *et al.*, 2003). Modulation of honey bee IIS by this competitive binding is consistent with patterns of worker nutrient-associated physiology, behavioral progression, stress, reversal, and survival. Explicitly, stress/JH, low nutrient availability/TOR signaling, or reduced vitellogenin storage/adiposity would work to elicit ILP1 in the brain, increase IIS/JH, encourage foraging activity, and reduce life expectancy (Fig. 4A). In nutrient-rich individuals, however, the response could be antagonized by release of ILP2 from the fat body, and facilitate nurse or *diutinus* physiology that confers longevity to worker bees (Fig. 4B). However, until these connections are tested, it cannot be excluded that honey bee vitellogenin affects InR–IRS binding or downstream pathway connectivity directly, as has been shown for some membrane-linked and cytosolic factors in other animals (see (Mardilovich *et al.*, 2009) for a review).

Social contact can facilitate, modulate, or potentiate some of the dynamics that involve vitellogenin and IIS in worker bees. Brood pheromone, for example, can make vitellogenin available for circulation in nurse bees by inhibiting its accumulation in the fat body (Smedal *et al.*, 2009). From the hemolymph, some of this vitellogenin is taken up by hypopharyngeal head glands where constituents are used in production of food for the larvae (Amdam *et al.*, 2003). Nurse bees further control the food-intake of the foragers, which receives secretions from the nurses' hypopharyngeal glands as well (Crailsheim, 1990). In the absence of this control, some foragers might ingest more of the colony's stored resources of honey and pollen, leading to back switch of ILP2 signaling, reversal, and survival.

Social trade-offs, adaptive 'shedding' and 'retention' of workers

In *Drosophila*, the negative effects of IIS/JH on lifespan could be explained as an energetic trade-off between reproduction and survival. IIS/JH may shuttle nutrients to reproduction at the expense of somatic maintenance (Tatar *et al.*, 2003), and recip-

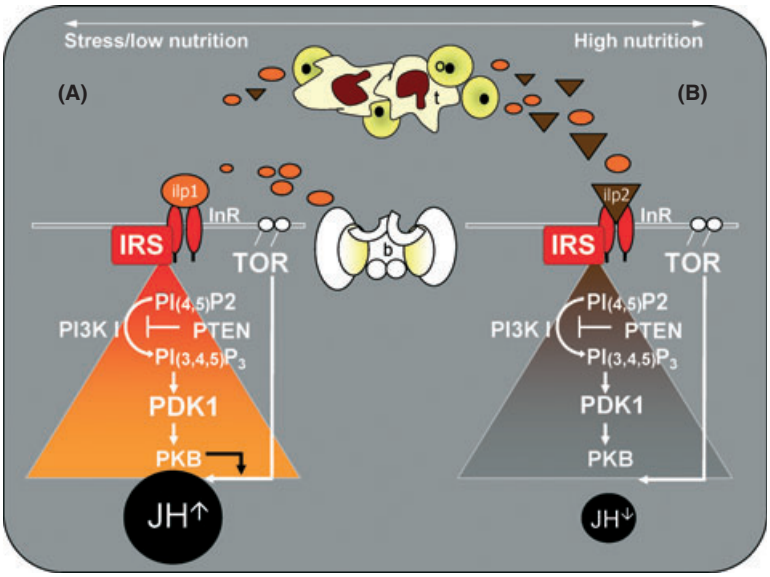

Fig. 4 A model of how honey bee insulin-like peptide 1 (ILP1) and 2 (ILP2) may regulate signaling upstream of juvenile hormone (JH). In (A), the binding of ILP1 to receptors, insulin receptor (InR), results in phosphorylation of the insulin receptor substrate (IRS). PI(3)K enables IRS to phosphorylate PI(4,5)P2 and produce the second messenger PI(3,4,5)P3. PDK1 and PKB are recruited via PI(3,4,5)P3-binding, and PDK1 can activate PKB. The activation may influence target of rapamycin via effects on TSC1–TSC2 (black arrow indicates interaction; TSC1–TSC2 complexes are not shown). During stress or nutrient deprivation (left), one outcome downstream of this pathway activity in worker brain (b, cartoon, center) can be elevated JH levels. In (B), competitive binding of ILP2 from fat body to the same InR molecules will reduce pathway activity and curb increasing JH levels in nutrient-rich individuals (right). o, oenocytes; t, trophocyte cells in the fat body.

rocally, IIS/JH and reproduction would be inhibited should a somatic investment be required (Diangelo *et al.*, 2009). Workers bees, in contrast, do not normally reproduce and IIS/JH-driven trade-offs must be appraised at the level of society (Amdam & Omholt, 2002). The connections between stress, stress reactivity, JH, and foraging onset in workers may provide one example.

By co-opting the insect stress response as a route to foraging behavior, individuals in poor condition because of nutritional, physical, immune- or social stress are likely to transition into a behavioral state from which they rapidly perish. The vast majority of foragers also die in the field (Gary, 1992), and transmittable agents that they carry are thus removed from the society. At colony level, this mechanism can be seen as a form of 'adaptive shedding' (Amdam & Seehuus, 2006). By reducing IIS/JH transduction, signaling via TOR, ILP2 and vitellogenin would antagonize the same pathway (Fig. 4B). This reverse mechanism can facilitate 'adaptive retention' to ensure that workers who are resourceful in brood rearing (healthy, rich in nutrients, high in vitellogenin) are unlikely to respond to social change or stressful colony events with foraging. Corresponding impacts on colony fitness could be confirmed by pharmacological or functional genomic approaches that would inhibit foraging onset after stress (blocking the 'shedding' system) and make forager recruitment independent of physiological nutrient stores (disabling 'retention'). Such tools, however, are not yet available for bees.

Synthesis and future work

Worker honey bees readily respond to signals and stressors in their social environment with flexible changes in lifespan. Some of the signals, like pheromones, are specific to the bee. Yet, they act on modules of behavior and physiology that are broadly present in animals. Examples are care behavior, like nursing young and gathering food, and behavioral physiology, such as changing levels of biogenic amines, hormones, and nutrient sensing.

Worker bees present an example of negligible senescence, i.e., during the facultative *diutinus* life-stage, and show potential for aging reversal that may involve largely conserved signaling pathways and somatic repair mechanisms. These outcomes of social contact can be studied at the level of molecular regulation, as suggested in putative connections between social feeding, nutrient sensing, and aging reversal. Moreover, the same outcomes can be assessed at the level of social (group) selection where adaptations that benefit society may not promote individual survival, as suggested in the coupling of stress reactivity to onset of foraging behavior. The sensitivity of worker bees to social relationships, thereby, provides a model system for effects of social contact during aging. Yet, the specialized 'helper' life-history of workers can imply that mechanisms of aging are not necessarily or directly comparable with aging in solitary or facultative social organisms that reproduce.

The bee is an emerging genetic system that can be studied in its natural colony environment as well as in the laboratory (Weinstock *et al.*, 2006). Fascination in science over the behavioral biology of this bee dates back to Aristotle and has fostered vibrant research communities for experimentation on cooperative behavior and conflict, communication, learning and memory, and for understanding the evolution of sociality *per se* (Seeley, 1995; Menzel *et al.*, 2006; Weinstock *et al.*, 2006). In

aging research, this model must now contribute alongside established and more amendable laboratory systems. The complex social biology of the bee provides a rich resource for this contribution. Future studies, moreover, can better utilize the animal's conveniently large size, amenability to RNA interference, and well-developed physiological tools to address how social and sociogenomic processes influence organs, tissues, cells and general physiological functions during aging.

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