The interplay between immunity and aging in Drosophila
[version 1; referees: 2 approved]

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Abstract

Here, we provide a brief review of the mechanistic connections between immunity and aging—a fundamental biological relationship that remains poorly understood—by considering two intertwined questions: how does aging affect immunity, and how does immunity affect aging? On the one hand, aging contributes to the deterioration of immune function and predisposes the organism to infections (“immuno-senescence”). On the other hand, excessive activation of the immune system can accelerate degenerative processes, cause inflammation and immunopathology, and thus promote aging (“inflammaging”). Interestingly, several recent lines of evidence support the hypothesis that restrained or curbed immune activity at old age (that is, optimized age-dependent immune homeostasis) might actually improve realized immune function and thereby promote longevity. We focus mainly on insights from Drosophila, a powerful genetic model system in which both immunity and aging have been extensively studied, and conclude by outlining several unresolved questions in the field.
Introduction

The ability to respond to the ubiquitous challenge by pathogens is essential throughout organismal life. The innate immune system provides a phylogenetically conserved strategy against a wide range of pathogens and has been thoroughly studied among other organisms—the fruit fly, Drosophila melanogaster, a powerful experimental model system.

After intruding microorganisms are recognized through receptors (for example, peptidoglycan recognized proteins, or PGRPs) which bind to common pathogen-associated molecular patterns (PAMPs), such as components of bacterial cell walls, a general immune response is induced: This includes activation of immune cells, localized production of reactive oxygen species (ROS) and nitrogen oxygen species, and the systemic release of immune effector molecules, so-called antimicrobial peptides (AMPs), which function as humoral “broadband antibiotics” that fight infections. The expression of AMPs is regulated by the Toll and immune deficiency (IMD) pathways via the activation of the nuclear factor-kappa B (NF-kB) transcription factors Dif (dorsal-related immunity factor, Toll pathway) and relish (IMD pathway). Whereas the Toll pathway is activated by Gram-positive bacteria and fungi, the IMD pathway is predominantly activated by Gram-negative bacteria; however, there is a certain amount of crosstalk between both pathways. The AMPs are produced mainly in the fly’s fat body, an organ that is equivalent to mammalian liver and adipose tissue. From the fat body, the AMPs are secreted into the hemolymph, the analog of vertebrate blood, where they kill off invading pathogens. The action of the AMPs is supplemented by a cellular defense response mediated by circulating hemocytes.

Although the immune system contributes vitally to survival and somatic maintenance by preventing mortality and limiting damage imposed by pathogens, it is itself subject to age-dependent deterioration (functional senescence). Moreover, the excessive induction of the immune system, especially at old age, can cause tissue damage and inflammation, which require costly repair and thus promote aging. Here, we discuss the interplay between immunity and aging by considering two interrelated questions: how does aging affect immunity, and how does the immune system affect aging and longevity? We do so by examining recent findings in the Drosophila model system. We conclude our mini-review by outlining some fundamental but currently unresolved questions in this fascinating field.

How does aging affect immunity?

The age-dependent decline of immune function and competence, called immuno-senescence, is a general hallmark of the aging process. In Drosophila, a large and growing body of experimental work has established that the immune system is strongly affected by physiological changes that accompany aging and that can lead to a presumably pathological upregulation of antimicrobial defenses and a reduced ability to combat infections.

Age-related changes in the microbiome contribute to fly aging

Epithelia exposed to the environment, such as the intestinal epithelium of the digestive tract as well as those of the respiratory and the reproductive systems, serve as major immunological barriers and mediate the interaction between the fly and its microbiome. Especially the gut, where the control of bacterial growth is essential for effective nutrient uptake, has received much attention in an attempt to understand the physiological effects of its microbiome composition and can have pervasive effects upon metabolic activity and gut physiology.

During the course of aging, the microbiome changes substantially, especially in terms of increased bacterial diversity and overall abundance. So, does the microbiome impact fly lifespan? If so, how?

Indeed, several studies have found effects of microbiota on the lifespan in fruit flies. For example, Brummel et al., using axenic versus control conditions, showed that the presence of bacteria during the first week of adult life can enhance lifespan but that later in life the presence of bacteria can reduce lifespan. This might suggest a beneficial impact of microbiota early in life but potentially lifespan-shortening effects of the microbiome at old age. In marked contrast, Ren et al., for reasons that remain unclear, failed to find differences in lifespan between flies reared conventionally or flies maintained under reduced bacterial load. More recently, Clark et al. have reported strongly extended lifespan under germ-free axenic conditions: in discussing the discrepancies among different studies, the authors speculate that, depending on the nutrient environment, the presence of gut-associated microbes might be either beneficial or deleterious. Another possibility is that different host strains exhibit different age-dependent dynamics of their microbiota, thus leading to different lifespan responses when the microbiome is altered.

In line with important effects of the microbiome on aging, recent studies focusing on microbial communities in the gut have found that age-dependent deregulation of the gut microbiota (dysbiosis) is associated with reduced metabolism, overproliferation of intestinal stem cells (ISCs), and a loss of intestinal barrier integrity, thus contributing to mortality in aging flies. For instance, Broderick et al. showed that the presence of microbiota strongly affects gut morphology and gene expression, inducing a local immune response (mainly through IMD signaling), upregulating the expression of genes for cell differentiation (JAK/STAT pathway), and altering metabolism. Consistent with these findings, Guo et al. observed that the gut epithelia of axenic flies exhibit reduced numbers of mitotically active cells, lower levels of tissue dysplasia, and decreased expression of immune genes. More recently, Clark et al. were able to link the age-dependent shift in microbial composition to gut epithelial deterioration and intestinal barrier failure. The authors showed that changes in the microbiota occur both before and after the loss of
gut integrity and that systemic infection—or the mounting of an immune defense response—drives mortality in aged flies. Thus, even though many details are not yet understood, it seems clear that the age-dependent dynamics of the microbiome can have profound effects on fly aging and physiology.

**Immune and defense response genes are predominantly upregulated with age**

Another major, well-documented hallmark of aging in *Drosophila* is the increased expression of genes of the stress and immune responses. These age-dependent transcriptional changes are shared between the sexes and observed on multiple levels, from pathogen recognition to the increased expression of AMPs produced downstream of both the IMD and the Toll pathways. For instance, Lai *et al.* compared gene expression during male and female aging and saw a strong sex-dependent upregulation with age of genes in the immune system, especially of AMPs (Attacins, Dipterincin, Defensin, Drosocin, and Metchnikowin). Similarly, a recent study by Carlson *et al.* observed that, across several time points, immune effectors and stress-induced genes (for example, *Turandot A* and *C*) are most consistently upregulated across time points from about 3 weeks until 72 days of age.

Such transcriptional responses to aging seem to be somewhat tissue dependent: in a comparison of multiple male tissues, Zhan *et al.* found that the expression of immune genes in the brain—in marked contrast to abdominal fat tissue exhibiting a strong upregulation of immune expression with age—was downregulated. In contrast, Kounatidis *et al.* reported a strong upregulation of AMPs in the heads and brains of aged flies, similar to earlier findings. Chen *et al.* observed that, while the aged fat body upregulates immune gene expression, as has been typically found—IMD activity in the gut is downregulated and that this suppression is a direct response to systemic inflammatory signals. How such tissue-dependent differences in immune gene expression affect fly aging is not well known, but, overall, most assays of whole flies or of fat body tissue, the main production site of AMPs, suggest that—globally speaking and on average—the upregulation of immune genes with age is the predominant pattern.

What are the causes and the functional consequences of this age-dependent upregulation? On the one hand, the acute and short-term activation of the immune response as a result of injury and pathogen invasion is crucial for survival and induces the repair of affected tissues. On the other hand, prolonged activation of the immune system at old age can induce chronic inflammation (“inflammaging”), which is associated with increased host mortality.

A key factor that likely contributes to a stronger immune activation with age is the increase in microbial load and pathogen diversity during aging. In support of this, flies reared under strongly reduced microbial load show a less-pronounced age-related increase in the expression of immune genes, yet even under axenic conditions signals of inflammation are observed. This state of “sterile inflammation” has been attributed in part to the accumulation of senescent cells that secrete a range of inflammatory cytokines, chemokines, and proteases when entering terminal growth arrest in response to stress and DNA damage. In vertebrates, cellular senescence and the inflammatory phenotype (the “senescence-associated secretory phenotype”, or SASP) are thought to be major drivers of chronic inflammation. A recent study by Nakamura *et al.* shows that this also occurs in invertebrates: in *Drosophila*, mitochondrial dysfunction in combination with the expression of the oncogene *Ras* induces both cellular senescence (accompanied by activation of JNK signaling) and systemic expression of proinflammatory cytokines of the *unpaired* (upd) family that impact tissue homeostasis. In a similar vein, Chen *et al.* observed that, during aging, cellular senescence in the fat body leads to a systemic inflammatory response which deregulates IMD signaling in the midgut. They further showed that the observed deregulation of immune gene expression is mainly driven by the age-related decline in nuclear Lamin-B, a marker for cellular senescence, which leads to a loss of heterochromatin-mediated repression.

In addition to immune activation by microbial imbalance, chronic inflammation in the gut is induced in part by overproliferation of ISCs. For example, Li *et al.* propose that the upregulation of JAK/STAT signaling through inflammatory signals (for example, *udp2* and *udp3*) initiates the loss of tissue homeostasis, even in the absence of a microbiome. The authors suggest that the age-dependent increase in JAK/STAT signaling causes the loss of gut compartmentalization, thereby facilitating a pathological shift in microbiota composition, which further induces the local immune response. Thus, overproliferation of ISCs and accumulation of undifferentiated intestinal cells weaken the epithelial barrier so that ingested bacteria can “leak” into the body cavity, causing systemic or chronic infections that lead to mortality.

Another cause of increased inflammatory signaling during aging might be oxidative stress, a notion supported by transcriptional similarities in patterns of immune gene expression between aging and oxidative stress. Mitochondria are a major source of cellular ROS, and impaired mitochondrial function has been proposed to strongly contribute to aging. Damaged mitochondria and deregulation of oxidative phosphorylation cause an inflammatory response, activate NF-κB signaling, and can contribute to intestinal dysfunction. A recent study by Rana *et al.* shows that preventing morphological changes in the mitochondria by overexpression of *Dynamin-related protein 1* (Drp1) improves mitochondrial respiratory function and increases lifespan, but the authors did not assess immune transcription. Interestingly, mutants of mitochondrial peroxiredoxins (*dPrx3* and *dPrx5*), involved in the regulation of ROS levels, exhibit increased activation of the immune response, whereas overexpression of these peroxiredoxins extends lifespan and delays the age-related inflammatory response.

In summary, it is still not entirely clear whether the strong age-dependent upregulation of immune transcription represents an adaptive and necessary physiological response in order to deal with the increase in pathogen load or whether it reflects the
age-progressive loss of the ability to fight off microbial infections. The overall consensus in the field seems to be that increased old-age immune expression probably represents a state of immunopathology (that is, inappropriate hyperactivation of the immune system and chronic inflammation). Moreover, since the immune system also plays an important role in the defense against non-biotic stresses and activates tissue repair mechanisms, the state of chronic inflammation that is commonly observed during aging is likely the cumulative outcome of several aspects of physiological deterioration.

Age-dependent decline of cellular and realized immune responses
What has been learned about age-related changes in cellular and realized immune responses (that is, the actual resistance to infection with different pathogens) in *Drosophila*? The evidence available to date suggests that overall both tend to decline with age in flies, even though some exceptions or discrepancies have been reported as well.

The cellular immune defense of *Drosophila* is performed by three distinct groups of hemocytes that respond to infection with encapsulation (lamellocytes), melanization (crystal cells), or phagocytosis (plasmatocytes). Phagocytes initially reduce pathogen load, contribute to an inflammatory state, and play an important role in the clearance of pathogens and in the regenerative response. For instance, Guillou et al. found that mutants of *croquemort* (*crq*), a scavenger receptor required for phagocytosis in the plasmatocytes, are vulnerable to environmental microbes and exhibit a chronic state of Imd activation, premature gut dysfunction, and reduced lifespan. With advancing age, both the number and the phagocytic activity of hemocytes decrease. Interestingly, Horn et al. found that the processing of phagocytosed vesicles is impaired with age, indicating a possible link to autophagy in hemocyte aging and providing positive evidence for a less-efficient cellular defense at advanced age.

In the terms of the ability of flies to clear out pathogens as a function of age, the observations available to date are somewhat inconsistent: for example, Ramsden et al. found no effect of age on bacterial clearance, yet other studies have observed that clearance ability differs strongly among genotypes and either declines or even increases with age. Thus, it is not necessarily always the case that old flies are worse at clearing out infections, as might be expected. Notably, Duneau et al. have found that most bacterial infections are in fact not cleared out efficiently but persist at low levels of pathogen burden; in turn, this could explain the typically observed upregulation of immune gene expression and symptoms of chronic inflammation. In support of a dysfunctional senescent immune response at old age, Zerofsky et al. found that the inducibility of the AMP response declines with age: under systemic infection, young flies reach peak expression of *Diptericin* after 12 hours, whereas old flies exhibit delayed but stronger and prolonged expression. In contrast, however, AMP induction in response to heat-killed bacteria was significantly weaker in older flies. This indicates that the reduced inducibility of the AMP response in old flies causes a major disadvantage in terms of the flies’ ability to curb bacterial growth, thus leading to delayed but stronger expression.

Together with the fact that the susceptibility to infections increases with age in flies, the results of Zerofsky et al. (above) strongly suggest that the functional capacity of the innate immune system declines with age in *Drosophila*. Interestingly, however, this immunosenescence might not always involve a decline in clearance ability: Ramsden et al. found that the ability of flies to clear an *Escherichia coli* infection is unaffected by age but that the ability to survive an infection strongly declines during aging. A further complication in understanding links between immunity and aging is that the senescent deterioration of the immune system might be sex specific: in male flies, susceptibility to the entomopathogenic fungus *Beauveria bassiana* is increased with age because of a failure of the barrier defenses, whereas female flies exhibit systemic immune senescence. Yet perhaps the most fundamental question is this: what causes the death of infected flies at old age? To date, our understanding of this issue remains very poor; ultimately, host survival will depend on the balance between the defensive response to infection, the consequences of pathogen-inflicted damage, and the effects of self-harm caused by a potentially prolonged, chronic immune response. We now turn to discussing the other side of the coin, namely how does the immune system impact senescence and organismal lifespan?

How does immunity affect aging and longevity?
Costs of immunity and trade-offs
As vital as the immune system is for survival, mounting an immune response is also metabolically costly and bears the potential of inflicting autoimmune damage that contributes to aging. That the immune system is costly is apparent from the tight regulation of its induction and the existence of physiological and evolutionary trade-offs between immunity and other life history traits such as developmental time, reproduction, and lifespan. In terms of detrimental effects of immune induction, Pursall and Rolff showed that, in the mealworm beetle *Tenebrio molitor*, provoking an immune response early in life causes reduced lifespan. In a more recent study of this beetle system, Khan et al. found that the immune-pathological consequences of infection on the Malpighian tubules can be ameliorated by limiting the expression of phenoloxidase (PO), thereby restoring normal lifespan after infection. Studies in insects have also yielded important insights into the antagonistic relationship between reproduction and immunity, as comprehensively reviewed by Schwenke et al. For instance, Zerofsky et al. observed that activation of the immune system by heat-killed bacteria decreases female fecundity and that this effect depends on the NF-kB transcription factor *relish*. Conversely, mating can suppress the immune system by upregulating the production of a gonadotropin but immunosuppressive hormone called juvenile hormone, as recently shown by Schwenke and Lazzaro. Thus, immunity can induce reproductive costs, and mating can impair immunity in flies. The fat body likely plays a central role in mediating many of the physiological trade-offs that involve immunity, since it represents a major site of both metabolic and endocrine functions important for growth, reproduction, and
lifespan (for example, nutrient sensing, storage and utilization, and endocrine signaling) and of immune function (for example, expression of AMPs)\(^{83}\).

**Metabolic consequences of an immune response**

An important aspect of trade-offs is that they are often mediated by competitive energy allocation and thus by metabolism. For example, during an immune response, energy metabolism is strongly disrupted and characterized by decreased insulin/insulin-like growth factor signaling (IIS)\(^{84-86}\), especially in response to systemic activation of Toll signaling\(^{86}\). Conversely, a long-lived mutant of the insulin receptor substrate chico shows strongly improved realized immunity and increased AMP induction after bacterial infection\(^{87}\). Becker et al. showed that IIS pathway mutants induce AMP expression through the IIS transcription factor FOXO independent of NF-κB activation and that, under conditions of energy shortage or stress, FOXO induces AMPs in several tissues, thereby probably ensuring epithelial defense\(^{88}\).

Other findings also underscore fundamental links between the immune response and metabolism. Mutants for *activating transcription factor 3* (Atf3), for example, show a transcriptional response characteristic of inflammatory stress and starvation while accumulating fat, indicating a loss of homoeostasis of metabolism and immunity\(^{89}\). Clark et al. identified Mef2 (*myocyte enhancer factor 2*) as a switch from anabolism to immune gene expression in response to bacterial infection\(^{90}\). In the healthy fly, phosphorylated Mef2 regulates the synthesis of fat and glyco- gen in the fat body and, in response to infection, Mef2 promotes the expression of several AMPs\(^{89}\). Interestingly, Mef2 is part of a pathway, the p38 MAP kinase (p38K)/Mef2/MnSOD pathway, that co-regulates stress and lifespan in flies *in vivo*\(^{91}\).

The crosstalk between metabolism and immunity can impose severe costs to mounting a persistent immune response; for example, during infection with *Mycobacterium marinum*, prolonged activation of FOXO can severely deplete storage fat and result in lethal “wasting”\(^{92}\). Similarly, Rera et al. found that flies overexpressing the AMP *Drosomycin* exhibit a strongly altered metabolic profile, including depletion of glycogen and triglyceride storage, and impaired IIS\(^{93}\). Changes in lipid metabolism have also been associated with an age-related decline in gut function\(^{94}\), and Karpac et al. report that such changes are caused by an increase in FOXO and JNK activity in intestinal enterocytes, leading to loss of lipid homeostasis in the gut\(^{95}\).

Beyond these findings, there is compelling evidence that the age-related dysregulation of metabolism, intestinal dysfunction, and the chronic upregulation of the immune system are tightly linked\(^{95,96,97}\), yet the chronological order and the mechanistic basis of the effects that lead to the loss of metabolic and immune homeostasis remain poorly understood. Thus, all in all, there are very good reasons to think that metabolism, immunity, and aging are linked in fundamental but still little-understood ways.

**Chronic immune activity shortens life but reduced NF-κB signaling extends it**

The metabolically costly and potentially auto-reactive nature of the innate immune response requires tight regulation in order to ensure effective pathogen control and limited self-harm\(^{98,99}\). As discussed previously, immune hyperactivation is a generally observed characteristic of aging\(^{100,101,102}\). On the other hand, there is growing evidence that the dysregulation of the immune system strongly contributes to aging. Thus, an interesting question in this context is whether and how immune genes impact organismal lifespan.

Overexpression of the Toll receptor in the fly gut decreases lifespan, and two independent studies reported that a loss-of-function mutant of *Dif* outlives wild-type flies\(^{103,104}\). Perhaps the clearest findings come from studies of chronic activation of IMD signaling: transgenic overexpression of *PGRP-LC* and *PGRP-LE*\(^{96}\) in the fly fat body shortens lifespan. Similarly, flies that overexpress *PGRP-LE* in the gut are shorter lived\(^{96}\). Consistent with these results, it has been found that loss-of-function mutations or RNA interference against negative regulators of IMD signaling\(^{97}\), such as *caudal*\(^{98}\), *trabid* and *pirk*\(^{99}\), and *PGRP-SC* and *PGRP-LB*\(^{100}\), dramatically decreases lifespan, demonstrating the existence of detrimental effects upon the lifespan of immune hyperactivity. In line with this interpretation, overexpression of the negative regulator *PGRP-SC2* in the gut increases lifespan by contributing to microbial balance and epithelial homeostasis\(^{54}\).

The importance of a well-regulated interaction between the gut microbiome and the intestinal barrier epithelium is highlighted by a study by Li et al., who showed that reduced JAK/STAT signaling delays dysbiosis and extends lifespan\(^{101}\). Yet other examples for the negative impact of dysregulated immunity are mutants of *big bang* (BBG), a gene important for the organization of septate junctions between gut endothelial cells\(^{102}\). Bonnay et al. found that BBG mutants exhibit chronically activated immunity due to reduced intestinal barrier function and thus suffer from systemic infections. These flies have shorter lives than average, a phenotype that can be rescued by the administration of antibiotics\(^{103}\).

Effects of chronic NF-κB signaling have also been associated with age-related neurodegeneration in the *Drosophila* brain and nervous system\(^{99,102}\). A mutant for *defense repressor 1* (*dnr1*), a negative regulator of IMD, exhibits shortened lifespan as well as neuropathology accompanied by increased AMP levels\(^{104}\). Kounatidis et al. recently found that the expression of AMPs (*Drosocin, AttacinC*, and *CecropinA1*) increases with age in the fly brain, leading to progressive neurodegeneration and reduced lifespan; suppression of IMD signaling in the glia cells, on the other hand, led to improved locomotion, an altered metabolic profile, and increased lifespan\(^{105}\).

However, AMPs expressed through NF-κB signaling are not necessarily always detrimental: Loch et al. have reported that overexpression of *CecropinA1* and *Drosocin* can actually increase lifespan (possibly by helping to prevent bacterial dysbiosis\(^{106}\)) yet simultaneously causes reduced lifetime activation of IMD and JAK/STAT signaling. In addition, it has been shown that flies that overexpress *Diptericin* exhibit increased antioxidant defense and increased tolerance to hyperoxia\(^{106}\).

Therefore, the work reviewed here suggests that a prolonged dysregulation of NF-κB signaling is highly detrimental for lifespan...
and that interventions that decrease immune activity—at least in the absence of pathogens—can potentially improve tissue homeostasis, delay aging, and prolong life, probably by alleviating the detrimental effects of immune hyperactivity and chronic inflammation. Thus, while the adaptive value of a properly functioning immune system is obvious, it is becoming increasingly clear that immunity represents a “double-edged sword”.

The role of immunity in the evolution of aging

Might there be a connection between the evolution of longer life and the evolution of immune function? Several studies have used laboratory artificial selection experiments to breed flies for postponed aging and increased lifespan; remarkably, despite differences in the methodological details, these studies indicate that evolutionary changes in immunity might make an important contribution to the evolution of longevity. Remolina et al. sequenced the genomes of fly populations after 50 generations of selection for increased lifespan and found a statistical over-representation of longevity candidate genes involved in “defense response to fungus”106. Similarly, another “evolve-and-rescue” study, by Carnes et al.107, examined the genomic and transcriptomic basis of longevity in an independent long-term selection experiment for postponed aging108. Although the authors did not observe any over-representation of immune genes at the genomic level, flies from the long-lived selected populations had a lower expression of immune transcripts than unselected controls; genes identified as candidates for postponed senescence included Metchnikowin, CecropinA1, and CecropinA2 in females and PRGP-LF and CecropinA2 in males107. Given the negative impact of too much NF-kB expression on lifespan (discussed above), the reduced expression of AMPs in long-lived selected flies makes perfect sense, but further experiments will be required to firmly establish causation. In general, still, very little is known about whether and how genes of the immune system affect organismal lifespan.

Outlook and open questions

We end by singling out three unresolved questions which, in our minds, would be worth studying in future work, yet there are obviously many more that would be interesting to address.

1. What are the age-related changes in other immune active organs?

Most previous work in the field has focused on the gut as a central element that shapes the relationship among the fly microbiome, tissue homeostasis, and inflammatory signals15,97,109. However, we clearly lack knowledge about age-dependent changes in other organs that play an important role in immunity. For example, the fat body, as a site of both metabolic and immunological activity, is an obviously interesting organ for much closer investigation in this respect, and many other organs would be of interest as well. More generally, tissue-specific immune signatures need to be considered in the context of the systems physiology of the whole fly, and this is clearly an area where more work is needed.

2. Does pathogen evolution within the host play a role in the systemic inflammation observed during aging?

In the light of gut physiology and tissue homeostasis, the Drosophila microbiome has gained a lot of attention15,16,19,110. The evolutionary biologist Graham Bell has proposed that senescence might be caused by infections that outcompete the host immune response in an evolutionary arms race111. With the rapid advances in sequencing technology and genomics, it would be very interesting to study pathogen evolution over the course of the Drosophila lifetime. This would allow us to investigate whether the evolution of commensals or pathogens to avoid and escape the immune system could explain the increased dysregulation of the host immune system observed with age.

3. What is the role of the Toll pathway in affecting aging and lifespan?

Whereas the dysregulation of IMD signaling has been shown to be detrimental in multiple studies22,30,98–100, the role of Toll signaling in aging and lifespan has not yet been studied in depth. This might be because of the focus on aging in the gut, as AMP expression in epithelia seems to be regulated predominantly through the IMD pathway12. Conversely, Toll is activated mainly during systemic infection and plays an important role in the fat body to regulate growth and metabolism10 and in activating hemocytes113. Both the contribution to systemic NF-kB activation and the metabolic impact of Toll signaling would merit close investigation with regard to aging and lifespan in the fly.

Conclusions

The Drosophila immune system is strongly affected by the degenerative processes that accompany aging. The widely observed state of chronic inflammation, a loss of cellular immunity, and the gradual deterioration of protective epithelial barriers all contribute to the functional senescence and increased pathogen susceptibility of aging flies7,114. In addition, the immune system itself can accelerate aging by inflicting collateral tissue damage13 and by impacting metabolism14–46. Interventions that reduce the age-associated dysregulation of NF-kB signaling have revealed that the immune system can have a strong impact on organismal aging and lifespan1,4,22,30,100. Great strides have also been made in our understanding of the physiological processes that occur during aging in the Drosophila gut2,17. Despite all of this impressive progress, the mechanistic connections between immunity and aging and longevity remain poorly understood, and there is much exciting work left to be done in this field.

Competing interests

The authors declare that they have no competing interests.

Grant information

This work was supported by Swiss National Science Foundation grants PP00P3_165836 and 310030E-164207 to TF.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We wish to thank François Leulier and Heinrich Jasper for helpful comments on an earlier version of our article and the editors of Faculty of 1000 for their invitation to contribute this review.
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F1000Research 2018, 7(F1000 Faculty Rev):160 Last updated: 07 FEB 2018
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Current Referee Status: ✔ ✔

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The referees who approved this article are:

1 Heinrich Jasper Buck Institute for Research on Aging, Novato, CA, USA
   Competing Interests: No competing interests were disclosed.

1 François Leulier Institut de Génomique Fonctionnelle de Lyon (IGFL), Université de Lyon, Ecole Normale Supérieure de Lyon, CNRS UMR 5242, Université Claude Bernard Lyon 1, Lyon, France
   Competing Interests: No competing interests were disclosed.

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