Social modulation of ageing in termites

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Summary

Biological ageing, namely the decline in bodily functions over time, poses unprecedented challenges for human society. In the past decades, enormous efforts have been made to understand the proximate and ultimate causes of ageing. These efforts have significantly enriched our knowledge about the mechanisms and evolutionary causes of ageing. However, the key question remains: how to delay or even reverse ageing? The disposable soma theory of ageing describes ageing as a resource-allocation trade-off between self-maintenance and reproduction. According to this theory, prolonged longevity entails negative side-effects on reproduction and vice versa. This seems to be a biological rule for most animals, except for a few social animals such as naked mole rats and social insects (termites, nearly all ants, some bees, and some wasps). So, how does a social life contribute to longevity?

In this thesis, I study the contribution of social life to ageing using small organisms, termites. Despite being often portrayed as pests, termites are actually ecologically and evolutionarily very successful insects. They help maintain a healthy ecosystem by decomposing dead plant materials and also by building mounds that shelter other animals. Their success is largely owing to their social life. Termites are the oldest social insects that have evolved a social life dating back to the Jurassic. A termite colony generally consists of reproducing individuals (the queen and the king) and non-reproducing ones (workers and soldiers). Within a colony, all individuals share the same genetic background as they are a family. Strikingly, the reproducing individuals outlive the non-reproducing ones by up to an order of magnitude, depending on the species' social complexity. The positive association between reproduction and longevity, as well as its correlation with a social life, makes termites promising model organisms for studying the effect of social life on ageing.

With the advancement in molecular technology, genes that play a pivotal role in regulating longevity and reproduction have been uncovered. Recently, these genes have been integrated into gene networks that regulate the longevity-reproduction trade-off in insects. However, how these "trade-off genes" are correlated with social life at the molecular level is not well-understood yet. In **Chapter 2**, I seek to understand the molecular basis underlying the remoulding of the longevity-reproduction trade-off by sociality using gene expression data of termite queens and workers. For the first time, we discovered that termite queens are characterised by a single gene network that contains all the essential pathways that are known to regulate the longevity-reproduction trade-off in solitary insects. We named this gene network the "Queen Central Module (QCM)". Strikingly, the QCM also contains many genes that are known to be involved in chemical communication in termites. This provides the first strong molecular evidence that the longevity-reproduction trade-off is linked with social communication in termites at a molecular level. We pharmacologically manipulated the endocrine component of the QCM to test the currently prevailing hypothesis that the social insect queens are able to overcome the trade-off constraint through the rewiring of the "trade-off gene network". Our results in termites reject this hypothesis, and rather emphasize the importance of social interactions in this life history gene network.

Ageing has been proposed to be the result of a resource-allocation trade-off between maintenance and reproduction. Therefore, resource availability might be able to modify the rate of ageing. Dietary restriction experiments in model organisms such as the fruit fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans* have demonstrated that food limitation can extend longevity, generally at the cost of reproduction. However, how this phenomenon can be modulated by social life is not well understood yet. In **Chapter 3**, we reduced resource availability in the termite *Cryptotermes secundus* to investigate how it affects the maintenance-reproduction trade-off at the individual and colony levels. We detected a reallocation of resources from maintenance to reproduction at the colony level but not at the individual level. The colony-level trade-off was achieved by workers giving up cooperation and developing into winged sexuals. These findings show how social behaviour interacts with resource availability and modulates central life-history trade-offs. Our results also reveal striking analogies between

totipotent termite workers and stem cells from hydra. This analogy provides a new perspective on relating social complexity and biological complexity.

Longevity in social insects varies significantly at both intra- and inter-specific levels. Within a colony, reproducing individuals outlive non-reproducing ones, despite the fact that they share the same genetic background. This longevity disparity between reproducing and non-reproducing individuals (i.e., caste-specific ageing) also varies across species of different social complexity. Understanding the evolutionary causes of these variations is of vital importance to comprehending why social life affects ageing. In **Chapter 4**, using individual-based simulations, we investigated how the degree of sociality and extrinsic mortality shape the variations in caste-specific ageing in termites. Our results demonstrate a causal role of both sociality and extrinsic mortality in shaping different rates of ageing. We highlight that the chance of nest inheritance is a game changer that alters the effect of extrinsic mortality on caste-specific ageing in termites. These findings contribute to fundamental insights into how and why social evolution reshapes ageing.

In **Chapter 5**, I discuss the general implications of all the findings that resulted from this thesis. I suggest that ultimately, social life can influence the rate of ageing by changing the strength and level of selection on longevity. This is because sociality can modify the direct and indirect fitness gains of individuals. At a proximate level, the social effect on ageing could be potentially enabled by rewiring gene networks that control ageing, embedding social communication genes into those networks, and duplicating genes from those networks. I summarised these ideas into a conceptual framework that could potentially guide future research into understanding idiosyncrasies of social effects on ageing.

Samenvatting

Biologische veroudering, namelijk de achteruitgang van lichaamsfuncties in de loop van de tijd, stelt de menselijke samenleving voor ongekende uitdagingen. In de afgelopen decennia zijn enorme inspanningen geleverd om de naaste en uiteindelijke oorzaken van veroudering te begrijpen. Deze inspanningen hebben onze kennis over de mechanismen en evolutionaire oorzaken van veroudering aanzienlijk verrijkt. De hamvraag blijft echter: hoe kan men veroudering vertragen of zelfs terugdraaien? De beschikbare soma-theorie van veroudering beschrijft veroudering als een afweging tussen zelfonderhoud en reproductie. Volgens deze theorie heeft een verlengde levensduur negatieve neveneffecten op de voortplanting en vice versa. Dit lijkt een biologische regel te zijn voor de meeste dieren, behalve voor enkele sociale dieren zoals naakte molratten en sociale insecten (termieten, bijna alle mieren, sommige bijen en sommige wespen). Dus, hoe draagt een sociaal leven bij aan een lang leven?

In dit proefschrift bestudeer ik de bijdrage van het sociale leven aan veroudering met behulp van kleine organismen, termieten. Ondanks dat ze vaak als ongedierte worden afgeschilderd, zijn termieten in feite ecologisch en evolutionair zeer succesvolle insecten. Ze helpen een gezond ecosysteem in stand te houden door dood plantaardig materiaal af te breken en ook door heuvels te bouwen die andere dieren beschermen. Hun succes is grotendeels te danken aan hun sociale leven. Termieten zijn de oudste sociale insecten die een sociaal leven hebben ontwikkeld dat teruggaat tot het Jura. Een termietenkolonie bestaat over het algemeen uit reproducerende individuen (de koningin en de koning) en niet-reproducerende individuen (arbeiders en soldaten). Binnen een kolonie delen alle individuen dezelfde genetische achtergrond als een familie. Opvallend is dat de reproducerende individuen de niet-reproducerende individuen tot een orde van grootte overleven, afhankelijk van de sociale complexiteit van de soort. De positieve associatie tussen reproductie en levensduur, evenals de correlatie met een sociaal leven, maakt termieten veelbelovende modelorganismen voor het bestuderen van het effect van het sociale leven op veroudering.

Met de vooruitgang in moleculaire technologie zijn genen ontdekt die een cruciale rol spelen bij het reguleren van de levensduur en reproductie. Onlangs zijn deze genen geïntegreerd in gennetwerken die de wisselwerking tussen levensduur en reproductie bij insecten reguleren. Hoe deze "ruilgenen" echter op moleculair niveau gecorreleerd zijn met het sociale leven, is nog niet goed begrepen. In hoofdstuk 2 probeer ik de moleculaire basis te begrijpen die ten grondslag ligt aan het hervormen van de wisselwerking tussen levensduur en reproductie door socialiteit met behulp van genexpressiegegevens van termietenkoninginnen en werksters. Voor het eerst ontdekten we dat termietenkoninginnen worden gekenmerkt door een enkel gennetwerk dat alle essentiële routes bevat waarvan bekend is dat ze de wisselwerking tussen levensduur en reproductie bij solitaire insecten reguleren. We noemden dit genennetwerk de "Queen Central Module (QCM)". Opvallend is dat de QCM ook veel genen bevat waarvan bekend is dat ze betrokken zijn bij chemische communicatie bij termieten. Dit levert het eerste sterke moleculaire bewijs dat de wisselwerking tussen levensduur en reproductie verband houdt met sociale communicatie bij termieten op moleculair niveau. We hebben de endocriene component van de QCM farmacologisch gemanipuleerd om de momenteel heersende hypothese te testen dat de sociale insectenkoninginnen in staat zijn om de wisselwerkingsbeperking te overwinnen door de herbedrading van het "inruilgenennetwerk". Onze resultaten in termieten verwerpen deze hypothese en benadrukken eerder het belang van sociale interacties in dit levensgeschiedenis-gennetwerk.

Er is voorgesteld dat veroudering het resultaat is van een afweging tussen onderhoud en reproductie van middelen. Daarom kan de beschikbaarheid van hulpbronnen de verouderingssnelheid wijzigen. Voedingsbeperkingsexperimenten in modelorganismen zoals de fruitvlieg Drosophila melanogaster en de nematode Caenorhabditis elegans hebben aangetoond dat voedselbeperking de levensduur kan verlengen, meestal ten koste van reproductie. Hoe dit fenomeen kan worden gemoduleerd door het sociale leven, is echter nog niet goed begrepen. In Hoofdstuk 3 hebben we de beschikbaarheid van hulpbronnen in de termiet Cryptotermes secundus verminderd om te onderzoeken hoe dit de wisselwerking tussen onderhoud en reproductie op individueel en kolonieniveau beïnvloedt. We ontdekten een herverdeling van middelen van onderhoud naar reproductie op kolonieniveau, maar niet op individueel niveau. De wisselwerking op kolonieniveau werd bereikt doordat arbeiders de samenwerking opgaven en zich ontwikkelden tot gevleugelde seksuelen. Deze bevindingen laten zien hoe sociaal gedrag interageert met de beschikbaarheid van hulpbronnen en de centrale afwegingen in de levensgeschiedenis moduleert. Onze resultaten onthullen ook opvallende analogieën tussen totipotente termietenwerkers en stamcellen van hydra. Deze analogie biedt een nieuw perspectief op de relatie tussen sociale complexiteit en biologische complexiteit.

De levensduur van sociale insecten varieert aanzienlijk op zowel intra- als interspecifiek niveau. Binnen een kolonie overleven reproducerende individuen niet-reproducerende individuen, ondanks het feit dat ze dezelfde genetische achtergrond delen. Dit verschil in levensduur tussen reproducerende en niet-reproducerende individuen (d.w.z. kaste-specifieke veroudering) varieert ook tussen soorten met verschillende sociale complexiteit. Het begrijpen van de evolutionaire oorzaken van deze variaties is van vitaal belang om te begrijpen waarom het sociale leven het ouder worden beïnvloedt. In Hoofdstuk 4 hebben we met behulp van op individuen gebaseerde simulaties onderzocht hoe de mate van sociale complexiteit en extrinsieke sterfte de variaties in kaste-specifieke veroudering bij termieten vormgeven. Onze resultaten tonen een causale rol aan van zowel sociale complexiteit als extrinsieke mortaliteit bij het vormgeven van verschillende verouderingssnelheden. We benadrukken dat de kans op nestovererving een game changer is die het effect van extrinsieke sterfte op kaste-specifieke veroudering bij termieten verandert. Deze bevindingen dragen bij aan fundamentele inzichten in hoe en waarom sociale evolutie veroudering hervormt.

In Hoofdstuk 5 bespreek ik de algemene implicaties van alle bevindingen die uit dit proefschrift zijn voortgekomen. Ik suggereer dat het sociale leven uiteindelijk de mate van veroudering kan beïnvloeden door de sterkte en het selectieniveau op de levensduur te veranderen. Dit komt omdat socialiteit de directe en indirecte fitheidswinst van individuen kan wijzigen. Op een nabij niveau kan het sociale effect op veroudering mogelijk worden mogelijk gemaakt door genennetwerken die veroudering beheersen, opnieuw te bedraden, sociale-communicatiegenen in die netwerken in te bedden en genen uit die netwerken te dupliceren. Ik heb deze ideeën samengevat in een conceptueel kader dat mogelijk als leidraad kan dienen voor toekomstig onderzoek naar het begrijpen van eigenaardigheden van sociale effecten op veroudering.

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