Abstract

Triggered by microbial ligands, inflammation serves as a "double-edged sword" to fight infections on the one hand, but on the other hand causing tissue damage due to oxidative stress if it is dysregulated. For example, chronic inflammation can contribute to *inflammaging*, which is now widely regarded as one of the causes of ageing. In my interdisciplinary dissertation, my colleagues and I investigated three interrelated aspects of inflammation, using an evolutionary framework and various free-living birds as models: (1) ecological and evolutionary determinants of gut microbiota (GM) composition and diversity, a driver of wild bird immunity, (2) diversity in immune genes affecting inflammatory responses in wild birds and (3) inflammation-related physiological senescence in a free-living passerine bird, the great tit (*Parus major*). Firstly, using *16S rRNA* gene metabarcoding, we revealed high intra- and interspecific variation in passerine gut microbiota (GM) dominated by the major phyla Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes. Although in mammals GM depends strongly on host phylogeny and diet, in birds we found only moderate effects of phylogeny and very limited effects of host geography and ecology on GM composition. While microbiota diverged between the upper and lower gastrointestinal tracts (GIT), the microbiota of the adjacent tissues in the lower GIT was very similar, which is consistent with the relatively homogeneous GIT morphology in passerines and parrots. To understand the initial recruitment of GM and the mechanisms behind it in birds, we further investigated the microbiome of avian egg content and developing embryos in the great tit. We found that bird eggs were nearly sterile before hatching, suggesting that GM must predominantly form only after hatching in passerines. All this shows that GM is different in passerines compared to mammals and highlights that results derived from mammalian GM studies cannot be generally translated to passerines. Secondly, we developed a broadly applicable methodological pipeline to detect adaptive variation in protein-coding genes based on structural evolutionary bioinformatics, positive selection and adaptive convergence testing. Adopting this pipeline, we revealed that receptors of innate immunity, such as Toll-like (*TLRs*) and RIG-like receptors (*RLRs*) were highly variable in their ligand-binding regions in birds and much of their variation evolved adaptively. For the first time, we detected multiple gene losses in viral-sensing *RLRs*, retinoic acid-inducible gene I (*RIG-I*) and melanoma differentiation-associated protein 5 (*MDA5*) across the avian phylogeny. We further discovered the intriguing gene loss of cannabinoid receptor 2 (*CNR2*) in parrots, which negatively regulates inflammation and whose loss led to increased brain neuroinflammation. Thirdly, using longitudinally monitored great tits, we demonstrated senescence in multiple physiological traits that differ in their lifetime trajectories Chronic inflammation, which was positively associated with general oxidative stress damage, increased with ageing, documenting for the first time *inflammaging* in birds. Conversely, induced cellular inflammatory responses underwent bell-curved trajectories, consistent with *immunosenescence*. The same polynomial age-related trend in male plasma testosterone documented *hormonal senescence*. In contrast, levels of heavy metals in blood were largely independent of age, showing that bird blood can be used to monitor current heavy metal exposure even if the age is not known. All this suggests that small passerines undergo similar age-related changes as mammals.