

## Genomics and ornithology

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**Abstract** Genomics is revolutionizing ornithology in the same ways it is reinvigorating other biological disciplines. In this review, I will highlight applications of genomics and genomics technologies to the study of the ecology and evolution of birds, focusing specifically on genome evolution, multilocus phylogeography, and gene expression in host–parasite interactions. Genomics is providing unprecedented insight into the processes of genetic change and adaptation in ways we could scarcely envision a few years ago. Genomics will help integrate genome evolution with a variety of fields, including phylogenetics, speciation, and adaptation, and place them on a common scale of gene interactions and genomic contingency.

**Keywords** Genomics · Evolution · Bird · Dinosaur · Microarray

### Introduction

Genomics is revolutionizing our understanding of birds, just as it is revolutionizing the study of all biology. The new millennium has ushered in a host of new, high-throughput approaches that have relevance for many areas traditional to ornithology, including behavior, evolution, systematics and

population genetics, physiology, and even anatomy. These approaches have been borrowed from biomedicine and other areas germane to model organisms, just as previous genetic technologies have in the past. What is different from the current revolution is its scale and that it has the capacity to survey structure, variation, expression, and function across the entirety of the genome. This mini-review will survey recent results from our laboratory in Cambridge applying genomic technologies to various questions in the evolution and ecology of birds. These technologies themselves, which include large-scale gene expression arrays (microarrays), bacterial artificial chromosome (BAC) libraries, and large-scale DNA sequencing, as well as novel computational tools and bioinformatics, will not be reviewed here; I refer the reader to a recent review of this topic (Bonneaud et al., submitted). I will also not review the very exciting developments and initial large-scale comparative genomics comparisons among two comprehensively analyzed genomics, the Chicken (*Gallus gallus*) and the Zebra Finch (*Taenopygia guttata*), conducted largely in Hans Ellegren's laboratory and also recently reviewed (Ellegren 2007). Thus, this overview will focus on three areas of interest to our group: comparative genomics, multilocus phylogeography, and the ecology of gene expression, each of which represents a different axis on which researchers focusing on non-model species are scaling up in terms of genomics (Fig. 1). These studies span the ecology as well as the long- and short-term history of birds, from their divergence from dinosaurs to the most recent tips of the avian Tree of Life.

### Long-term genome evolution

The history of birds begins some 310 MYA when the amniotes first began to diversify after diverging from

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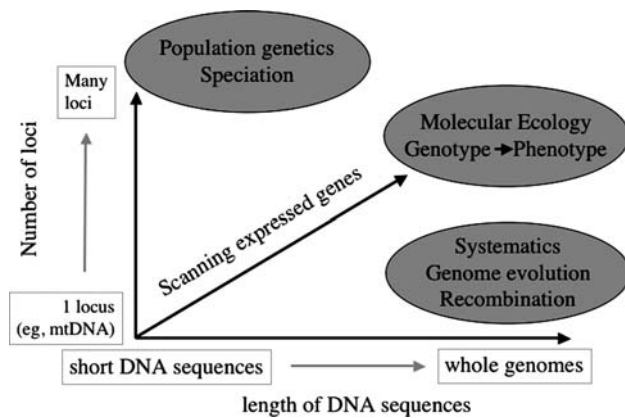
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Plenary essay for the International Ornithological Congress, Hamburg, Germany.

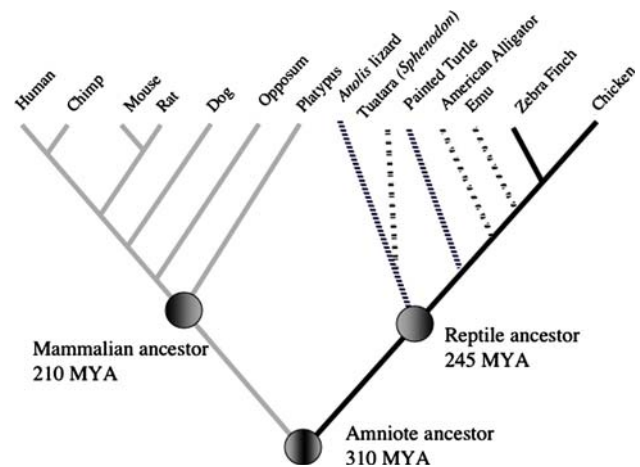
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**Fig. 1** Three types of genomic upscaling for evolutionary biology. Researchers can scale up in terms of the number of loci applied to phylogenetic and phylogeographic problems (*y*-axis). Researchers can scale up in terms of the length or sequencing depth of genomes to discover new things about genome evolution and recombination (*x*-axis). Finally, researchers may probe the expressed genome and the intersection of organisms and their changing environments through techniques such as microarrays (*z*-axis). All three types of approaches are applied in the text to ornithological problems

amphibians (Shedlock and Edwards 2007). In some respects, extant avian genomes bear conspicuous imprints of their non-avian past, yet in others this past has been largely erased as the avian lineage became specialized. The avian genome is known to be substantially smaller than that of mammals, non-avian reptiles, and most other vertebrates, besides some fish (Ellegren 2007). However, little is known of genome-wide patterns of sequence structure at the nucleotide level in reptiles, despite the fact that such information is essential to understanding long-term trends in avian genome evolution. Recently a bird (Zebra Finch; *Taeniopygia guttata*), a lizard (*Anolis carolinensis*) and a turtle (*Chrysemys picta*) were added to list of amniote species whose genomes would be sequenced to 6X or 8X coverage (Fig. 2). But these data are still not completed. To better understand the genomic context from which the avian genome arose, we undertook a large-scale BAC-end sequencing survey facilitated by BAC libraries recently created from six reptiles in collaboration with Drs. Chris Amemiya and Robert Macey: Emu (*Dromaius novaehollandiae*); American Alligator (*Alligator mississippiensis*); Tuatara (*Sphenodon punctatus*; see Wang et al. 2006b); Painted Turtle (*Chrysemys picta*); Garter Snake (*Thamnophis sirtalis*); and a Gila Monster (*Hiloderma suspectum*). These libraries, are publicly available through Sym-Bio Corporation (<http://www.sym-bio.com>). In addition, we harnessed the sequencing power of three genome centers—The Institute for Genomics Research, the Broad Institute of Harvard/MIT, and the Washington University at St. Louis Genome Center—to build up a library of sequences from these and other libraries, including the Bahamian Green



**Fig. 2** Phylogenetic overview of whole-genome projects in amniotes. Only a subset of the mammalian genome projects (*light gray*) are presented, principally those with dense (6X–8X) genome coverage. Branches leading to avian genome projects are in *black*. Branches leading to projects for non-avian reptile projects (Bahamian Green Anole *Anolis smaragdinus* and Painted Turtle *Chrysemys picta*) are *densely striped*, whereas those leading to species for which only BAC and other genome resources are available (Tuatara *Sphenodon punctatus*, Emu *Dromaius novaehollandiae*, American Alligator *Alligator mississippiensis*) are *less densely striped*

Anole (*Anolis smaragdinus*). This work (Shedlock et al. 2007a) has resulted in over 13 Mb of new sequence deposited and publicly available in Genbank and the National Center for Biotechnology Information Trace Archives, only part of which has been analyzed with even the most basic bioinformatics tools, not to mention the several BAC clones from tuatara, emu, and alligator that have been shotgun-sequenced to near completion by the National Human Genome Research Institute comparative genomics sequencing effort.

What have we learned from amassing all this sequence? Our sequencing strategy, consisting of thousands of short (500–700 bp) reads distributed randomly across the chromosomes, makes genome-wide features, such as base composition, transposable elements, and simple-sequence repeats, the most accessible (Shedlock et al. 2007b). In our first published analysis, we studied the sequence content of the *Anolis*, Alligator and Turtle genomes and compared them to information from Chicken, mouse and human (Shedlock et al. 2007a). We found that the guanine-cytosine (GC) content of the non-avian reptiles was in each case several percent higher than in Chicken and human, with the *Anolis* sequences possessing a GC-content (41.5%) closest to Chicken and human. The mammal- and bird-like GC-content of *Anolis* may signify a historical imprint of the ancestral amniote genome that still survives in *Anolis*, given that the lizard branch is among the first to have diverged from the amniote ancestor.

The sequence survey, as well as investigation of additional reptile sequences in the electronic data bases (Shedlock 2006), also revealed a diversity of retroelements, including Chicken-repeat 1 (CR1) elements and mammalian-interspersed repeats (MIR). The CR1s are examples of long-interspersed nuclear elements (LINEs), whereas the MIRs are short-interspersed elements (SINEs). These elements are variously common and rare in the genomes of diverse vertebrates, from fish to mammals, but the estimated abundance of these elements in the reptiles was substantially higher than in the Chicken. A phylogenetic analysis of 308 reptile elements suggested a high degree of lineage specificity, although the low resolution of our taxon sampling means that the lineage specificity we observed will be an upper limit. Regardless, the survey revealed a rich diversity of retroelements, with the highest level of lineage-specificity found in *Anolis*, again consistent with an ancient ancestry for this genome among reptiles. The *Anolis* genome appears divergent and mammal-like with regard to simple-sequence repeats (microsatellites) as well, with a preponderance of AT-rich microsatellites similar to those found in rodents. By contrast, the chicken genome possesses far fewer microsatellites than either reptiles or mammals (Primmer et al. 1997; Hughes and Piontkivska 2005). The non-avian reptile sequences also revealed an intriguing suite of tandemly-repeated 50-bp units that thus far have no parallels in mammals or birds. These novel structures may have arisen due to a lineage-specific bias in mutation or repair, perhaps mediated by DNA polymerases or other enzymes involved in the process of DNA replication (Shedlock et al. 2007a).

What about the speed of genome evolution in reptiles? Our survey, comprised as it was of non-homologous, unalignable sequence reads, made such as assessment challenging. Nonetheless, we were able to decompose each genome into oligonucleotides which served as metrics by which we could place all the genomes on a similar scale. We counted the frequency and rate of change of ~65,000 8-letter oligonucleotides across each genome, and found that the pattern of divergence of these word frequencies closely matched that predicted from the phylogenetic relationships of species. This suggests that change in the DNA ‘language’ of these genomes occurs in a time-dependent manner. Still, the fact that the amount of word-frequency change in the mammal lineage was still up to 10 times higher than in the reptile lineage means that, on top of this time-dependence, there is a substantial lineage-effect on these rates. The slow rate of word-frequency change in reptiles predicts that other features of genomic change in reptiles and birds, such as rates of point substitution, gene rearrangement, and gene duplication, may take place on a similarly slow scale compared to mammals (Edwards et al. 2005a).

Our survey of reptile genomes provides a useful context in which to interpret the streamlined avian genome. But when did the avian genome assume its present form, small and depauperate in repeats and microsatellites? We addressed this by estimating the genome size and structure in non-avian dinosaurs, such as theropods and ornithischians (Organ et al. 2007). We accomplished this by using bone cell (osteocyte) size as a surrogate of these genomic features. Significant correlations between osteocyte size, genome size, and retroelement fraction, and a robust phylogeny of reptiles, including extinct theropods thought to have given rise to modern birds, facilitated phylogenetically-controlled estimation of these parameters in extinct birds and dinosaurs in a Bayesian framework. The analysis suggested that the small genome size of extant birds, as well as the low retroelement fraction of avian genomes, was achieved strikingly early in the dinosaur lineage, approximately at the base of the origin of theropods some 220 MYA. For example, *Allosaurus* and *Deinonychus*, both on the lineage leading to modern birds, were estimated to have genome sizes of 1.7 and 1.62 pg, falling approximately between genome sizes for volant and flightless birds. In addition, extinct birds such as *Diatryma* and *Hesperornis* were estimated to have genome sizes of 1.95 and 1.65 pg, again significantly smaller than those of extant non-avian reptiles and mammals. The estimated repeat fractions of extinct birds and dinosaurs were also compellingly similar to those of modern birds, hovering around 8–15%. By contrast, several ornithischian dinosaurs were estimated to have genomes of a size and structure similar to those of modern non-avian reptiles. These results imply that the form of the modern avian genome is quite old, and that a substantial period of genome stasis occurred once this form was achieved at the base of the theropod branch (Organ et al. 2007).

### Multilocus phylogeography

Sequence surveys such as the clone-end survey described above have the additional benefit of yielding thousands of genomic markers for phylogenetics and phylogeography. These markers tend to be in functionally uncharacterized and often unannotated regions of the genome, hence their designation as ‘anonymous’ markers (Karl and Avise 1993). It is generally agreed that multiple genetic markers are a positive benefit to phylogeography and phylogenetics, despite the fact that mitochondrial DNA harbors a disproportionate amount of information for a single gene (Brumfield et al. 2003). This high-information content of mtDNA derives from its rapid rate of mutation, but even more importantly from its small effective population size compared to nuclear genes (Moore 1995). This small

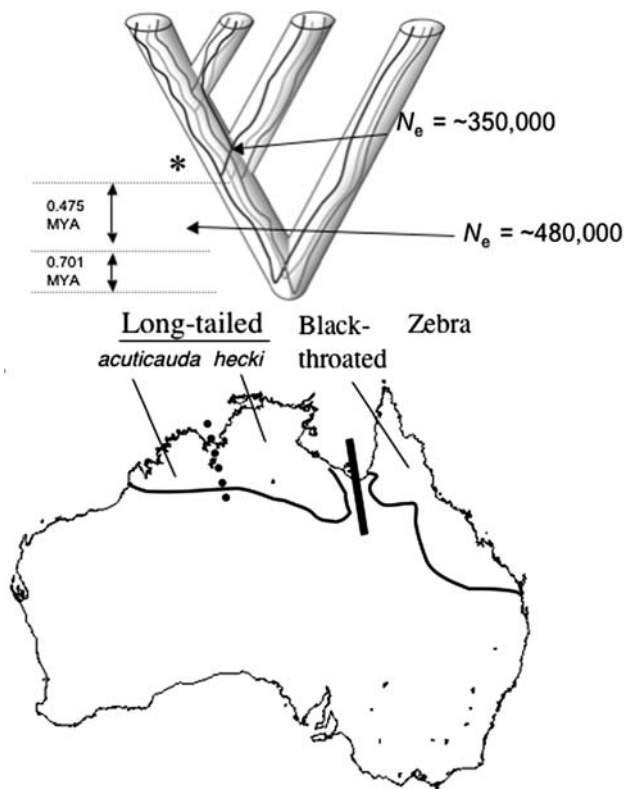
effective population size means that mtDNA will track speciation events and population divergence events more faithfully than will nuclear genes. Still, it is the number of independently segregating loci, not the length or signal in any individual locus, that will determine our accuracy of reconstructing phylogeographic history (Felsenstein 2006). The traditional focus on gene trees has, however, caused an undue focus on the confidence of gene trees, and has prevented a synthetic view of population trees and demographic history that is the real focus of biogeography and population history. The gene-centric view of phylogeography also means that our confidence in various phylogeographic events is grossly distorted by focusing on a single gene, since confidence in a gene tree is generally likely to be much higher than confidence in the species tree or hypothesis of population history. The avalanche of novel nuclear loci that are being unleashed through genome projects and bioinformatics means that there will be no shortage of nuclear markers for phylogenetic studies (Backström et al. 2007). A greater challenge will be defining and choosing among a set of analytical approaches that will encompass the diversity of events that typically occur in phylogeography (divergence in isolation, isolation with migration, gene flow, and population growth and contraction).

A glimpse of the phylogenetic heterogeneity we can expect from different independent loci has been revealed in a few recent multilocus studies in birds (Congdon et al. 2000; Bensch et al. 2006). Indeed, we expect there to be heterogeneity, particularly when population sizes have been large and times between speciation events short. Our recent analysis of 30 different nuclear loci in the Australian Grassfinch genus *Poephila* (*P. cincta*, *P. acuticauda* and *P. hecki*, with the Zebra Finch as an outgroup; Jennings and Edwards 2005) showed that such gene tree heterogeneity will be the norm for birds. Our rather simple sampling scheme in this study—sampling only a single allele per locus across four species—nonetheless provided some clarity to the gene tree results. We found that 16 of the 30 gene trees (53%) matched the hypothesized tree for the species implied by biogeography and morphology (*P. cincta* vs *P. acuticauda/hecki*), with another 8 (27%) linking alleles from *P. acuticauda* and *P. cincta*, and 5 (17%) linking *P. hecki* and *P. cincta* (one locus was unresolved). Is such phylogenetic heterogeneity noise getting in the way of simple inference of the phylogeny of these species? No. So long as we resist the temptation to read the species tree directly from a gene or gene trees, meaningful demographic information, in addition to the phylogeny itself, can be extracted from such data (Edwards et al. 2007; Liu and Pearl 2007).

Using the Bayesian and likelihood algorithms in the software MCMCcoal (Rannala and Yang 2003), we were

able to estimate divergence times and ancestral population sizes of these grassfinches from this heterogeneous multilocus data, something that could not be done with mtDNA alone. Our estimates suggested that the lineage had uniformly large populations, of the order of several hundreds of thousands of birds, and that the divergence times were relatively recent, of the order of 500,000 to 700,000 years, well within the Pleistocene, assuming mutation rates similar to those of noncoding regions in gamebirds (Axelsson et al. 2004). In principle, none of the heterogeneity in gene trees in our study implies hybridization or gene flow; these forces might play a role, but in fact there is little evidence from the field for hybridization amongst these taxa. Thus, the scenario that we have reconstructed, one with large populations, devoid of bottlenecks, and with relatively short divergence times, is precisely the scenario in which we should expect heterogeneity of gene trees. A novel method of phylogenetic analysis in which the species tree rather than the gene trees are directly estimated was recently applied to these data (Fig. 3). This analysis also suggested an ‘open’ population history of these species, and furthermore estimated a phylogeny consistent with that assumed in the previous study and implied by other characters (Liu and Pearl 2007).

What do examples such as the *Poephila* imply about the process of speciation in birds? If the level of gene tree heterogeneity discovered in this clade is at all representative of other groups, it implies that there may be ample opportunity for natural selection during the speciation process (Edwards et al. 2005b). The loci that we have used to estimate the speciation history of this group are neutral, and this partly explains why their polymorphisms have persisted throughout the history of this genus—forces such as directional selection would have rapidly fixed polymorphisms in each species, causing gene trees to clearly track the species tree, with each locus achieving reciprocal monophyly. By contrast, it is at the level of the phenotype—plumage, behavior, song, etc.—where we often see fixed, diagnostic differences between sister species, whether sympatric or allopatric. The pattern of fixed differences in phenotypic characters, as occurs in *Poephila* (Cracraft 1986), combined with abundant shared polymorphisms at the level of neutral genes, implies that selection has driven phenotypes apart during speciation. The quantitative contrast between genes and phenotype is a powerful argument for selection, one that complements and is relevant over longer time scales than are field studies of selection in the wild. The prevalence of selection in birds has recently been argued on the basis of plausible links between phenotypic characters, environmental change, mate choice and mate preference, and other aspects of ‘social selection’ (Price 2007). But, even with the large estimates of ancestral population size in *Poephila*, drift



**Fig. 3** Species tree analysis of Australian Grassfinches (*Poephila*) made possible by multilocus sequencing. The analysis is based on 30 anonymous, noncoding loci presented in Jennings and Edwards (2005) and re-analyzed by Liu and Pearl (2007). *Top* Phylogenetic relationships of four finch species. The asterisk indicates an estimated confidence (posterior probability) of the species tree branch at 0.88. Species divergence times for the ingroups are indicated, as are estimated effective population sizes. The 95% confidence limits (CI) on the *P. hecki*–*acuticauda* divergence are 0.18–0.72 MYA, with a confidence limit on effective size of the ancestral population of ~48,000–~1,195,000. *P. cincta* is estimated to have diverged 1.18 MYA (CI: 0.95–1.46 MYA), with an ancestral effective size confidence range of ~201,000–~580,000. *Bottom* Geographic ranges of species analyzed, with the Carpentarian (solid) and Kimberley/Arnhemland (dotted) barriers indicated

cannot be ignored. What is needed now are further examples in which the relative roles of drift and selection during speciation can be determined, and an evaluation of the prevalence of both forces in causing divergence (Clegg et al. 2002). A multilocus approach, facilitated no doubt by genomics, will surely play an important role in this evaluation.

### Gene expression in a host-parasite interactions

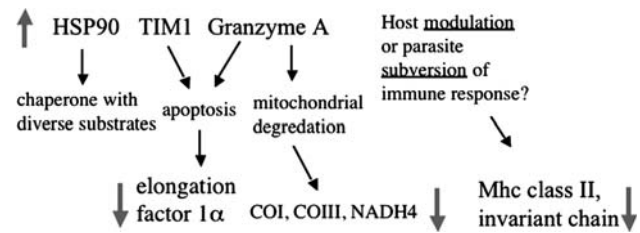
Our final example of genomics in ornithology focuses on a fascinating interaction between a bacterial parasite and an introduced, invasive avian host in North America. The bacterium *Mycoplasma gallisepticum* is thought to have

recently expanded its host range from poultry to a novel avian host, the House Finch (*Carpodacus mexicanus*; Roberts et al. 2001). In collaboration with Geoffrey Hill and Sharon Roberts, we have been investigating the evolution of gene expression and other genetic changes in the house finch in response to the epizootic involving *Mycoplasma*. By investigating differences in the gene expression profile of experimentally infected and uninfected birds, we hope to identify evolutionary changes in the House Finch that might have facilitated evolved resistance to the *Mycoplasma* as it spreads throughout the House Finch range.

We used a genomics approach called suppression-subtractive hybridization (SSH) to conduct a large-scale screen for gene expression changes in House Finches experimentally infected with *Mycoplasma* versus uninfected control birds (Wang et al. 2006a). SSH is an excellent approach for such screens, particularly in ornithology, because it can be conducted on species whose genomes are essentially unknown. By contrast, microarray analysis of gene expression usually requires extensive characterization of expressed-sequence tags (ESTs) and cloned cDNAs prior to or as part of the analysis (Bonneaud et al., submitted). On the downside, SSH is considerably less sensitive than are microarrays, not due to problems with hybridization kinetics, but because the method is amplification-based, and predicated on completely eliminating transcripts that do not show expression changes through a series of initial hybridizations of tracer (low abundance RNA pool) and driver (overabundant pool) RNAs (control and affected sample, or vice versa). Thus, in practice, many cDNAs implied to be differentially expressed by the initial hybridization steps are later on found out not to be. In addition, it is difficult to quantify the degree of gene expression change, whereas such quantification is straightforward with microarrays. Still, SSH is an extremely useful tool for a course analysis of gene expression. Indeed, our study was the first large-scale screen for gene expression change in a wild bird (compare Morgan et al. 2001; Karaca et al. 2004), and sets the stage for more genomically-informed approaches based on whole-genome sequences and deep sequencing of transcript pools.

Using the spleen as a source of RNA, we created a cDNA array consisting of 7,296 clones produced using an infected bird as the ‘driver’ and 9,216 clones in which an infected bird was the ‘tester’. Using these two pools, as well as downstream hybridizations using cDNA pools from both infected and uninfected birds, allowed us to determine whether genes were up- or down-regulated upon infection with *Mycoplasma*. We found a total of 220 genes that were up- or down-regulated to a degree that was detectable by our method. We suspect in fact that

many more genes in our cDNA pools exhibit changes in gene expression, but that our method failed to detect them. The 220 transcripts corresponded to a total of 34 different genes, although further analysis of these clones in the light of the Chicken and Zebra Finch genomes will no doubt yield further annotated transcripts. A number of genes that are plausible players in an avian immune response were revealed in our analysis. Heat-shock protein 90 was by far the most commonly encountered up-regulated gene; this gene is widely observed to play a role in individual stress, whether to physiological demands or to infection. It is a highly pleiotropic chaperone with many target proteins of diverse functions. Several genes of more specific relevance to immune responses were also discovered. These include genes such as: Granzyme A, involved in killing of infected cells via oxygen-mediated and other pathways for cell death; T-cell immunoglobulin mucin (TIM) I, a member of a new gene family with roles in viral clearance and T-cell maturation; and interferon-stimulated gene 12, a protein stimulated by cytokines and of likely relevance to immune responses in vertebrates. Are these genes specific to the response to *Mycoplasma*? Probably not. In all likelihood, we have scraped the tip of the expression iceberg by identifying broadly expressed genes that are of general relevance to immune responses to bacteria. There are likely numerous other genes of interest to bacterial infections in birds, such as Toll-like receptors and genes expressed in natural killer cells. We also expect classical and highly polymorphic immune genes, such as genes of the major histocompatibility complex (MHC) to be involved, although our initial investigation, surprisingly, suggested down-regulation of a House Finch MHC class II (Hess et al. 2007). Such down-regulation may be a result of modulation of the host-immune response to prevent an autoimmune disease, or, more insidiously, could imply active down-regulation of the host immune response by the pathogen. Such intriguing scenarios await more detailed analysis via genomics and cellular immunological methods. Still, the few genes that were implicated in the House Finch immune response suggest a hierarchy of interactions among genes, and in particular suggest specific links between primary effector genes responding to infected cells and genes whose expression may be up- or down-regulated as a direct result of genetic interactions or due to killing of cell types in which those genes are expressed (Fig. 4). For example, the upregulation of genes such as Granzyme A and TIM1 may be associated with the observed decreased expression of mitochondrial genes (Fig. 4). Overall, our results provided a glimpse of a passerine immune response at the molecular level and a useful survey on which more detailed studies of individual genes can be based.



**Fig. 4** Putative interactions among gene products implied by macroarray analysis of gene expression in House Finches (*Carpodacus mexicanus*) infected with *Mycoplasma gallisepticum* (Wang et al. 2006). Gray arrows indicate up- and down-regulation of specific genes in comparison with control (uninfected) birds. Black arrows indicate hypothesized effects of major genes showing changes in expression (top row) on putative downstream genes (bottom row)

## Conclusion

Genomics and ornithology are in some ways two unlikely bedfellows. The mystery and beauty of birds tends to lead researchers in the direction of the field, behavioral ecology, song, and conservation. But all of these endeavors stand to be enriched by a genomics approach. The genome sequencing of a second avian species, the Zebra Finch, will provide a powerful map of the genomes of many species of birds that are models for ecology and behavior, and the initial comparisons of Chicken and Zebra Finch, in particular for the Z-chromosome, are very promising in terms of increasing the accessibility of the genomes of all 10,000 species of birds (Backström et al. 2007; Ellegren 2007). Even the impending sequencing of a turtle genome will no doubt have important implications for ornithology, given the increased phylogenetic proximity of birds and turtles resolved in recent years. Neurobiology and endocrinology are two other fields that will benefit from a genomics approach, as they already have (Luo et al. 2006). All of these fields will be profitably integrated with the structure of the avian genome and will thereby have a new common yardstick, the genome, by which different research programs can be compared on similar genomic scales. Genomics will help tie together genome evolution with a variety of fields, including phylogenetics, speciation and adaptation, and conservation, and place them on a common scale of gene interactions and genomic contingency. The key for ornithologists is to maintain focus on the age-old questions in ecology and behavior that have been intractable because of a dearth of approaches able to monitor the state of the genome. On top of this, genomics is likely to usher in a completely new set of questions based on newly discovered actors in the evolutionary play for birds.

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