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Host gene expression in wildlife disease: making sense of species-level responses

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Abstract

Emerging infectious diseases are significant threats to wildlife conservation, yet the impacts of pathogen exposure and infection can vary widely among host species. As such, conservation biologists and disease ecologists have increasingly aimed to understand species-specific host susceptibility using molecular methods. In particular, comparative gene expression assays have been used to contrast the transcriptomic responses of disease-resistant and disease-susceptible hosts to pathogen exposure. This work usually assumes that the gene expression responses of disease-resistant species will reveal the activation of molecular pathways contributing to host defence. However, results often show that disease-resistant hosts undergo little gene expression change following pathogen challenge. Here, we discuss the mechanistic implications of these "null" findings and offer methodological suggestions for future molecular studies of wildlife disease. First, we highlight that muted transcriptomic responses with minimal immune system recruitment may indeed be protective for non-susceptible hosts if they limit immunopathology and promote pathogen tolerance in systems where susceptible hosts suffer from genetic dysregulation. Second, we argue that overly narrow investigation of responses to pathogen exposure may overlook important, constitutively active molecular pathways that underlie species-specific defences. Finally, we outline alternative study designs and approaches that complement interspecific transcriptomic comparisons, including intraspecific gene expression studies and genomic methods to detect signatures of selection. Collectively, these insights will help ecologists extract maximal information from conservation-relevant transcriptomic data sets, leading to a deeper understanding of host defences and, ultimately, the implementation of successful conservation interventions.

KEYWORDS
comparative transcriptomics, conservation management, constitutive gene expression, emerging infectious disease, host susceptibility, host-pathogen interactions

1 | PUZZLING "NULL" FINDINGS IN CONSERVATION-RELEVANT WILDLIFE TRANSCRIPTOMICS

Recently emerged wildlife diseases that threaten population- or species-level persistence have forced conservation biologists to direct their attention toward disease processes, including transmission dynamics and host responses to pathogen exposure (Daszak et al., 2000; Fisher et al., 2012; Frick et al., 2015; Lorch et al., 2016; Martel et al., 2014; McCallum, 2008). Although disease acts fundamentally on host individuals and can therefore be influenced by individual-level host variation (Gervasi et al., 2015; Lloyd-Smith

et al., 2005; Pemberton et al., 2011), species have often emerged as a natural unit for research and prioritization of conservation actions to mitigate novel disease threats. For example, characterization of species-level susceptibility to emerging diseases provides a preliminary assessment of potential disease impact (Martel et al., 2014), and, following the acquisition of such baseline data, disease monitoring can focus on species most at-risk (Langwig et al., 2015). Further, in multihost disease systems where host species show different disease outcomes, understanding the mechanisms underlying host susceptibility promises to inform assisted selection and other targeted management strategies that could introduce or maintain traits conferring disease resistance in species of conservation concern (Allendorf et al., 2010; Bernard et al., 2020; Gewin, 2008; Harrisson et al., 2014; Langwig et al., 2015; Woodhams et al., 2011).

Conservation biologists and disease ecologists have pursued this research agenda in part by embracing the genomics revolution, which has provided a flexible toolkit for detailed genetic investigation of non-model species (Connon et al., 2018; DeCandia et al., 2018; Ekblom & Galindo, 2011; Longo et al., 2014; Lozier & Zayed, 2017). In particular, studies of host gene expression can provide a tissue-specific assay of the genes and cellular pathways involved in pathogen response (Blanchong et al., 2016; Ekblom & Galindo, 2011; Jenner & Young, 2005; Wang et al., 2009). This approach seems tailor-made for parsing the molecular basis of species-specific wildlife disease progression (Barreiro & Tung, 2012; DeCandia et al., 2018; Greenwood et al., 2016; Gupta et al., 2020; Shepack & Catenazzi, 2020; Zamudio et al., 2020): presumably, the gene expression responses of disease-resistant hosts following pathogen exposure should reveal the molecular processes that distinguish their favourable disease outcome from those of less fortunate species. Candidate genes can then be targeted to further investigate specific modes of adaptation (Shultz & Sackton, 2019). Critically, comparative work that characterizes pathogen response across host species might eventually build an evidence base able to distinguish between idiosyncratic pathogen defence strategies and those that are widely shared among host species able to avoid disease pathology (Ellison et al., 2015; Evans, 2015; Fuess et al., 2017).

Indeed, a number of studies in emerging disease systems have compared the gene expression responses of putatively disease-resistant hosts with those of susceptible species. Where experimental hypotheses are made explicit, researchers usually anticipate that increased expression of immunological, anti-inflammatory, and tissue repair pathways will characterize disease-resistant hosts (Davy et al., 2017; Lilley et al., 2019). However, contrary to these expectations, data show that disease-resistant host species often undergo minimal gene expression change in response to pathogen exposure. Wildlife disease researchers have yet to fully unpack the mechanistic insight to be gleaned from these seemingly "null" results. Here, we examine this phenomenon in detail, leveraging a quantitative summary of the existing literature to discuss the implications of current findings and outline productive analytical directions for wildlife disease ecologists interested in understanding host susceptibility.

2 | COMPILING THE CURRENT EVIDENCE BASE

To identify research studies that characterized the gene expression responses of wild animal hosts that differ in disease susceptibility, we searched the Web of Science Core Collection on 29 January 2021 using the topic query string "(emerging infectious disease* OR population decline*) AND (gene expression OR transcriptom*) AND (susceptib* OR resistan* OR toleran*) AND respon*". We included the search strings related to "emerging infectious disease" and "population decline" to narrow our search to papers that were likely to address contemporary disease threats to wild animals, thereby limiting the number of irrelevant query results about domestic animal and plant disease systems, which are more commonly studied. We reviewed abstracts of the resulting records ($n = 256$, all of which are listed in the project GitHub repository), retaining studies that conducted gene expression response comparisons (Figure S1).

To maintain a focus on species-level differences in wildlife disease response, we excluded any studies that investigated intraspecific variability in host responses (i.e., comparisons among genotypes, ecotypes, etc.). We feel multihost disease systems warrant initial examination at the species-level as this is the scale that will be most immediately relevant to conservation management action. Subsequent focus on fine scale processes that may shape differential disease outcome within species will provide important, but fundamentally different, insights for managing disease in wild populations. Similarly, we excluded studies that only characterized the gene expression response of a single wildlife host species to pathogen exposure or the responses of multiple species that had identical disease outcomes. While such work provides useful qualitative context for the results presented here, reported gene expression patterns in these studies are not easily comparable with other research, even within the same disease system, because of major differences in study design, execution, and analysis. Thus, we strictly focused on studies that present data for both disease-resistant and disease-susceptible host species, thereby more effectively controlling for study-level variation in methodology. Of special note, we further excluded two multihost studies from the white-nose syndrome disease system because these studies used a distinct sampling approach that compared gene expression in paired samples of apparently infected versus uninfected tissues within infected individuals rather than from exposed versus unexposed individuals (Davy et al., 2020; Lilley et al., 2019). While these comparisons can identify localized responses to pathogen infection, they are not directly analogous to the other research designs considered here, which used unexposed animals as controls.

We also opportunistically supplemented our Web of Science Core Collection search with any appropriate papers that were cited in the literature we reviewed in-depth or relevant papers that we otherwise encountered during the drafting of this manuscript. Two papers were added to the final set for downstream analysis in these ways (Figure S1).

Once we gathered a set of papers appropriate for further analysis, we recorded the reported gene expression changes between exposed and control hosts for all host species, time points, exposure treatments, and tissues, where relevant for each study. More specifically, within studies, host species, time points, exposure treatments, and tissues, we summed the number of genes/contigs/probes that were differentially expressed, whether upregulated or downregulated relative to controls. This sum served as our metric of total differential expression, which was then converted to a proportion of differentially expressed genes/contigs/probes, given the total number of genes/contigs/probes under investigation in a given study. We recorded differential expression as reported in the original research papers, accepting the methods applied by the authors.

Like other aspects of study design and execution, we recognize that the analytical choices made in the work we review here are idiosyncratic, with potentially significant consequences for downstream transcriptomic results. We therefore accounted for study-level variation in gene expression findings using hierarchical Bayesian models. Such an approach also allows us to explicitly evaluate the effect of host species type (i.e., susceptible to disease or nonsusceptible to disease) on the likelihood of observing differential gene expression following pathogen exposure. More specifically, we first constructed a hierarchical model with a binomial outcome distribution and a logit link function (Bolker et al., 2009; Harrison et al., 2018; McElreath, 2016), using the number of differentially expressed genes/contigs/probes as the response variable and the total number of genes/contigs/probes under investigation as the binomial trial size. In this model, we evaluated potential differences in gene expression response between host species types using a binary predictor (susceptible vs. nonsusceptible), and we included a varying effect (i.e., random effect) of study to account for study-level variation in experimental methodology. More intuitively, the inclusion of study-level varying effects allows us to account for the fact that certain studies may tend to report relatively low or high amounts of differential expression overall, regardless of host species.

Additionally, we considered the possibility that differential gene expression results could be biased in cases where the original studies analysed large numbers of unannotated contigs, some of which may represent artifacts of the sequencing and analysis process rather than biologically-meaningful transcripts. Therefore, we fit the same Bayesian model to an alternative data set, considering, where possible, only those genes/contigs/probes that were annotated with functional information and the proportion of those annotated genetic features that were differentially expressed. As with the total differential expression counts, here we recorded differential expression as in the original studies, characterizing genes/contigs/probes as annotated according to the particular functional assignment workflows used in the original work (usually Gene Ontology [GO] annotations).

Finally, as a further check of the robustness of our results, we fit two more complex binomial models using the full differential expression data set. The purpose of these supplemental models was to determine whether the influence of host species type (susceptible vs. nonsusceptible) on observed differential expression varied across different data subsets. In particular, since three out of seven studies in our final data set were of the amphibian pathogen *Batrachochytrium dendrobatidis* (*Bd*), we were interested in whether the strength of the host species type effect differed according to pathogen type (defined as *Bd* vs. non-*Bd* studies). In addition, we wanted to investigate whether assay type (microarray vs. RNA-seq studies) influenced the host species type effect. Operationalizing these ideas at a statistical level, we fit two additional models that included interaction effects to allow for the host species type effect to vary in strength (or direction) across different data subsets. Both of these models built upon the basic model structure described above (main effect of host species type and study-level varying effects): the first added a main effect of pathogen type and an interaction term between pathogen type and host species type, while the second added a main effect of assay type and an interaction term between assay type and host species type.

We specified and fit the hierarchical Bayesian models using the Stan programming language (Carpenter et al., 2017) accessed through the 'rethinking' package interface in R (McElreath, 2016, 2020). For all model fits, we used four independent Markov chains, each with 7500 iterations. Given that 2500 iterations were used as warmup, we based our inferences on a total of 20,000 posterior samples from each model (5000 post-warmup iterations each from four chains). We performed post-hoc model diagnostics to ensure good model fits. These checks included visual inspection of chains using trace plots and confirmed convergence of the potential scale reduction statistic, $\hat{R}$, towards one for all model parameters (Gelman & Rubin, 1992). Although all model parameters are estimated on the log-odds scale (as a result of the logit link function), we converted parameter posteriors to the probability scale for ease of interpretation, where relevant.

3 | SUMMARY OF COMPARATIVE STUDIES EVALUATING HOST TRANSCRIPTOMIC RESPONSES IN WILDLIFE DISEASE

Our data compilation efforts resulted in identification of seven gene expression studies spanning five disease systems and four biological classes of host organism (Eskew et al., 2021). Collectively, these studies suggest that gene expression responses of disease-resistant hosts to pathogen or parasite exposure tend to be muted relative to those of disease-susceptible hosts (Figure 1). Because individual studies sometimes tested multiple wildlife host species in response to different exposure treatments and/or assayed multiple tissues at multiple time points, we identified 40 unique gene expression data points among the seven studies, representing 26 disease-resistant/disease-susceptible host gene expression response comparisons (Figure 1a). In 19 of the 26 comparisons (73%), exposed disease-resistant hosts showed less gene expression change than exposed disease-susceptible hosts. Across studies, there are multiple

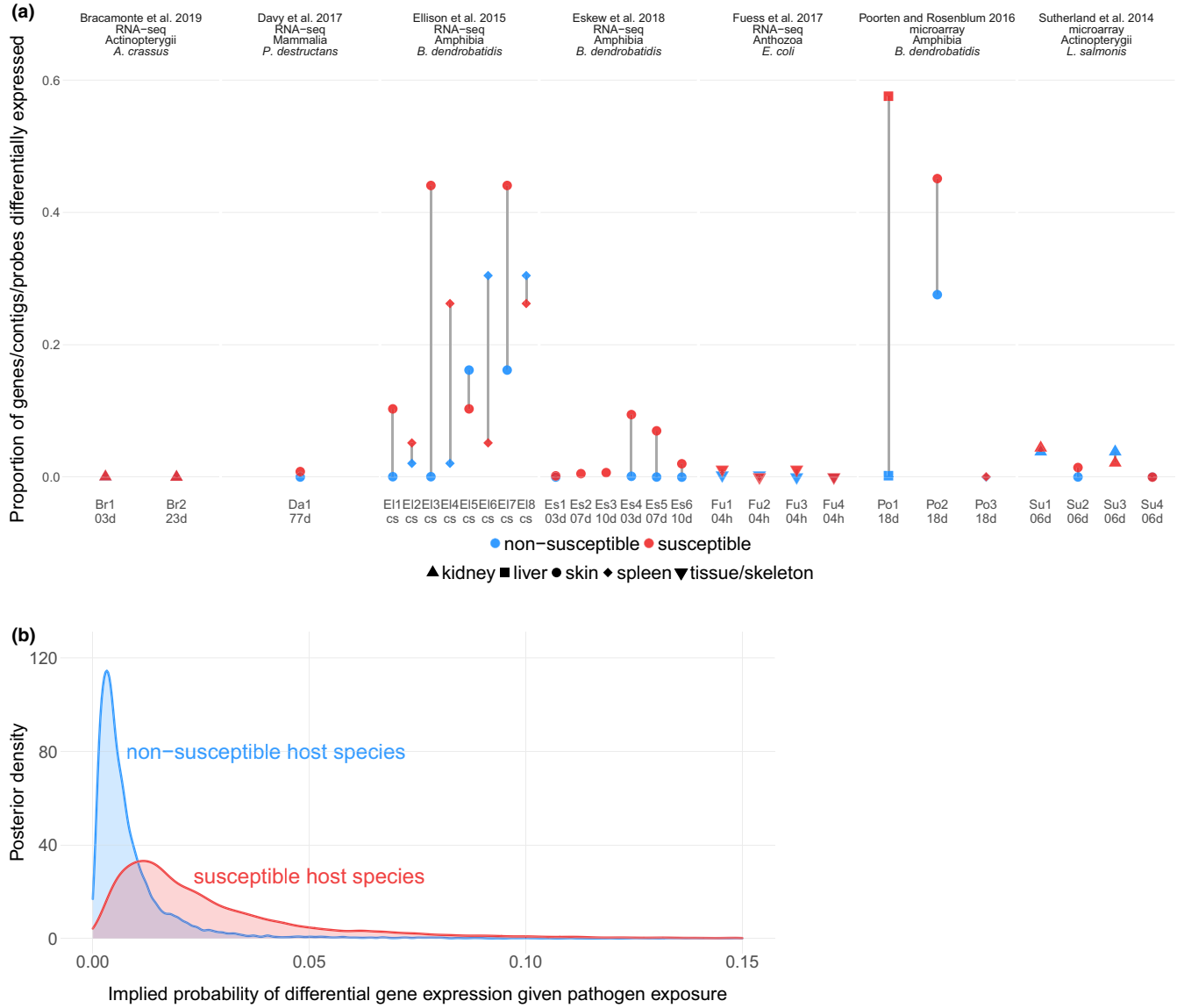

FIGURE 1 Gene expression responses of nonsusceptible and susceptible host species to pathogen challenge. (a) Across seven original research studies, we summarized observed differential expression for all relevant combinations of host species, exposure treatments, time points, and tissues. Each nonsusceptible/susceptible host expression response comparison appears with an associated label along the bottom of the x-axis, and the y-axis shows the proportion of differentially expressed genes/contigs/probes observed in exposed individuals relative to controls. Labels along the top of the figure panel indicate the study, gene expression assay method, class of host organism, and pathogen. We refer to host species as either "nonsusceptible" (blue) or "susceptible" (red) to disease in order to remain agnostic about the specific defence mechanisms employed by nonsusceptible hosts, which could include resistance and/or tolerance strategies (Bonneaud et al., 2019; Medzhitov et al., 2012; Read et al., 2008; Schneider & Ayres, 2008). Point shape represents the tissue used in the gene expression assay. Comparison labels on the bottom of the figure panel are accompanied by information about the timing of sample collection, whether in hours post-exposure ("h"), days post-exposure ("d"), or upon the observation of clinical symptoms ("cs"). Further details about the gene expression comparisons are given in Table S1. Note that "comparisons" Es2 and Es3 do not contain data on nonsusceptible hosts and are visualized here only to show temporal patterns in gene expression. (b) Implied probability of observing differential gene expression in nonsusceptible and susceptible host species following pathogen challenge. These posterior probability distributions were derived from the parameter posteriors of a hierarchical Bayesian model fit to the data shown in (a). Model diagnostics and posterior summaries for all raw model parameters are displayed in Figure S2, S3 [Colour figure can be viewed at wileyonlinelibrary.com]

instances where disease-resistant hosts show no detectable gene expression change relative to controls while disease-susceptible hosts in identical treatments demonstrate differential gene regulation.

Bayesian statistical models supported this descriptive interpretation of our compiled data. In the first model fit to the full differential expression data set, the posterior for the effect of host species type (susceptible to disease as opposed to nonsusceptible) was positive over the entire 95% highest posterior density interval (mean [95% HPDI]: 1.28 [1.25–1.31]; Figure S2, S3). Thus, the posterior distribution for this key parameter indicated that susceptible

species were expected to have an increased probability of observed differential gene expression (Figure 1a; Figure S3), even as we used random effects to account for variation in the overall proportion of differentially expressed gene/contigs/probes detected across studies. Translating model posteriors from the log-odds to the probability scale revealed that nonsusceptible species were expected to have a mean probability of differential gene expression of 0.01 [0.00–0.03] whereas susceptible species were expected to have a mean probability of differential gene expression approximately three times greater (0.03 [0.00–0.09]; Figure 1b). An intuitive interpretation of these modeling results is that, in a typical gene expression study, researchers would expect to find ~1% of all genes under investigation to be differentially expressed in exposed nonsusceptible host species whereas ~3% of genes would be differentially expressed in exposed susceptible host species.

Consideration of alternative data subsets and model structures led to very similar results. For example, including only data from annotated genes/contigs/probes within our modeling framework (n = 36 data points) did not change overall inference. With the alternative, annotated differential expression data set, the effect of host species type on observed differential gene expression was still strictly positive (1.04 [1.01–1.07]; Figure S4, S5). When more complex models including interactions between host species type and pathogen type (*Bd* vs. non-*Bd* studies; Figure S6, S7) or assay type (microarray vs. RNA-seq studies; Figure S8, S9) were fit to the full differential expression data set, they also resulted in similar conclusions. In the model including an interaction between host species type and pathogen type (Figure S7), the posterior distribution for host species type was strictly positive in the 95% HPDI (1.20 [1.08–1.33]), while the interaction term overlapped zero (0.08 [−0.05–0.22]), suggesting the strength of the host species type effect was not different between *Bd* and non-*Bd* studies. In the model including an interaction between host species type and assay type (Figure S9), the posterior distribution for the baseline host species type effect (corresponding to the host species type effect within RNA-seq studies) was again strictly positive in the 95% HPDI (1.31 [1.28–1.35]). The interaction term in this model spanned only negative values (−0.20 [−0.28 to −0.11]), indicating that the host species type effect was smaller in microarray studies compared to RNA-seq studies. However, these parameter posterior distributions still imply that, even within microarray studies, susceptible species have an increased probability of differential expression relative to nonsusceptible species (adding together the baseline host species type effect posterior and the interaction term's posterior yields: 1.11 [1.03–1.19]).

4 | SYNTHESIZING CURRENT INSIGHTS ON HOST GENE EXPRESSION RESPONSES IN WILDLIFE DISEASE AND FUTURE DIRECTIONS

Our quantitative summary suggests that disease-resistant host species often show limited gene expression change in response to pathogen challenge. Importantly, these hosts are of primary interest from a disease management perspective because we often seek to learn about beneficial response mechanisms in disease-resistant hosts for subsequent application in management of susceptible hosts. What, then, do these results reveal about the protective strategies of disease-resistant species? We explore this question in the remainder of our text, highlighting important insights already gained and suggesting several study design considerations and research practice improvements that should help to facilitate fruitful molecular investigations of host susceptibility.

4.1 | Broadening our understanding of protective host responses to pathogen exposure

The work examined here suggests we should broadly revise our notions of the ways in which host responses confer protection from pathogen threat. More specifically, multiple studies show that the gene expression responses of disease-resistant hosts do not necessarily involve robust recruitment of immune system processes, as might be assumed (Bracamonte et al., 2019; Davy et al., 2017; Eskew et al., 2018; Lilley et al., 2019; Poorten & Rosenblum, 2016; Savage et al., 2020). In some cases, such as the bat white-nose syndrome disease system, these comparative transcriptomic findings have been validated through additional studies on disease-resistant species using complementary methods (e.g., quantification of protein and metabolite abundance, white blood cell counts) that confirm apparently limited immune response to pathogen exposure (Fritze et al., 2019; Hecht-Höger et al., 2020).

Interestingly, these patterns are also mirrored in systems relevant to human disease, which are more well-studied. For example, some nonhuman primates are tolerant of simian immunodeficiency viruses (the precursors to human immunodeficiency virus [HIV]), and host response to viral infection in these species is characterized by a rapid resolution of immune system activation that limits chronic immunopathology (Chahroudi et al., 2012). As a result, primate hosts capable of harbouring persistent, nonpathogenic viral infections may show an acute, transient immune response followed by minimal immune-related gene expression activity differences compared to uninfected controls (Simons et al., 2019). Similarly, in a mouse model of Ebola virus disease, tolerant animals demonstrate a carefully orchestrated immune gene expression response during the early stages of infection, whereas lethal outcomes are associated with larger amounts of differential gene expression at later time points, indicative of dysregulated inflammatory signaling (Price et al., 2020). *Peromyscus leucopus*, an important natural reservoir of *Borrelia burgdorferi*, the causative agent of Lyme disease, also adopts a restrained immune and inflammatory response to infection (Long et al., 2019). Finally, dampened inflammatory responses in bat cells following immune challenge are thought to promote tolerance to viral infections (Ahn et al., 2019; Guito et al., 2021; Xie et al., 2018), partly explaining bats' important role in emerging zoonotic diseases (Brook & Dobson, 2015; Hayman, 2019; Irving et al., 2021). In sum,

these examples suggest that, depending upon the disease system and sampling timeframe, wildlife disease researchers should adopt a broad perspective on what may constitute an effective host response to pathogen challenge, including responses with relatively limited immune system recruitment and inflammation (Medzhitov et al., 2012; Savage et al., 2020; Viney et al., 2005).

We must also recognize that the gene expression changes detected in disease-resistant hosts, while quite minimal in many cases, may indeed be the primary responses of interest. In other words, limited change in gene expression activity does not necessarily imply limited importance of those changes. For example, successful disease defence could occur through the activity of only a small number of genes with substantial effects (Simons et al., 2019), although genes with large fitness impacts tend to be rare (Evans, 2015). Further, while muted gene expression responses to pathogen challenge are certainly not always protective (Farrer et al., 2017), they can be carefully tailored, beneficial strategies, particularly in cases where the focal pathogen drives immunosuppression in the host (Figure 2). For example, Bonneaud et al. (2012) were interested in the host immune processes that determine mycoplasmosis development in experienced (resistant) and naïve (susceptible) populations of house finches. While naïve birds showed downregulation of immune genes through both experimental time points, birds from resistant populations showed no detectable downregulation in immune genes during the experiment. The authors interpreted the relative stability in gene regulation in resistant host individuals as evidence of a beneficial host response that counteracted parasite-mediated immune manipulation. Thus, disease ecologists should recognize that valuable insight may be extracted from gene expression studies even when disease-resistant hosts show little gene expression change. However, this will require moving beyond gross comparisons of exposure response among species towards dissection of the genes that are dysregulated in susceptible hosts yet remain unaffected in resistant conspecifics.

Given that existing evidence suggests wildlife disease researchers should expect potentially subtle gene expression signals of host response, future studies attempting to parse host susceptibility need to craft the temporal aspect of their sampling regimes to adequately characterize such responses. Although genomic-scale methods have rapidly decreased in cost, researchers still face economic and other logistical constraints in study design that may limit the number of samples they collect (Alvarez et al., 2015). In addition, when pathogen exposure experiments are coupled with gene expression analyses, there are critical choices to be made regarding the timing and circumstances of tissue sampling. Does one attempt to collect tissues at the onset of clinical symptoms in any of the study organisms (as in Poorten & Rosenblum, 2016) or at predetermined time points for all host treatments (as in Eskew et al., 2018)? The former choice seems to guarantee data collection at a time when at least some hosts may be responding to pathogen challenge but risks overlooking the critical initial surges in a potential cascade of gene expression changes (Alvarez et al., 2015; Grogan, Cashins, et al., 2018; Zamudio et al., 2020). Similarly, the latter choice could generate gene expression assays that miss the most relevant time periods for disease response if disease progresses faster or slower than expected.

There is no simple resolution for this dilemma, but the data synthesized here suggest that greater attention to gene expression responses earlier in disease time-courses may be broadly warranted (Figure 1a). In the studies we summarized that involved temporally-stratified sampling, both susceptible and nonsusceptible hosts generally exhibited decreasing differential expression over time following exposure, suggesting there is valuable gene regulatory activity to assay in the earliest stages of pathogen response (Bracamonte et al., 2019; Eskew et al., 2018; Sutherland et al., 2014). Bolstering this argument, Grogan, Cashins, et al. (2018), in an investigation of multiple frog populations exposed to the amphibian pathogen *Bd*, explicitly advocate for the study of early transcriptomic responses, thereby avoiding undue focus on gene expression late in disease progression which may largely reflect nonprotective immunopathology (Grogan et al., 2020; Zamudio et al., 2020). Of course, this strategy could run the risk of overcorrection: in some systems and tissues, sampling early in the disease time-course can result in no detectable gene expression change at all (Rosenblum et al., 2009, 2012).

This design dilemma may be partially resolved through careful consideration of the disease system, pathogen type, and potential host defences under investigation. Sample timing can be informed by baseline disease data, either on symptoms and clinical course from captive animals or, potentially, longitudinal sampling of wild hosts. Further, animals possess a diverse suite of immune defences, and distinct pathogen threats may be met with different types of immune responses over varying timescales (Rollins-Smith, 2020; Rollins-Smith et al., 2011; Spellberg & Edwards, 2001; Sutherland et al., 2014; Turchetto et al., 2020; Viney et al., 2005). Ideally, prior information about the specific host responses likely to be at play will help guide decisions about how sampling effort can be best allocated in any gene expression study with a time-course design.

4.2 | The importance of constitutive gene expression

Analyses contrasting gene expression responses of hosts to pathogen exposure could overlook a critical possibility: the relevant genetic features leading to species-specific disease outcomes may in fact be constitutively expressed. In depth study of gene expression in model organisms has shown that genes with functional importance for coping with environmental challenges tend to be those that are stably expressed yet serve to modify the activity of a large number of other genes (Evans, 2015). Similarly, constitutively expressed genes might play a major role in the specific context of pathogen response (Fuess et al., 2020; Hamilton et al., 2008). For example, bats are known to host a diverse suite of zoonotic viruses with aclinical infections, and constitutive expression of interferon (a signaling molecule of the innate immune system) is hypothesized to contribute to limited viral pathology in some bat taxa (Hayman, 2019; Irving et al., 2021; Zhou et al., 2016). Although some of the

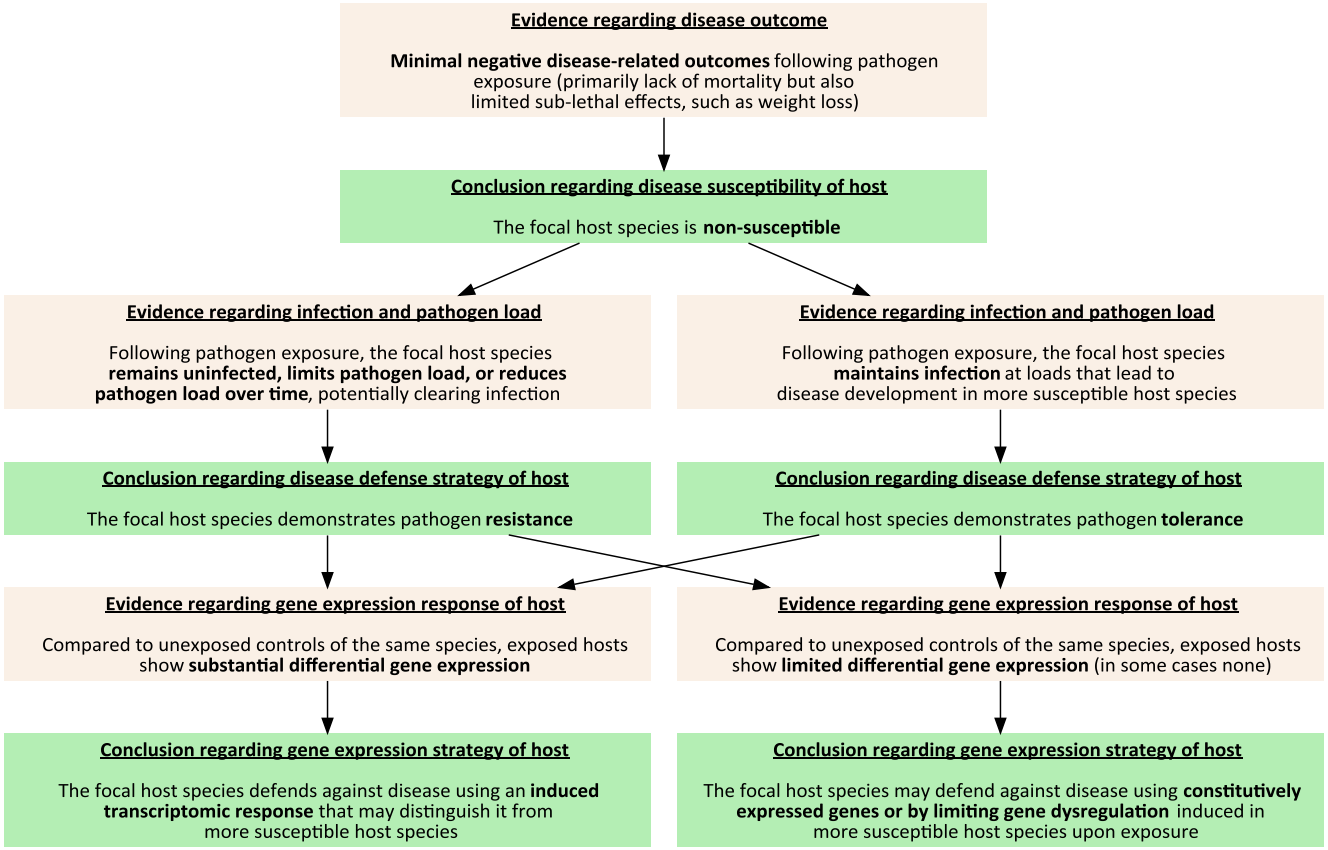

FIGURE 2 Flow diagram illustrating potential evidence and conclusions in gene expression studies of nonsusceptible wildlife host species' response to pathogen challenge. Evidence, in the form of hypothetical experimental observations, is highlighted in the tan boxes, while the implications of such evidence for wildlife disease outcome and defence are shown in the green boxes [Colour figure can be viewed at wileyonlinelibrary.com]

research reviewed here has speculated on the importance of constitutive, species-specific host defences (Eskew et al., 2018), rarely do wildlife disease studies follow the lead of other ecological genomics subfields and explicitly consider baseline differences in gene expression profiles among the host species of interest (Maynard et al., 2018; Rivera et al., 2021), even as such differences have provided key insights into the role of plasticity in local adaptation (Velotta & Cheviron, 2018) and preformed defence strategies in plants (Grand et al., 2012; Peng et al., 2012).

Fortunately, this oversight has an easy remedy that may not place any additional burden on sample collection efforts but rather could be implemented at the data analysis stage. We recommend that future studies explicitly compare gene expression profiles between unexposed host individuals across species to identify any consistent differences in constitutive gene expression (Rivera et al., 2021). These gene sets, especially when supplemented with functional information, may suggest important elements of host-specific pathogen response that could otherwise be overlooked. While this is a potentially powerful analytical strategy, we also highlight the caveat that interspecific comparisons of basal gene expression profiles are less useful outside of rigorously controlled experimental contexts. For example, if host species of interest are sampled in the wild, constitutive gene expression between species is likely to differ due to a wide array of confounding environmental factors. Thus, if the goal is to understand baseline differences in gene expression that may contribute to distinct host defences, the most appropriate constitutive gene expression comparisons will be between individuals of different species that have been reared and maintained in captive conditions, where possible.

Additionally, network-based methods, such as weighted correlation network analysis, can help identify "genes that matter" and are not necessarily predicated on the detection of differential expression, thus facilitating the study of constitutive gene expression (Evans, 2015; Joehanes, 2018). Network approaches can be used in conjunction with gene set enrichment analyses to functionally categorize coregulated gene modules, helping to contextualize the biological processes involved in genetic dysregulation and characterize important systemic responses to stressors that may not have been detected from differential expression alone (Fraser et al., 2018). Indeed, gene co-expression networks have been constructed in some of the work considered here with the explicit goal of identifying interacting genes that might be overlooked in typical differential expression analyses (Ellison et al., 2015). In general, however, network-based methods remain underutilized in wildlife disease transcriptomic studies. Finally, analysis of differential isoform usage (Davidson et al., 2017) could identify genes for which there

is no differential gene expression (i.e., constitutive gene expression) but where isoform variants may be differentially expressed, with potential functional consequences for host response to pathogen challenge (Shelley et al., 2013). Given that studies of other environmental stressors often find that constitutively expressed genes actually have the strongest links to organismal fitness (Barshis et al., 2013; Evans, 2015; Geisel, 2011), investigation of constitutive gene expression, regardless of the specific approach used, is a particularly critical addition to the analytical toolbox of wildlife disease ecologists.

Interpretation of host-pathogen studies is further complicated by the fact that nonsusceptible hosts may respond to pathogen challenge with two distinct defence strategies: resistance strategies seek to minimize or eliminate pathogen burden, while tolerance strategies serve to minimize the negative health impacts of a given pathogen burden (Bonneaud et al., 2019; Read et al., 2008; Schneider & Ayres, 2008). Both mechanisms can contribute to better disease outcome for the host and thus can sometimes be glossed over in discussion of "nonsusceptible" hosts (Figure 2). This could be especially problematic in cases where individuals within a host species do not uniformly adopt either resistance or tolerance as a pathogen defence strategy. In these scenarios, divergent responses of nonsusceptible host individuals could hinder the detection of differential gene expression, which relies on consistent gene expression signals within treatment groups. We recommend that researchers pay special attention to this analytical hurdle, especially when the clinical disease courses of nonsusceptible hosts indicate a potential mix of resistance and tolerance strategies (Figure 2). Methods for dimensionality reduction applied to gene expression data, such as principal component analysis (PCA) and multidimensional scaling (MDS), may also give an initial indication as to whether individual hosts within treatment groups have similar or divergent gene expression profiles (e.g., Ellison et al., 2015; Eskew et al., 2018). Adding another layer of complexity, the two pathogen defence strategies are not mutually exclusive as the responses of nonsusceptible host species may be characterized by both increased resistance and tolerance relative to more susceptible hosts (Bonneaud et al., 2019; Davy et al., 2017; Eskew et al., 2015; Schneider & Ayres, 2008; Sutherland et al., 2014).

We suggest that either induced gene expression responses or constitutive gene expression could underlie both resistance and tolerance, and this is a major area of interest for further research (Figure 2). For example, there may be instances where host gene expression pathways that are activated upon pathogen exposure serve to limit either pathogen load (resistance) or host damage (tolerance). Yet it is also plausible that constitutive, species-specific defences could contribute to either of these two distinct defence strategies. Regardless of whether they drive pathogen resistance or tolerance, induced gene expression responses in nonsusceptible hosts highlight an obvious set of genes and pathways that are deserving of more detailed study, reinforcing the utility of comparative transcriptomics as a valuable methodology in wildlife disease. By contrast, when tolerant hosts show limited differential gene expression following exposure, we suggest that constitutively expressed genes may be involved in pathogen response and should therefore be subject to further investigation (Figure 2). The same may be said of cases where limited host gene expression responses are accompanied by observations of low or no pathogen loads (i.e., host resistance), but this particular scenario may also point to the importance of gross morphology, such as skin structure in the case of epidermal pathogens, in limiting initial pathogen establishment (Davy et al., 2020; Eskew et al., 2018; Ohmer et al., 2017; Van Rooij et al., 2012).

4.3 | Considering other study designs and molecular methods

Species-level gene expression studies are but one of several viable approaches available to disease ecologists interested in differential disease outcome. While interspecific transcriptomic comparisons can be quite powerful (Evans, 2015), designs targeting intraspecific differences can also be used to address key questions in wildlife disease. These investigations are particularly informative when they contrast populations with varying historical pathogen exposure regimes: persistent exposure may drive divergence in gene expression, including gene regulation differences associated with the evolution of host resistance, which population-level gene expression assays can dissect (Bonneaud et al., 2012; Campbell et al., 2018; Grogan, Cashins, et al., 2018; Ronza et al., 2018). Such approaches have been used to identify genes in exposed populations that are potential targets of selection for host resistance, even when the history of exposure is relatively brief in an evolutionary sense (i.e., decades). As with interspecific designs, intraspecific studies will be most informative when study organisms are selected and managed in order to reduce individual-level variation in basic biological factors such as age, sex, and reproductive status, thereby better isolating disease outcome as the primary characteristic that varies across host groups.

Looking beyond gene regulation as the primary molecular process of interest, genomic (Blanchong et al., 2016; Longo et al., 2014), epigenomic (Bandyopadhaya et al., 2016; Garcia et al., 2019), proteomic (Heck & Neely, 2020; Horvatić et al., 2016; Neely et al., 2021), and metabolomic (Grogan, Skerratt, et al., 2018) methods are also highly relevant to the study of host-pathogen interactions and wildlife disease outcome. For example, genomic methods commonly used to parse organismal adaptation to environmental stressors, such as genome-wide association mapping and selection scans (Brennan et al., 2018; Elbers et al., 2018; Reid et al., 2016), can identify loci that are under selection due to pathogen pressure (Alves et al., 2019; Auteri & Knowles, 2020; Gignoux-Wolfsohn et al., 2021; Gupta et al., 2020; Schwensow et al., 2020). It is worth noting that selection scans, like gene expression assays, are often employed without regard to the specific phenotypes that contribute to the ecological outcomes of interest (i.e., disease susceptibility) (Brennan et al., 2018). Consequently, the identification of loci under selection may only hint at the particular host defence mechanisms that underlie

disease response, necessitating follow-up studies. Unlike gene expression methods, however, selection scans are explicitly focused on identifying genomic regions that show evidence of adaptive change, a potential benefit of the approach. Further, epigenomic alterations, such as DNA methylation, may have important influences on host resistance to pathogens (Garcia et al., 2019). In some instances, host methylation patterns can also be directly modified by the pathogen, highlighting the complex interplay of host and pathogen contributions that shape host susceptibility (Bandyopadhaya et al., 2016). Because epigenomic methods can make effective use of nonlethal samples, they may be particularly valuable additions to the toolkit of researchers studying cutaneous wildlife pathogens, such as the pathogenic fungi that cause several of the most severe wildlife diseases (Eskew & Todd, 2013; Fisher et al., 2012; Lorch et al., 2016).

While genomic, epigenomic, and transcriptomic methods have inferential value when they can be linked to disease outcomes of interest, looking above the level of gene expression, proteomic and metabolomic approaches move disease ecologists even closer towards a functional understanding of the suite of molecules that drive organismal disease response. Importantly, direct study of protein expression through proteomic methods mitigates a major inferential issue inherent in transcriptomic studies: mRNA abundance is only imperfectly correlated with protein abundance, which most proximately shapes phenotypes (Diz et al., 2012; Heck & Neely, 2020). Although proteomics is not without its own technical challenges and biases (Evans, 2015), its accessibility to disease ecologists will continue to expand rapidly (Heck & Neely, 2020; Müller et al., 2020). Already, proteomic methods have been applied to study non-model bat species in the white-nose syndrome disease system (Hecht-Höger et al., 2020); this research showed no protein expression change between uninfected and infected individuals of a disease-resistant host, *Myotis myotis*, findings that are congruent with some previous transcriptomic work on this species (Davy et al., 2017; Lilley et al., 2019). Indeed, proteomic data may be especially valuable when combined with transcriptomic data sets to build a strong evidence base regarding the key molecular pathways contributing to disease-related phenotypes (Ricci et al., 2019). A metabolomics perspective expands the protein-focused scope of proteomics out to all small molecules and has been used, for example, to better understand disease pathology in the amphibian-chytridiomycosis system (Grogan, Skerratt, et al., 2018). We end with the caveat that proteomics and metabolomics, indeed any "-omics" methodology, will be maximally useful only when the wildlife disease system of interest has been thoroughly characterized, including a basic understanding of disease progression and pathology, tissue tropism, species-specific clinical disease outcomes, and the potential relationship between pathogen dose and disease severity.

5 | CONCLUSIONS

Emerging diseases are increasingly significant threats to wildlife conservation (Smith et al., 2012; Tompkins et al., 2015), and infectious disease is likely to remain a primary conservation stressor given that climate change (Carlson et al., 2020) and globalized trade and transport (Liu et al., 2013; O'Hanlon et al., 2018; Yap et al., 2015) will continue to reshape host-pathogen associations with unprecedented speed. As such, timely scientific insight on factors driving host disease susceptibility is urgently needed to inform conservation management, and researchers have often turned to gene expression assays in the hopes of generating such information. While valuable contributions have already been made across multiple disease systems, investigations that harness gene expression methods remain limited compared to other ecological subfields. Undoubtedly, substantial knowledge gaps remain to be filled through further transcriptomic studies of wildlife disease that leverage the analytical approaches and insights of gene expression studies on other wildlife stressors (Fraser et al., 2018; Maynard et al., 2018; Velotta et al., 2018). The methodological advice offered here should inform the design of robust transcriptomic studies and will help wildlife disease researchers extract maximal information from the resulting data sets. When used in conjunction with complementary molecular methods, these strategies in gene expression assay design and analysis will facilitate a comprehensive understanding of host disease response that better contributes to wildlife conservation in a rapidly changing world.

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AUTHOR CONTRIBUTIONS

Evan A. Eskew, Devaughn Fraser, Maarten J. Vonhof, and Brooke Maslo conceived the idea for the article. Evan A. Eskew gathered and analysed the data for the quantitative summary and drafted the manuscript. Devaughn Fraser, Maarten J. Vonhof, Malin L. Pinsky, and Brooke Maslo made comments and edits that shaped the final version of the manuscript.

DATA AVAILABILITY STATEMENT

All data collated for use in the quantitative summary and R code to reproduce the analyses are freely available via GitHub at https://github.com/eveskew/wild_expression. Additionally, this repository and data therein are publicly archived on Zenodo (Eskew et al., 2021).

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REFERENCES

Ahn, M., Anderson, D. E., Zhang, Q., Tan, C. W., Lim, B. L., Luko, K., Wen, M., Chia, W. N., Mani, S., Wang, L. C., Ng, J. H. J., Sobota, R. M., Dutertre, C.-A., Ginhoux, F., Shi, Z.-L., Irving, A. T., & Wang, L.-F. (2019). Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. *Nature Microbiology*, *4*, 789–799. https://doi.org/10.1038/s41564-019-0371-3

Allendorf, F. W., Hohenlohe, P. A., & Luikart, G. (2010). Genomics and the future of conservation genetics. *Nature Reviews Genetics*, *11*, 697–709. https://doi.org/10.1038/nrg2844

Alvarez, M., Schrey, A. W., & Richards, C. L. (2015). Ten years of transcriptomics in wild populations: what have we learned about their ecology and evolution? *Molecular Ecology*, *24*, 710–725. https://doi.org/10.1111/mec.13055

Alves, J. M., Carneiro, M., Cheng, J. Y., Lemos de Matos, A., Rahman, M. M., Loog, L., Campos, P. F., Wales, N., Eriksson, A., Manica, A., Strive, T., Graham, S. C., Afonso, S., Bell, D. J., Belmont, L., Day, J. P., Fuller, S. J., Marchandeau, S., Palmer, W. J., … Jiggins, F. M. (2019). Parallel adaptation of rabbit populations to myxoma virus. *Science*, *363*, 1319–1326. https://doi.org/10.1126/science.aau7285

Auteri, G. G., & Knowles, L. L. (2020). Decimated little brown bats show potential for adaptive change. *Scientific Reports*, *10*, 3023. https://doi.org/10.1038/s41598-020-59797-4

Bandyopadhaya, A., Tsurumi, A., Maura, D., Jeffrey, K. L., & Rahme, L. G. (2016). A quorum-sensing signal promotes host tolerance training through HDAC1-mediated epigenetic reprogramming. *Nature Microbiology*, *1*, 16174. https://doi.org/10.1038/nmicrobiol.2016.174

Barreiro, L. B., & Tung, J. (2012). Getting under—and through—the skin: ecological genomics of chytridiomycosis infection in frogs. *Molecular Ecology*, *21*, 3095–3097. https://doi.org/10.1111/j.1365-294x.2012.05624.x

Barshis, D. J., Ladner, J. T., Oliver, T. A., Seneca, F. O., Traylor-Knowles, N., & Palumbi, S. R. (2013). Genomic basis for coral resilience to climate change. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 1387–1392. https://doi.org/10.1073/pnas.1210224110

Bernard, R. F., Reichard, J. D., Coleman, J. T. H., Blackwood, J. C., Verant, M. L., Segers, J. L., Lorch, J. M., White, J. P., Moore, M. S., Russell, A. L., Katz, R. A., Lindner, D. L., Toomey, R. S., Turner, G. G., Frick, W. F., Vonhof, M. J., Willis, C. K. R., & Grant, E. H. C. (2020). Identifying research needs to inform white-nose syndrome management decisions. *Conservation Science and Practice*, *2*, e220. https://doi.org/10.1111/csp2.220

Blanchong, J. A., Robinson, S. J., Samuel, M. D., & Foster, J. T. (2016). Application of genetics and genomics to wildlife epidemiology. *The Journal of Wildlife Management*, *80*, 593–608. https://doi.org/10.1002/jwmg.1064

Bolker, B. M., Brooks, M. E., Clark, C. J., Geange, S. W., Poulsen, J. R., Stevens, M. H. H., & White, J.-S. S. (2009). Generalized linear mixed models: a practical guide for ecology and evolution. *Trends in Ecology and Evolution*, *24*, 127–135. https://doi.org/10.1016/j.tree.2008.10.008

Bonneaud, C., Balenger, S. L., Zhang, J., Edwards, S. V., & Hill, G. E. (2012). Innate immunity and the evolution of resistance to an emerging infectious disease in a wild bird. *Molecular Ecology*, *21*, 2628–2639. https://doi.org/10.1111/j.1365-294X.2012.05551.x

Bonneaud, C., Tardy, L., Giraudeau, M., Hill, G. E., McGraw, K. J., & Wilson, A. J. (2019). Evolution of both host resistance and tolerance to an emerging bacterial pathogen. *Evolution Letters*, *3*, 544–554. https://doi.org/10.1002/evl3.133

Bracamonte, S. E., Johnston, P. R., Monaghan, M. T., & Knopf, K. (2019). Gene expression response to a nematode parasite in novel and native eel hosts. *Ecology and Evolution*, *9*, 13069–13084. https://doi.org/10.1002/ece3.5728

Brennan, R. S., Healy, T. M., Bryant, H. J., La, M. V., Schulte, P. M., & Whitehead, A. (2018). Integrative population and physiological genomics reveals mechanisms of adaptation in killifish. *Molecular Biology and Evolution*, *35*, 2639–2653. https://doi.org/10.1093/molbev/msy154

Brook, C. E., & Dobson, A. P. (2015). Bats as 'special' reservoirs for emerging zoonotic pathogens. *Trends in Microbiology*, *23*, 172–180. https://doi.org/10.1016/j.tim.2014.12.004

Campbell, L. J., Hammond, S. A., Price, S. J., Sharma, M. D., Garner, T. W. J., Birol, I., Helbing, C. C., Wilfert, L., & Griffiths, A. G. F. (2018). A novel approach to wildlife transcriptomics provides evidence of disease-mediated differential expression and changes to the microbiome of amphibian populations. *Molecular Ecology*, *27*, 1413–1427. https://doi.org/10.1111/mec.14528

Carlson, C. J., Albery, G. F., Merow, C., Trisos, C. H., Zipfel, C. M., Eskew, E. A., Olival, K. J., Ross, N., & Bansal, S. (2020). Climate change will drive novel cross-species viral transmission. *bioRxiv*, https://doi.org/10.1101/2020.01.24.918755.

Carpenter, B., Gelman, A., Hoffman, M. D., Lee, D., Goodrich, B., Betancourt, M., Brubaker, M. A., Guo, J., Li, P., & Riddell, A. (2017). Stan: a probabilistic programming language. *Journal of Statistical Software*, *76*, 1–32. https://doi.org/10.18637/jss.v076.i01

Chahroudi, A., Bosinger, S. E., Vanderford, T. H., Paiardini, M., & Silvestri, G. (2012). Natural SIV hosts: showing AIDS the door. *Science*, *335*, 1188–1193. https://doi.org/10.1126/science.1217550

Connon, R. E., Jeffries, K. M., Komoroske, L. M., Todgham, A. E., & Fangue, N. A. (2018). The utility of transcriptomics in fish conservation. *Journal of Experimental Biology*, *221*, jeb148833. https://doi.org/10.1242/jeb.148833

Daszak, P., Cunningham, A. A., & Hyatt, A. D. (2000). Emerging infectious diseases of wildlife - threats to biodiversity and human health. *Science*, *287*, 443–449. https://doi.org/10.1126/science.287.5452.443

Davidson, N. M., Hawkins, A. D. K., & Oshlack, A. (2017). SuperTranscripts: a data driven reference for analysis and visualisation of transcriptomes. *Genome Biology*, *18*, 148. https://doi.org/10.1186/s13059-017-1284-1

Davy, C. M., Donaldson, M. E., Bandouchova, H., Breit, A. M., Dorville, N. A. S., Dzal, Y. A., Kovacova, V., Kunkel, E. L., Martínková, N., Norquay, K. J. O., Paterson, J. E., Zukal, J., Pikula, J., Willis, C. K. R., & Kyle, C. J. (2020). Transcriptional host–pathogen responses of *Pseudogymnoascus destructans* and three species of bats with white-nose syndrome. *Virulence*, *11*, 781–794. https://doi.org/10.1080/21505594.2020.1768018

Davy, C. M., Donaldson, M. E., Willis, C. K. R., Saville, B. J., McGuire, L. P., Mayberry, H., Wilcox, A., Wibbelt, G., Misra, V., Bollinger, T., & Kyle, C. J. (2017). The other white-nose syndrome transcriptome: Tolerant and susceptible hosts respond differently to the pathogen *Pseudogymnoascus destructans*. *Ecology and Evolution*, *7*, 7161–7170. https://doi.org/10.1002/ece3.3234

DeCandia, A. L., Dobson, A. P., & vonHoldt, B. M. (2018). Toward an integrative molecular approach to wildlife disease. *Conservation Biology*, *32*, 798–807. https://doi.org/10.1111/cobi.13083

Diz, A. P., Martínez-Fernández, M., & Rolán-Alvarez, E. (2012). Proteomics in evolutionary ecology: linking the genotype with phenotype. *Molecular Ecology*, *21*, 1060–1080. https://doi.org/10.1111/j.1365-294X.2011.05426.x

Ekblom, R., & Galindo, J. (2011). Applications of next generation sequencing in molecular ecology of non-model organisms. *Heredity*, *107*, 1–15. https://doi.org/10.1038/hdy.2010.152

Elbers, J. P., Brown, M. B., & Taylor, S. S. (2018). Identifying genome-wide immune gene variation underlying infectious disease in wildlife populations – a next generation sequencing approach in the gopher tortoise. *BMC Genomics*, *19*, 64. https://doi.org/10.1186/s12864-018-4452-0

Ellison, A. R., Tunstall, T., DiRenzo, G. V., Hughey, M. C., Rebollar, E. A., Belden, L. K., Harris, R. N., Ibáñez, R., Lips, K. R., & Zamudio, K. R. (2015). More than skin deep: functional genomic basis for resistance to amphibian chytridiomycosis. *Genome Biology and Evolution*, *7*, 286–298. https://doi.org/10.1093/gbe/evu285

Eskew, E. A., Fraser, D., Vonhof, M. J., Pinsky, M. L., & Maslo, B. (2021). *wild_expression: gene expression data on wildlife hosts of emerging infectious diseases (Version 1.2.0)*. Zenodo. https://doi.org/10.5281/zenodo.5204652.

Eskew, E. A., Shock, B. C., LaDouceur, E. E. B., Keel, K., Miller, M. R., Foley, J. E., & Todd, B. D. (2018). Gene expression differs in susceptible and resistant amphibians exposed to *Batrachochytrium dendrobatidis*. *Royal Society Open Science*, *5*, 170910. https://doi.org/10.1098/rsos.170910

Eskew, E. A., & Todd, B. D. (2013). Parallels in amphibian and bat declines from pathogenic fungi. *Emerging Infectious Diseases*, *19*, 379–385. https://doi.org/10.3201/eid1903.120707

Eskew, E. A., Worth, S. J., Foley, J. E., & Todd, B. D. (2015). American bullfrogs (*Lithobates catesbeianus*) resist infection by multiple isolates of *Batrachochytrium dendrobatidis*, including one implicated in wild mass mortality. *EcoHealth*, *12*, 513–518. https://doi.org/10.1007/s10393-015-1035-2

Evans, T. G. (2015). Considerations for the use of transcriptomics in identifying the 'genes that matter' for environmental adaptation. *Journal of Experimental Biology*, *218*, 1925–1935. https://doi.org/10.1242/jeb.114306

Farrer, R. A., Martel, A., Verbrugghe, E., Abouelleil, A., Ducatelle, R., Longcore, J. E., James, T. Y., Pasmans, F., Fisher, M. C., & Cuomo, C. A. (2017). Genomic innovations linked to infection strategies across emerging pathogenic chytrid fungi. *Nature Communications*, *8*, 14742. https://doi.org/10.1038/ncomms14742

Fisher, M. C., Henk, D. A., Briggs, C. J., Brownstein, J. S., Madoff, L. C., McCraw, S. L., & Gurr, S. J. (2012). Emerging fungal threats to animal, plant and ecosystem health. *Nature*, *484*, 186–194. https://doi.org/10.1038/nature10947

Fraser, D., Mouton, A., Serieys, L. E. K., Cole, S., Carver, S., Vandewoude, S., Lappin, M., Riley, S. P. D., & Wayne, R. (2018). Genome-wide expression reveals multiple systemic effects associated with detection of anticoagulant poisons in bobcats (*Lynx rufus*). *Molecular Ecology*, *27*, 1170–1187. https://doi.org/10.1111/mec.14531

Frick, W. F., Puechmaille, S. J., Hoyt, J. R., Nickel, B. A., Langwig, K. E., Foster, J. T., Barlow, K. E., Bartonička, T., Feller, D., Haarsma, A.-J., Herzog, C., Horáček, I., van der Kooij, J., Mulkens, B., Petrov, B., Reynolds, R., Rodrigues, L., Stihler, C. W., Turner, G. G., & Kilpatrick, A. M. (2015). Disease alters macroecological patterns of North American bats. *Global Ecology and Biogeography*, *24*, 741–749. https://doi.org/10.1111/geb.12290

Fritze, M., Costantini, D., Fickel, J., Wehner, D., Czirják, G. Á., & Voigt, C. C. (2019). Immune response of hibernating European bats to a fungal challenge. *Biology Open*, *8*, bio046078. https://doi.org/10.1242/bio.046078

Fuess, L. E., Pinzón C, J. H., Weil, E., Grinshpon, R. D., & Mydlarz, L. D. (2017). Life or death: disease-tolerant coral species activate autophagy following immune challenge. *Proceedings of the Royal Society B*, *284*, 20170771. https://doi.org/10.1098/rspb.2017.0771

Fuess, L. E., Weber, J. N., den Haan, S., Steinel, N. C., Shim, K. C., & Bolnick, D. I. (2020). A test of the Baldwin Effect: Differences in both constitutive expression and inducible responses to parasites underlie variation in host response to a parasite. bioRxiv, 2020.07.29.216531. https://doi.org/10.1101/2020.07.29.216531

Garcia, M. J., Rodríguez-Brenes, S., Kobisk, A., Adler, L., Ryan, M. J., Taylor, R. C., & Hunter, K. L. (2019). Epigenomic changes in the túngara frog (*Physalaemus pustulosus*): possible effects of introduced fungal pathogen and urbanization. *Evolutionary Ecology*, *33*, 671–686. https://doi.org/10.1007/s10682-019-10001-8

Geisel, N. (2011). Constitutive versus responsive gene expression strategies for growth in changing environments. *PLoS One*, *6*, e27033. https://doi.org/10.1371/journal.pone.0027033

Gelman, A., & Rubin, D. B. (1992). Inference from iterative simulation using multiple sequences. *Statistical Science*, *7*, 457–511. https://doi.org/10.1214/ss/1177011136

Gervasi, S. S., Civitello, D. J., Kilvitis, H. J., & Martin, L. B. (2015). The context of host competence: a role for plasticity in host–parasite dynamics. *Trends in Parasitology*, *31*, 419–425. https://doi.org/10.1016/j.pt.2015.05.002

Gewin, V. (2008). Riders of a modern-day ark. *PLoS Biology*, *6*, e24. https://doi.org/10.1371/journal.pbio.0060024

Gignoux-Wolfsohn, S. A., Pinsky, M. L., Kerwin, K., Herzog, C., Hall, M., Bennett, A. B., Fefferman, N. H., & Maslo, B. (2021). Genomic signatures of selection in bats surviving white-nose syndrome. *Molecular Ecology*, https://doi.org/10.1111/mec.15813

Grand, X., Espinoza, R., Michel, C., Cros, S., Chalvon, V., Jacobs, J., & Morel, J. B. (2012). Identification of positive and negative regulators of disease resistance to rice blast fungus using constitutive gene expression patterns. *Plant Biotechnology Journal*, *10*, 840–850. https://doi.org/10.1111/j.1467-7652.2012.00703.x

Greenwood, J. M., Ezquerra, A. L., Behrens, S., Branca, A., & Mallet, L. (2016). Current analysis of host–parasite interactions with a focus on next generation sequencing data. *Zoology*, *119*, 298–306. https://doi.org/10.1016/j.zool.2016.06.010

Grogan, L. F., Cashins, S. D., Skerratt, L. F., Berger, L., McFadden, M. S., Harlow, P., Hunter, D. A., Scheele, B. C., & Mulvenna, J. (2018). Evolution of resistance to chytridiomycosis is associated with a robust early immune response. *Molecular Ecology*, *27*, 919–934. https://doi.org/10.1111/mec.14493

Grogan, L. F., Humphries, J. E., Robert, J., Lanctôt, C. M., Nock, C. J., Newell, D. A., & McCallum, H. I. (2020). Immunological aspects of chytridiomycosis. *Journal of Fungi*, *6*, 234. https://doi.org/10.3390/jof6040234

Grogan, L. F., Skerratt, L. F., Berger, L., Cashins, S. D., Trengove, R. D., & Gummer, J. P. A. (2018). Chytridiomycosis causes catastrophic organism-wide metabolic dysregulation including profound failure of cellular energy pathways. *Scientific Reports*, *8*, 8188. https://doi.org/10.1038/s41598-018-26427-z

Guito, J. C., Prescott, J. B., Arnold, C. E., Amman, B. R., Schuh, A. J., Spengler, J. R., Sealy, T. K., Harmon, J. R., Coleman-McCray, J. A. D., Kulcsar, K. A., Nagle, E. R., Kumar, R., Palacios, G. F., Sanchez-Lockhart, M., & Towner, J. S. (2021). Asymptomatic infection of Marburg virus reservoir bats is explained by a strategy of immunoprotective disease tolerance. *Current Biology*, *31*, 257–270.e5. https://doi.org/10.1016/j.cub.2020.10.015

Gupta, P., Robin, V. V., & Dharmarajan, G. (2020). Towards a more healthy conservation paradigm: integrating disease and molecular ecology to aid biological conservation. *Journal of Genetics*, *99*, 65. https://doi.org/10.1007/s12041-020-01225-7

Hamilton, R., Siva-Jothy, M., & Boots, M. (2008). Two arms are better than one: parasite variation leads to combined inducible and constitutive innate immune responses. *Proceedings of the Royal Society B*, *275*, 937–945. https://doi.org/10.1098/rspb.2007.1574

Harrison, X. A., Donaldson, L., Correa-Cano, M. E., Evans, J., Fisher, D. N., Goodwin, C. E. D., Robinson, B. S., Hodgson, D. J., & Inger, R. (2018). A brief introduction to mixed effects modelling and multi-model inference in ecology. *PeerJ*, *6*, e4794. https://doi.org/10.7717/peerj.4794

Harrisson, K. A., Pavlova, A., Telonis-Scott, M., & Sunnucks, P. (2014). Using genomics to characterize evolutionary potential for conservation of wild populations. *Evolutionary Applications*, *7*, 1008–1025. https://doi.org/10.1111/eva.12149

Hayman, D. T. S. (2019). Bat tolerance to viral infections. *Nature Microbiology*, *4*, 728–729. https://doi.org/10.1038/s41564-019-0430-9

Hecht-Höger, A. M., Braun, B. C., Krause, E., Meschede, A., Krahe, R., Voigt, C. C., Greenwood, A. D., & Czirják, G. Á. (2020). Plasma proteomic profiles differ between European and North American myotid bats colonized by *Pseudogymnoascus destructans*. *Molecular Ecology*, *29*, 1745–1755. https://doi.org/10.1111/mec.15437

Heck, M., & Neely, B. A. (2020). Proteomics in non-model organisms: a new analytical frontier. *Journal of Proteome Research*, *19*, 3595–3606. https://doi.org/10.1021/acs.jproteome.0c00448

Horvatić, A., Kuleš, J., Guillemin, N., Galan, A., Mrljak, V., & Bhide, M. (2016). High-throughput proteomics and the fight against pathogens. *Molecular BioSystems*, *12*, 2373–2384. https://doi.org/10.1039/C6MB00223D

Irving, A. T., Ahn, M., Goh, G., Anderson, D. E., & Wang, L.-F. (2021). Lessons from the host defences of bats, a unique viral reservoir. *Nature*, *589*, 363–370. https://doi.org/10.1038/s41586-020-03128-0

Jenner, R. G., & Young, R. A. (2005). Insights into host responses against pathogens from transcriptional profiling. *Nature Reviews Microbiology*, *3*, 281–294. https://doi.org/10.1038/nrmicro1126

Joehanes, R. (2018). Network analysis of gene expression. In N. Raghavachari, & N. Garcia-Reyero (Eds.), *Gene Expression Analysis: Methods and Protocols* (pp. 325–341). Humana Press.

Langwig, K. E., Voyles, J., Wilber, M. Q., Frick, W. F., Murray, K. A., Bolker, B. M., Collins, J. P., Cheng, T. L., Fisher, M. C., Hoyt, J. R., Lindner, D. L., McCallum, H. I., Puschendorf, R., Rosenblum, E. B., Toothman, M., Willis, C. K. R., Briggs, C. J., & Kilpatrick, A. M. (2015). Context-dependent conservation responses to emerging wildlife diseases. *Frontiers in Ecology and the Environment*, *13*, 195–202. https://doi.org/10.1890/140241

Lilley, T. M., Prokkola, J. M., Blomberg, A. S., Paterson, S., Johnson, J. S., Turner, G. G., Bartonička, T., Bachorec, E., Reeder, D. M., & Field, K. A. (2019). Resistance is futile: RNA-sequencing reveals differing responses to bat fungal pathogen in Nearctic *Myotis lucifugus* and Palearctic *Myotis myotis*. *Oecologia*, *191*, 295–309. https://doi.org/10.1007/s00442-019-04499-6

Liu, X., Rohr, J. R., & Li, Y. (2013). Climate, vegetation, introduced hosts and trade shape a global wildlife pandemic. *Proceedings of the Royal Society B*, *280*, 20122506. https://doi.org/10.1098/rspb.2012.2506

Lloyd-Smith, J. O., Schreiber, S. J., Kopp, P. E., & Getz, W. M. (2005). Superspreading and the effect of individual variation on disease emergence. *Nature*, *438*, 355–359. https://doi.org/10.1038/nature04153

Long, A. D., Baldwin-Brown, J., Tao, Y., Cook, V. J., Balderrama-Gutierrez, G., Corbett-Detig, R., Mortazavi, A., & Barbour, A. G. (2019). The genome of *Peromyscus leucopus*, natural host for Lyme disease and other emerging infections. *Science Advances*, *5*, eaaw6441. https://doi.org/10.1126/sciadv.aaw6441

Longo, A. V., Burrowes, P. A., & Zamudio, K. R. (2014). Genomic studies of disease-outcome in host–pathogen dynamics. *Integrative and Comparative Biology*, *54*, 427–438. https://doi.org/10.1093/icb/icu073

Lorch, J. M., Knowles, S., Lankton, J. S., Michell, K., Edwards, J. L., Kapfer, J. M., Staffen, R. A., Wild, E. R., Schmidt, K. Z., Ballmann, A. E., Blodgett, D., Farrell, T. M., Glorioso, B. M., Last, L. A., Price, S. J., Schuler, K. L., Smith, C. E., Wellehan, J. F. X., & Blehert, D. S. (2016). Snake fungal disease: an emerging threat to wild snakes. *Philosophical Transactions of the Royal Society B*, *371*, 20150457. https://doi.org/10.1098/rstb.2015.0457

Lozier, J. D., & Zayed, A. (2017). Bee conservation in the age of genomics. *Conservation Genetics*, *18*, 713–729. https://doi.org/10.1007/s10592-016-0893-7

Martel, A., Blooi, M., Adriaensen, C., Van Rooij, P., Beukema, W., Fisher, M. C., Farrer, R. A., Schmidt, B. R., Tobler, U., Goka, K., Lips, K. R., Muletz, C., Zamudio, K. R., Bosch, J., Lötters, S., Wombwell, E., Garner, T. W. J., Cunningham, A. A., Spitzen-van der Sluijs, A., … Pasmans, F. (2014). Recent introduction of a chytrid fungus endangers Western Palearctic salamanders. *Science*, *346*, 630–631. https://doi.org/10.1126/science.1258268

Maynard, A., Bible, J. M., Pespeni, M. H., Sanford, E., & Evans, T. G. (2018). Transcriptomic responses to extreme low salinity among locally adapted populations of Olympia oyster (*Ostrea lurida*). *Molecular Ecology*, *27*, 4225–4240. https://doi.org/10.1111/mec.14863

McCallum, H. (2008). Tasmanian devil facial tumour disease: lessons for conservation biology. *Trends in Ecology and Evolution*, *23*, 631–637. https://doi.org/10.1016/j.tree.2008.07.001

McElreath, R. (2016). *Statistical Rethinking: A Bayesian Course with Examples in R and Stan*. CRC Press.

McElreath, R. (2020). rethinking: Statistical Rethinking book package. R package version 2.01.

Medzhitov, R., Schneider, D. S., & Soares, M. P. (2012). Disease tolerance as a defense strategy. *Science*, *335*, 936–941. https://doi.org/10.1126/science.1214935

Müller, J. B., Geyer, P. E., Colaço, A. R., Treit, P. V., Strauss, M. T., Oroshi, M., Doll, S., Winter, S. V., Bader, J. M., Köhler, N., Theis, F., Santos, A., & Mann, M. (2020). The proteome landscape of the kingdoms of life. *Nature*, *582*, 592–596. https://doi.org/10.1038/s41586-020-2402-x

Neely, B. A., Janech, M. G., Fenton, M. B., Simmons, N. B., Bland, A. M., & Becker, D. J. (2021). Surveying the vampire bat (*Desmodus rotundus*) serum proteome: a resource for identifying immunological proteins and detecting pathogens. *Journal of Proteome Research*, *20*, 2547–2559. https://doi.org/10.1021/acs.jproteome.0c00995

O'Hanlon, S. J., Rieux, A., Farrer, R. A., Rosa, G. M., Waldman, B., Bataille, A., Kosch, T. A., Murray, K. A., Brankovics, B., Fumagalli, M., Martin, M. D., Wales, N., Alvarado-Rybak, M., Bates, K. A., Berger, L., Böll, S., Brookes, L., Clare, F., Courtois, E. A., … Fisher, M. C. (2018). Recent Asian origin of chytrid fungi causing global amphibian declines. *Science*, *360*, 621–627. https://doi.org/10.1126/science.aar1965

Ohmer, M. E. B., Cramp, R. L., Russo, C. J. M., White, C. R., & Franklin, C. E. (2017). Skin sloughing in susceptible and resistant amphibians regulates infection with a fungal pathogen. *Scientific Reports*, *7*, 3529. https://doi.org/10.1038/s41598-017-03605-z

Pemberton, J. M., Beraldi, D., Craig, B. H., & Hopkins, J. (2011). Digital gene expression analysis of gastrointestinal helminth resistance in Scottish blackface lambs. *Molecular Ecology*, *20*, 910–919. https://doi.org/10.1111/j.1365-294X.2010.04992.x

Peng, X., Hu, Y., Tang, X., Zhou, P., Deng, X., Wang, H., & Guo, Z. (2012). Constitutive expression of rice *WRKY30* gene increases the endogenous jasmonic acid accumulation, *PR* gene expression and resistance to fungal pathogens in rice. *Planta*, *236*, 1485–1498. https://doi.org/10.1007/s00425-012-1698-7

Poorten, T. J., & Rosenblum, E. B. (2016). Comparative study of host response to chytridiomycosis in a susceptible and a resistant toad species. *Molecular Ecology*, *25*, 5663–5679. https://doi.org/10.1111/mec.13871

Price, A., Okumura, A., Haddock, E., Feldmann, F., Meade-White, K., Sharma, P., Artami, M., Lipkin, W. I., Threadgill, D. W., Feldmann, H., & Rasmussen, A. L. (2020). Transcriptional correlates of tolerance and lethality in mice predict Ebola virus disease patient outcomes. *Cell Reports*, *30*, 1702–1713.e6. https://doi.org/10.1016/j.celrep.2020.01.026

Read, A. F., Graham, A. L., & Råberg, L. (2008). Animal defenses against infectious agents: is damage control more important than pathogen control? *PLoS Biology*, *6*, e1000004. https://doi.org/10.1371/journal.pbio.1000004

Reid, N. M., Proestou, D. A., Clark, B. W., Warren, W. C., Colbourne, J. K., Shaw, J. R., Karchner, S. I., Hahn, M. E., Nacci, D., Oleksiak, M. F., Crawford, D. L., & Whitehead, A. (2016). The genomic landscape

of rapid repeated evolutionary adaptation to toxic pollution in wild fish. *Science*, *354*, 1305–1308. https://doi.org/10.1126/science.aah4993

Ricci, C. A., Kamal, A. H. M., Chakrabarty, J. K., Fuess, L. E., Mann, W. T., Jinks, L. R., Brinkhuis, V., Chowdhury, S. M., & Mydlarz, L. D. (2019). Proteomic investigation of a diseased gorgonian coral indicates disruption of essential cell function and investment in inflammatory and other immune processes. *Integrative and Comparative Biology*, *59*, 830–844. https://doi.org/10.1093/icb/icz107

Rivera, H. E., Aichelman, H. E., Fifer, J. E., Kriefall, N. G., Wuitchik, D. M., Wuitchik, S. J. S., & Davies, S. W. (2021). A framework for understanding gene expression plasticity and its influence on stress tolerance. *Molecular Ecology*, *30*, 1381–1397. https://doi.org/10.1111/mec.15820

Rollins-Smith, L. A. (2020). Global amphibian declines, disease, and the ongoing battle between *Batrachochytrium* fungi and the immune system. *Herpetologica*, *76*, 178–188. https://doi.org/10.1655/0018-0831-76.2.178

Rollins-Smith, L. A., Ramsey, J. P., Pask, J. D., Reinert, L. K., & Woodhams, D. C. (2011). Amphibian immune defenses against chytridiomycosis: impacts of changing environments. *Integrative and Comparative Biology*, *51*, 552–562. https://doi.org/10.1093/icb/icr095

Ronza, P., Cao, A., Robledo, D., Gómez-Tato, A., Álvarez-Dios, J. A., Hasanuzzaman, A. F. M., Quiroga, M. I., Villalba, A., Pardo, B. G., & Martínez, P. (2018). Long-term affected flat oyster (*Ostrea edulis*) haemocytes show differential gene expression profiles from naïve oysters in response to *Bonamia ostreae*. *Genomics*, *110*, 390–398. https://doi.org/10.1016/j.ygeno.2018.04.002

Rosenblum, E. B., Poorten, T. J., Settles, M., & Murdoch, G. K. (2012). Only skin deep: shared genetic response to the deadly chytrid fungus in susceptible frog species. *Molecular Ecology*, *21*, 3110–3120. https://doi.org/10.1111/j.1365-294X.2012.05481.x

Rosenblum, E. B., Poorten, T. J., Settles, M., Murdoch, G. K., Robert, J., Maddox, N., & Eisen, M. B. (2009). Genome-wide transcriptional response of *Silurana* (*Xenopus*) *tropicalis* to infection with the deadly chytrid fungus. *PLoS One*, *4*, e6494. https://doi.org/10.1371/journal.pone.0006494

Savage, A. E., Gratwicke, B., Hope, K., Bronikowski, E., & Fleischer, R. C. (2020). Sustained immune activation is associated with susceptibility to the amphibian chytrid fungus. *Molecular Ecology*, *29*, 2889–2903. https://doi.org/10.1111/mec.15533

Schneider, D. S., & Ayres, J. S. (2008). Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. *Nature Reviews Immunology*, *8*, 889–895. https://doi.org/10.1038/nri2432

Schwensow, N., Pederson, S., Peacock, D., Cooke, B., & Cassey, P. (2020). Adaptive changes in the genomes of wild rabbits after 16 years of viral epidemics. *Molecular Ecology*, *29*, 3777–3794. https://doi.org/10.1111/mec.15498

Shelley, L. K., Osachoff, H. L., van Aggelen, G. C., Ross, P. S., & Kennedy, C. J. (2013). Alteration of immune function endpoints and differential expression of estrogen receptor isoforms in leukocytes from 17β-estradiol exposed rainbow trout (*Oncorhynchus mykiss*). *General and Comparative Endocrinology*, *180*, 24–32. https://doi.org/10.1016/j.ygcen.2012.09.014

Shepack, A., & Catenazzi, A. (2020). Transcriptomics reveal immune downregulation of newts overwhelmed by chytrid co-infection. *Molecular Ecology*, *29*, 3167–3169. https://doi.org/10.1111/mec.15576

Shultz, A. J., & Sackton, T. B. (2019). Immune genes are hotspots of shared positive selection across birds and mammals. *eLife*, *8*, e41815. https://doi.org/10.7554/eLife.41815

Simons, N. D., Eick, G. N., Ruiz-Lopez, M. J., Hyeroba, D., Omeja, P. A., Weny, G., Zheng, H., Shankar, A., Frost, S. D. W., Jones, J. H., Chapman, C. A., Switzer, W. M., Goldberg, T. L., Sterner, K. N., & Ting, N. (2019). Genome-wide patterns of gene expression in a wild primate indicate species-specific mechanisms associated with tolerance to natural simian immunodeficiency virus infection. *Genome Biology and Evolution*, *11*, 1630–1643. https://doi.org/10.1093/gbe/evz099

Smith, K. F., Acevedo-Whitehouse, K., & Pedersen, A. B. (2012). The role of infectious diseases in biological conservation. *Animal Conservation*, *12*, 1–12. https://doi.org/10.1111/j.1469-1795.2008.00228.x

Spellberg, B., & Edwards, J. E. Jr (2001). Type 1/type 2 immunity in infectious diseases. *Clinical Infectious Diseases*, *32*, 76–102. https://doi.org/10.1086/317537

Sutherland, B. J. G., Koczka, K. W., Yasuike, M., Jantzen, S. G., Yazawa, R., Koop, B. F., & Jones, S. R. M. (2014). Comparative transcriptomics of Atlantic *Salmo salar*, chum *Oncorhynchus keta* and pink salmon *O. gorbuscha* during infections with salmon lice *Lepeophtheirus salmonis*. *BMC Genomics*, *15*, 200. https://doi.org/10.1186/1471-2164-15-200

Tompkins, D. M., Carver, S., Jones, M. E., Krkošek, M., & Skerratt, L. F. (2015). Emerging infectious diseases of wildlife: a critical perspective. *Trends in Parasitology*, *31*, 149–159. https://doi.org/10.1016/j.pt.2015.01.007

Turchetto, S., Obber, F., Rossi, L., D'Amelio, S., Cavallero, S., Poli, A., Parisi, F., Lanfranchi, P., Ferrari, N., Dellamaria, D., & Citterio, C. V. (2020). Sarcoptic mange in wild Caprinae of the Alps: could pathology help in filling the gaps in knowledge? *Frontiers in Veterinary Science*, *7*, 193. https://doi.org/10.3389/fvets.2020.00193

Van Rooij, P., Martel, A., D'Herde, K., Brutyn, M., Croubels, S., Ducatelle, R., Haesebrouck, F., & Pasmans, F. (2012). Germ tube mediated invasion of *Batrachochytrium dendrobatidis* in amphibian skin is host dependent. *PLoS One*, *7*, e41481. https://doi.org/10.1371/journal.pone.0041481

Velotta, J. P., & Cheviron, Z. A. (2018). Remodeling ancestral phenotypic plasticity in local adaptation: a new framework to explore the role of genetic compensation in the evolution of homeostasis. *Integrative and Comparative Biology*, *58*, 1098–1110. https://doi.org/10.1093/icb/icy117

Velotta, J. P., Ivy, C. M., Wolf, C. J., Scott, G. R., & Cheviron, Z. A. (2018). Maladaptive phenotypic plasticity in cardiac muscle growth is suppressed in high-altitude deer mice. *Evolution*, *72*, 2712–2727. https://doi.org/10.1111/evo.13626

Viney, M. E., Riley, E. M., & Buchanan, K. L. (2005). Optimal immune responses: immunocompetence revisited. *Trends in Ecology and Evolution*, *20*, 665–669. https://doi.org/10.1016/j.tree.2005.10.003

Wang, Z., Gerstein, M., & Snyder, M. (2009). RNA-Seq: a revolutionary tool for transcriptomics. *Nature Reviews Genetics*, *10*, 57–63. https://doi.org/10.1038/nrg2484

Woodhams, D. C., Bosch, J., Briggs, C. J., Cashins, S., Davis, L. R., Lauer, A., Muths, E., Puschendorf, R., Schmidt, B. R., Sheafor, B., & Voyles, J. (2011). Mitigating amphibian disease: strategies to maintain wild populations and control chytridiomycosis. *Frontiers in Zoology*, *8*, 8. https://doi.org/10.1186/1742-9994-8-8

Xie, J., Li, Y., Shen, X., Goh, G., Zhu, Y., Cui, J., Wang, L.-F., Shi, Z.-L., & Zhou, P. (2018). Dampened STING-dependent interferon activation in bats. *Cell Host & Microbe*, *23*, 297–301.e4. https://doi.org/10.1016/j.chom.2018.01.006

Yap, T. A., Koo, M. S., Ambrose, R. F., Wake, D. B., & Vredenburg, V. T. (2015). Averting a North American biodiversity crisis. *Science*, *349*, 481–482. https://doi.org/10.1126/science.aab1052

Zamudio, K. R., McDonald, C. A., & Belasen, A. M. (2020). High variability in infection mechanisms and host responses: a review of functional genomic studies of amphibian chytridiomycosis. *Herpetologica*, *76*, 189–200. https://doi.org/10.1655/0018-0831-76.2.189

Zhou, P., Tachedjian, M., Wynne, J. W., Boyd, V., Cui, J., Smith, I., Cowled, C., Ng, J. H. J., Mok, L., Michalski, W. P., Mendenhall, I. H., Tachedjian, G., Wang, L.-F., & Baker, M. L. (2016). Contraction of the type I IFN locus and unusual constitutive expression of

IFN-α in bats. *Proceedings of the National Academy of Sciences of the United States of America*, *113*, 2696–2701. https://doi.org/10.1073/pnas.1518240113

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