Conservation Physiology

Volume 9 • 2021 10.1093/conphys/coab037

SEB SOCIETY FOR EXPERIMENTAL BIOLOGY

Review

Harnessing the potential of cross-protection stressor interactions for conservation: a review

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Conservation becomes increasingly complex as climate change exacerbates the multitude of stressors that organisms face. To meet this challenge, multiple stressor research is rapidly expanding, and the majority of this work has highlighted the deleterious effects of stressor interactions. However, there is a growing body of research documenting cross-protection between stressors, whereby exposure to a priming stressor heightens resilience to a second stressor of a different nature. Understanding cross-protection interactions is key to avoiding unrealistic 'blanket' conservation approaches, which aim to eliminate all forms of stress. But, a lack of synthesis of cross-protection interactions presents a barrier to integrating these protective benefits into conservation actions. To remedy this, we performed a review of cross-protection interactions among biotic and abiotic stressors within a conservation framework. A total of 66 publications were identified, spanning a diverse array of stressor combinations and taxonomic groups. We found that cross-protection occurs in response to naturally co-occurring stressors, as well as novel, anthropogenic stressors, suggesting that cross-protection may act as a 'pre-adaptation' to a changing world. Cross-protection interactions occurred in response to both biotic and abiotic stressors, but abiotic stressors have received far more investigation. Similarly, cross-protection interactions were present in a diverse array of taxa, but several taxonomic groups (e.g. mammals, birds and amphibians) were underrepresented. We conclude by providing an overview of how cross-protection interactions can be integrated into conservation and management actions and discuss how future research in this field may be directed to improve our understanding of how cross-protection may shield animals from global change.

Key words: Cross talk, cross tolerance, inducible stress tolerance, multiple stressors, preconditioning, stressor interactions

Editor: Steven Cooke

Received 3 December 2020; Revised 15 March 2021; Editorial Decision 6 May 2021; Accepted 9 May 2021

Cite as: Rodgers EM, Gomez Isaza DF (2021) Harnessing the potential of cross-protection stressor interactions for conservation: a review. *Conserv Physiol* 9(1): coab037; doi:10.1093/conphys/coab037.

Introduction

Species persistence in a changing world will depend on their capacity to cope with a multivariate set of stressors in their habitat (Todgham and Stillman, 2013). Here we define stressors (and stress) as changes in an organism's habitat that compromise fitness or performance (Schulte, 2014). Organisms are frequently faced with multiple biotic and abiotic stressors in concert, and global climate change is expected to increase the intensity and number of stressors in habitats (Todgham and Stillman, 2013). Multiple-stressor research has primarily focused on the negative consequences of concurrent stressor

exposure on organisms (Côté *et al.*, 2016). However, organismal responses to stressors sometimes share protective mechanisms (termed 'cross-tolerance') or share signalling/regulatory pathways that activate independent protective mechanisms (termed 'cross-talk') (Sinclair *et al.*, 2013). When protective mechanisms or signalling pathways are shared among stressors, increased tolerance to one stressor is associated with increased tolerance to another stressor (Anttila *et al.*, 2013). This protective phenomenon is currently overlooked in the context of biological conservation, but a greater understanding of these interactions will allow for the development of more effective management of multiple stressors.

Cross-protection interactions (encompassing both cross-tolerance and cross-talk) are hypothesized to have evolved in response to natural, predictable stressor cycles in habitats. For example, intertidal species are generally exposed to predictable stressors (e.g. heat, hypoxia, desiccation and salinity fluctuations) linked to the ebb and flow of tides. This synchronicity of stressors may explain why cross-protection among stressors has been observed in intertidal fish (Todgham *et al.*, 2005). Similarly, dry conditions are often coupled with low temperatures during winter in many habitats, and this may explain why cross-protection between desiccation stress and cold temperatures has been widely documented in polar insects (Sinclair *et al.*, 2013). Remarkably, cross-protection has also been observed among novel, anthropogenic stressors. For instance, a range of species, from nematodes to fishes, can develop resistance to the normally toxic effects of pesticides and pollutants following exposure to mild heat- or hypoxia-stress (Alzahrani and Ebert, 2018, Dolci *et al.*, 2013, Zou *et al.*, 2020). Similarly, livestock can be protected from disease spread by pre-exposure to a mild stressor [e.g. osmotic or heat stress; Huising *et al.*, 2003, Rosenberg *et al.*, 2020].

When faced with stress, organisms launch an endocrine stress response via the activation of the hypothalamic–pituitary–adrenal (HPA) axis in birds, mammals and reptiles and the hypothalamic–pituitary–interrenal (HPI) axis in fishes (Pankhurst, 2011, Romero and Butler, 2007). This activation stimulates the production of catecholamines and glucocorticoids in vertebrates, or a peptide protein (e.g. adipokinetic hormone; Orchard *et al.*, 1993) in most invertebrates—all of which work to mobilize energy substrates towards defence mechanisms (e.g. molecular chaperones, antioxidant defences) and the restoration of homeostasis (Romero and Butler, 2007). However, chronic elevations in glucocorticoids arising from long-term stress can be costly and are associated with immunosuppression, reduced fecundity, slowed growth and higher mortality rates (Romero and Butler, 2007). For this reason, the protective benefits induced by a priming stressor are strongly dependent on the severity (i.e. magnitude and duration) of the priming stressor. If the priming stressor is too severe, cross-protection may not develop or the organism may require a recovery period (RP) before cross-protection is expressed (Fig. 1; Todgham *et al.*, 2005). Understanding the nuances among stressor severity and the development of cross-protection is essential before integrating these interactions into species recovery/protection plans.

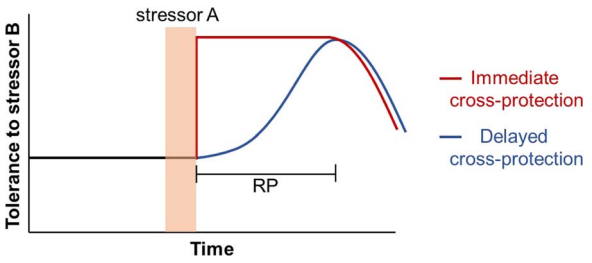

Figure 1: Conceptual diagram of cross-protection responses. Cross-protection occurs when exposure to a priming stressor (stressor A) elicits a beneficial response that heightens organismal tolerance to a stressor of a different nature (stressor B). The orange shaded panel represents the time period that an organism is exposed to stressor A before tolerance to stressor B is increased. Increased tolerance of stressor B can be immediate (immediate cross-protection; red line) when no RP is required, whereas delayed cross-protection (blue line) requires an RP before tolerance to stressor B is increased.

Phenotypes arising from cross-tolerance and cross-talk are the same; mild exposure to an initial priming stressor elicits a beneficial response that protects the organism from a subsequent stressor of a different nature. However, the mechanisms underlying these interaction types are distinct. With cross-tolerance interactions, the priming stressor initiates cellular defences that offer protection from subsequent stress. For example, cold and desiccation stress have similar effects at the cellular level (e.g. osmotic stress) and can be countered by overlapping compensatory mechanisms (e.g. upregulation of cryoprotectants, osmoprotectants and molecular chaperones) (Sinclair *et al.*, 2013). In contrast, with cross-talk interactions, the priming stressor and the secondary stressor share signalling pathways, which facilitate the expression of independent protective mechanisms. For instance, exposure to cold stress can strengthen immune responses in polar insects; but, physiological mechanisms of cold protection generally do not overlap with immune protection, and heightened immunity in the cold is likely linked to shared stress signalling pathways (Sinclair *et al.*, 2013).

Cross-tolerance and cross-talk interactions are present in a diverse array of taxa. Yet, this protective phenomenon is currently overlooked in the context of biological conservation. The unprecedented rates of biodiversity loss worldwide has stimulated a call for species management plans to be placed within a global change context (Reid *et al.*, 2019, Simmonds, 2018). A lack of synthesis of cross-protection interactions presents a barrier to moving forward with new management and conservation actions. Moreover, managers are often unaware of the data that currently exists and how this knowledge can be useful in preventing further population declines. Understanding cross-protection interactions is immensely beneficial in developing science-informed con-

servation actions. For example, identifying cross-tolerance interactions is essential when developing management actions that target the mitigation of stressors that do not provide protective benefits. Here, we used a review protocol to synthesize cases of cross-tolerance within a conservation framework. The aim of this review was fivefold: (i) to synthesize cross-protection interactions among abiotic and biotic stressors, (ii) to identify physiological changes associated with cross-protection interactions, (iii) to evaluate the importance of stressor severity on interactions, (iv) to highlight opportunities where cross-protection interactions can be integrated into conservation plans and (v) to identify knowledge gaps to direct research efforts.

Review protocol

Our review protocol followed PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Fig. S1; Moher *et al.*, 2015) and a ROSES (RepOrting standards for Systematic Evidence Syntheses; Haddaway *et al.*, 2017) form is included as a supplementary file (S2). We searched for studies that observed cross-protection among two or more stressors in non-human animals. Searches were conducted using Scopus and Web of Science's (WoS) core collection on 3 September 2020. We used the following search strings: TOPIC: ('cross-tolerance' OR 'cross tolerance' OR 'cross-talk' OR 'cross talk' OR 'cross-protection' OR 'cross protection' OR 'inducible stress tolerance' OR 'pre∗conditioning' OR 'pre∗treatment' OR 'rapid stress hardening' OR 'hormesis') AND ('stress∗') NOT ('human∗' OR 'medic∗' OR 'clinic∗' OR 'plant∗' OR 'crop∗' OR 'germinat∗' OR 'cell∗' OR 'rat∗' OR 'mouse' OR 'mice') in WoS, and TITLE-ABS-KEY: ('cross-tolerance' OR 'cross tolerance' OR 'cross-talk' OR 'cross talk' OR 'cross-protection' OR 'cross protection' OR 'inducible stress tolerance' OR 'pre∗conditioning' OR 'pre∗treatment' OR 'rapid stress hardening' OR 'hormesis') AND ('stress∗') AND NOT ('human∗' OR 'medic∗' OR 'clinic∗' OR 'plant∗' OR 'crop∗' OR 'germinat∗' OR 'cell∗' OR 'rat∗' OR 'mouse' OR 'mice') in Scopus. We identified 798 and 759 studies meeting the search terms in WoS and Scopus, respectively. A total of 238 duplicates were removed, leaving 1319 papers for title and abstract screening (Fig. S1, PRISMA). We cross-referenced our search with three related review or perspective papers (Berry and López-Martínez, 2020, Sinclair *et al.*, 2013, Todgham and Stillman, 2013) and included any papers missed in our initial search ($N = 40$). Title and abstract screening were conducted in Rayyan (Ouzzani *et al.*, 2016). We excluded studies that (i) were reviews or commentaries, (ii) were conducted on humans or biomedical models, or (iii) did not find evidence of cross-tolerance or cross-talk between two or more stressors. Studies that showed stress-hardening to the same stressor (e.g. heat hardening, cold hardening, hypoxia acclimation) were not included. Following these exclusion steps, we identified 66 papers to include in the review. For each priming stressor we compiled a list of biological effects, associated physiological changes and taxonomic groups in which cross-protection interactions has been observed (Tables 1–3).

Cross-protection among abiotic stressors

Elevated temperatures

As habitat temperatures rise worldwide, it is essential that we understand circumstances where heat stress provides cross-protection against stress of a different nature. Exposure to both short-term and long-term temperature increases can sometimes elicit protection against different stressors in both ectothermic and endothermic species (e.g. Kalra *et al.*, 2017, Peaydee *et al.*, 2014, Rosenberg *et al.*, 2020). These observations suggest that habitat warming has the potential to protect organisms from additional threats, although the extent of this protection is highly dependent on the severity of thermal stress. Studies investigating cross-protection between heat stress and additional stress generally prime organisms with exposure to elevated temperatures. Experimentally priming organisms with acute rises in temperature is referred to as heat shock (HS). In HS experiments, organisms are typically held at an elevated temperature for 1–2 h and then returned to a lower ambient temperature for a RP, lasting between 2 and 12 h. Following recovery, tolerance to a secondary stressor (e.g. a pollutant or hypoxia) is assessed and compared to control organisms that were not exposed to HS. Alternatively, chronic thermal acclimation experiments involve maintaining organisms at sub-lethal, elevated temperatures for prolonged periods (typically ≥4 weeks) and subsequently assessing tolerance to a secondary stressor. Both experimental approaches provide a powerful approach to investigating the impact of heat stress in a global change context when realistic warming scenarios and/or HS conditions are applied.

The effects of heat priming are particularly well studied in fish, and exposure to mild heat stress can provide heightened tolerance to a range of abiotic stressors (Table 1). For example, in killifish (*Fundulus heteroclitus*), 6 weeks of acclimation to an elevated temperature (23°C) markedly improved tolerance to subsequent hypoxia stress compared to cold-acclimated (15°C) fish when tested at the same test temperature (23°C) (McBryan *et al.*, 2016). This interaction was linked to an increase in gill surface area due to a reduction in cell mass in warm-acclimated fish. The protective interaction between heat and hypoxia can also remain when hypoxia is the stressor initially encountered (see Hypoxic and anoxic stress). For example, the survival of tidepool sculpins (*Oligocottus maculosus*) briefly exposed to hypoxic conditions (priming stressor, 0.33mg O_2 L^{-1} for 2 h) increased by 41% during a subsequent HS (secondary stressor, +12°C for 2 h), compared to controls that were held under normoxic conditions (Todgham *et al.*, 2005). It is important to note that the 2 h HS exposure used by Todgham *et al.* (2005) does not represent natural tidepools where peak

Table 1: List of studies identified through a systematic search showing cross-protection interactions in fishes

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross-tolerance conferred	Associated physiological changes	Species	Reference
Elevated temperatures	+8 °C (23°C) for 6 weeks	Hypoxia	0.4 kPa oxygen	Increased time to loss of equilibrium	708% increase	Increased total lamellar surface area	Northern mummichog *F. heteroclitus*	McBryan et al., 2016
	+8 °C (23°C) for 6 weeks	Hypoxia	0.4 kPa oxygen	Increased time to loss of equilibrium	97% increase	Increased total lamellar surface area	Southern mummichog *F. heteroclitus*	McBryan et al., 2016
	+12°C (22°C) for 2 h	Hypoxia	0.33 mg O_2/L for 2 h	Increased survival under hypoxic challenge	56% increase	-	Tidepool sculpin *O. maculosus*	Todgham et al., 2005
	+12°C (22°C) for 2 h	Salinity	90 ppt for 2 h	Increased survival under osmotic challenge	43% increase	-	Tidepool sculpin *O. maculosus*	Todgham et al., 2005
	+12°C (26°C) for 15 min	Salinity	45 ppt	Increased survival under osmotic challenge	25%–60% increase	Induction of HSP70 in branchial and hepatic tissue	Atlantic salmon *S. salar*	DuBeau et al., 1998
	+4 °C (32°C) for 8 weeks	Nitrate (NO_3^-)	100 mg NO_3^-/L for 8 weeks	Absolute aerobic scope maintained	26% increase	Cardiorespiratory system (gills, ventricle) remodelling	Silver perch *B. bidyanus*	Gomez Isaza et al., 2020, 2021
Hypoxia	50% air saturation for 7 days	Heat	Heating rate (0.5°C/min)	Increased CTmax	2% increase	Increased cardiovascular capacity	Channel catfish *I. punctatus*	Burleson and Silva, 2011
	50% air saturation throughout rearing	Heat	Heating rate (0.3 °C/min)	Increased CTmax	10% increase	-	Chinook salmon *O. tshawytscha*	Del Rio et al., 2020
	36%–51% air saturation for 10 days	Manganese (Mn)	4.2–16.2 mg Mn/L for 10–15 days	Reduced Mn accumulation in tissues Reduced Mn-induced oxidative damage	33%–248% decrease 18% decrease	Decreased lipid peroxidation and protein carbonyl in tissues. Reduced hormonal disruption	Silver catfish *R. quelen*	Dolci et al., 2013, 2014, 2017
	45% air saturation for 4–100 h post-fertilization	Copper (Cu)	0.1 mg Cu/L for 4–100 h post-fertilization	Increased survival under Cu exposure	>200% increase	Hypoxia inducible factor activation	Zebrafish *D. rerio*	Fitzgerald et al., 2016

Continued

Table 1: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross-tolerance conferred	Associated physiological changes	Species	Reference
Starvation or food limitation	Fasting for 48–96 h	Cold	−17C (11°C) for 48 h	Increased survival under cold exposure	48%–126% increase	Repression of mechanistic target of rapamycin (mTOR) pathway Lipid catabolism Cell damage attenuation	Zebrafish *D. rerio*	Lu et al., 2019
	Fasting for 10–14 days	Hypoxia	Progressive oxygen decline	Improved P_{crit}	37% decrease in P_{crit}	-	Amazonian oscars *A. ocellatus*	De Boeck et al., 2013
Nitrate	50–250 mg NO_3^-/L for 7 days	Parasite (*Gyrodactylus turnbulli*)	Inoculated with two individual gyrodactylids	Reduced parasite infection intensity	30%–84% decrease	Altered epidermal structure (thickness)	Trinidadian guppies *Poecilia reticulate*	Smallbone et al., 2016

HSP, heat shock protein; CTmax, critical thermal maxima; *P*crit, critical oxygen tensions.
Cross-protection can occur when exposure to a priming stressor increases tolerance to a secondary stressor. Where identified, physiological changes associated with cross-protection are presented.

temperature is gradually approached over many hours. Future work would therefore benefit from using environmentally realistic tidepool warming scenarios (i.e. warming throughout a hot day) to examine if hypoxic conditions (0.33mg O_2 L^{-1} for 2 h) induce cross-protection. Cross-protection among elevated temperatures and hypoxia is particularly relevant in a global change context because both stressors are predicted to intensify moving forward (Breitburg *et al.*, 2018, Diaz, 2001). Overlapping compensatory responses (e.g. increases in oxygen uptake/transport capacity) between these stressors may facilitate the development of phenotypes that can cope with complex stressor combinations.

HS can also improve tolerance to osmotic stress in fish. For instance, tidepool sculpins (*O. maculosus*) primed with a +12°C HS experienced a marked reduction in mortality when exposed to an osmotic challenge (90 ppt for 2 h), compared to controls (Todgham *et al.*, 2005). However, the magnitude of the initial HS determined whether cross-protection was developed: a +10°C HS provided no protective benefits, whereas a +15°C HS increased fish susceptibility to osmotic stress. The RP between the two stressors was also critical. Fish required an 8-h RP following the +12°C HS before cross-protection developed, potentially reflecting the timeframe required to upregulate cellular defences. The sensitivity of this interaction to the RP may reflect natural timings of stress in the intertidal zone. Todgham *et al.* (2005) reflected that the 8-h RP required for cross-protection development is similar to the interval between high and low tides, but more research is required to confirm if cross-protection occurs in the field. The protective effect of heat stress on tolerance to osmotic stress has also been investigated in an aquaculture context. Dubeau *et al.* (1998) found that priming hatchery-reared Atlantic salmon (*Salmo salar*) with a brief HS (26°C for 15min) prior to exposing fish to a severe osmotic challenge (45 ppt exposure; similar to being transferred to seawater pens) significantly increased survival rates (Box 1). This was a particularly promising finding because transferring salmon to seawater pens is a necessary but stressful process, which can curb fish growth and cause mortality.

Heat stress can also increase the resilience of fish, crustaceans and nematodes to a range of pollutants. For example, Wang *et al.* (2020) found that priming nematodes (*Caenorhabditis elegans*) with a 1-h HS at 35°C before exposing them to heavy metal (cadmium) pollution, dramatically increased survival rates compared to non-HS controls. Heat-shocked nematodes were also protected from the usual toxic effects of cadmium (i.e. compromised intestinal barriers and a bagging phenotype) and showed an increased expression of heat shock protein (HSP)-16.2. (*HSP-16.2*). Further to this, Wang *et al.* (2020) demonstrated that the protective effects of HS were absent when an *HSP-16.2* loss-of-function mutation was induced in the nematodes, suggesting the expression of *HSP-16.2* was essential for cross-protection to develop. Heat stress can also protect organisms from organic pollutants, like nitrogenous waste accumulating in aquatic habitats from fertilizers, livestock manure and urban runoff. Heat-shocked (35°C for 2 h) tiger shrimp (*Penaeus monodon*) experienced heightened tolerance to ammonia pollution (15% higher survival rates at 0.69 NH_3-N mg l^{-1}) compared to non-HS controls (Peaydee *et al.*, 2014). Similarly, the negative effects of nitrate pollution (i.e. reductions in aerobic scope, swimming performance and heat tolerance) were ameliorated in silver perch (*Bidyanus bidyanus*) following an 8-week acclimation period to a climate warming scenario (+4°C) (Gomez Isaza *et al.*, 2020, Gomez Isaza *et al.*, 2021).

Exposure to elevated temperatures can also induce cross-protection to insecticides in pests, suggesting that climate warming may reduce the efficacy of some insecticides. For example, phosphine is a fumigant commonly used worldwide to control insect pests in stored food, like grain. Alzahrani and Ebert (2018) found that nematodes exposed to HS (30°C for 4h) were approximately three times more tolerant of phosphine compared to controls, suggesting higher doses may be required under warmer conditions. Moreover, food stores are

Box 1. Cross-protection in an aquaculture species

Atlantic salmon (*Salmo salar*) are an economically valuable species, but they face a major osmotic challenge when they are transferred from freshwater hatcheries to seawater pens. This osmotic challenge is far more severe in an aquaculture setting, because fish are moved directly from freshwater to seawater, instead of a gradual transition, which occurs during natural migrations. Compounding this stress, fish are sometimes moved before they have developed osmoregulatory capabilities (parr-smolt transformation). For these reasons, transferring salmon to seawater pens often leads to stunted growth or death. Dubeau *et al.* (1998) investigated whether salmon could be protected against this osmotic challenge by priming fish with a heat shock. Fish were exposed to a heat shock (26°C for 15 min) before being exposed to a severe osmotic challenge (45 ppt), and control fish were not primed with a heat shock. Heat-shocked salmon showed significantly improved survival during the osmotic challenge compared to control salmon. This was the first study to demonstrate that heat shock can confer protection against osmotic stress in a living animal. *Image by Daniel Gomez Isaza.*

commonly treated by combining heat stress with insecticides (Fields and White, 2002), without realizing that heat stress may be increasing insecticide resistance in some pests. HS can also heighten insecticide resistance in disease vectors, like mosquitoes. For example, exposure to high sub-lethal temperatures (39°C for 1–3 h) in mosquito larvae (*Anopheles stephensi* and *Anopheles aegypti*) provided cross-protection to propoxur, a carbamate insecticide (Patil *et al.*, 1996). Moreover, mosquitos reared at warmer temperatures can also tolerate higher virus loads (Hurlbut, 1973). Taken together, these findings suggest appropriate insecticide doses moving into the future should account for potential cross-protection interactions between heat stress and insecticide resistance.

Cold stress

At the opposite end of the thermal spectrum, mild cold stress can provide protection against a range of stressors in ectotherms, including desiccation stress, food limitation, pathogens and even heat stress (Table 2; Le Bourg, 2016, Le Bourg *et al.*, 2009, Scharf *et al.*, 2019, Williams and Lee, 2011). Cross-tolerance and cross-talk are well documented among polar insects (reviewed in Everatt *et al.*, 2015, Sinclair *et al.*, 2013), where insects must survive harsh winter temperatures bundled with additional stress, like low water availability (Danks, 2000). At sub-zero temperatures, the vapour pressure of ice is lower than liquid or body fluids and the environment becomes severely desiccating. Cold and desiccation stress exert similar effects at the cellular level (dehydration and osmotic stress), but these stressors also share cellular defences, such as the upregulation of cryoprotectants. Therefore, it is unsurprising that insects that are cold hardy also tend to be desiccation hardy. Numerous studies have shown that exposure to cold shock can heighten desiccation resilience in insects (Table 2). For example, following cold acclimation, the goldenrod gall fly (*Eurosta solidaginis*) experienced reduced water loss and was concomitantly less susceptible to desiccation (Williams and Lee, 2011). Cross-protection between cold and desiccation stress generally remains when desiccation is the priming stress (see Desiccation stress; Levis *et al.*, 2012, Yi *et al.*, 2017). For instance, desiccation exposure (4% relative humidity, RH for 3 h) improved larval pupariation rates following cold shock (−9°C for 2 h) by 12% in the flesh fly (*Sarcophaga bullata*) (Yi *et al.*, 2017).

Cold, winter-related stress is often bundled with limited food availability. In some species, cold shock or cold acclimation can increase tolerance to food limitation. Female red flour beetles (*Tribolium castaneum*), for example, experienced stronger starvation tolerance following cold shock compared to controls. But, this stronger starvation tolerance was traded-off against reproductive success (Scharf *et al.*, 2019) and cross-protection between cold and starvation resistance is far from universal among insects (Kenny *et al.*, 2008, Pathak *et al.*, 2018). Cold stress can also stimulate preparatory mechanisms that aid organisms in coping with pathogens (Table 2). Strong links have been established between cold stress and the upregulation of immune system responses in insects (reviewed in Sinclair *et al.*, 2013). In general, insects exposed to cold conditions exhibit an upregulation in immunity-related genes and heightened tolerance to fungal infections (Le Bourg *et al.*, 2009, Marshall *et al.*, 2011, Salehipour-shirazi *et al.*, 2017, Zhang *et al.*, 2011). For example, *Drosophila melanogaster* exposed to cold stress (daily exposure to 0°C for 1 h) exhibited heightened resistance to a fungal infection (*Beauveria bassiana*), and this protection persisted throughout their lifetime (Le Bourg *et al.*, 2009).

Desiccation stress

Desiccation stress often coincides with thermal stress: freezing temperatures reduce the availability of free water, whereas warming triggers faster evaporation rates (Danks, 2000). Exposure to desiccation stress can confer increased resilience to subsequent thermal stress, and cross-protection between dehydration stress and thermal stress is well documented in arthropods (Table 2). In particular, desiccation and cold stress are often coupled during winter for insects living in polar habitats; insects stop drinking during dormancy, and free water becomes less available (Sinclair *et al.*, 2013). Desiccation and cold stress also exert similar effects (dehydration and osmotic stress) at a cellular level, and can therefore be counteracted by similar compensatory responses (Sinclair *et al.*, 2013). Overlapping compensatory responses include the generation of cryoprotectants and molecular chaperone proteins, as well as the alteration of cell membrane structures (Table 2). For example, acute desiccation in the Antarctic midge (*Belgica antarctica*) increased survival by ~50% during a freeze challenge (−14°C) (Kawarasaki *et al.*, 2019). This cross-protection was linked to both freezing and desiccation stress independently increasing the accumulation of shared cryoprotectants (glycerol and erythritol) (Robert Michaud *et al.*, 2008), which reduce extracellular ice formation, prevent cell membrane damage and prevent low-temperature denaturation of proteins (Tang and Pikal, 2005, Tsvetkova and Quinn, 1994). Enhanced cold tolerance can also be rapidly induced by desiccation—a phenomenon termed 'drought-induced rapid cold hardening'. Desiccation (4% RH) in the goldenrod gall fly (*E. solidaginis*), for instance, induced cellular protection within just 1 h (Gantz and Lee, 2015). This rapid response occurs within a similar timeframe to rapid cold hardening, where cold tolerance is quickly heightened in response to chilling. Although cold and desiccation stress share some protective mechanisms, these stressors appear to have distinct signalling pathways (Sinclair *et al.*, 2007, Sørensen *et al.*, 2010), so cross-protection between these stressors likely evolved as cross-tolerance rather than cross-talk (Sinclair *et al.*, 2013).

Desiccation stress can also boost heat tolerance in many tropical insects (Table 2). High temperatures and desiccation stress are often coupled, particularly in drought-prone

Table 2: List of studies identified through a systematic search showing cross-protection interactions in arthropods

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Elevated temperatures	Heat stress (37°C) for 1 h	Cold temperatures	−9 °C for 2 h	Increased survival at cold temperature	56% increase	-	Codling moth *Cydia pomonella*	Chidawanyika and Terblanche, 2011
	Heat stress (41°C) for 2 h	Cold temperatures	CTmin cooling rate (0.25°C/min)	Decreased CTmin (i.e. towards cooler temperatures)	34% decrease	-	Spotted stalk borer *C. partellus*	Mutamiswa et al., 2018
	+4°C (34°C) throughout development	Cold temperatures	Ice exposure (∼0 °C) for 2 h	Reduced chill-coma recovery time	21% decrease	-	Red flour beetle *T. castaneum*	Scharf et al., 2015
	HS (38 °C) for 5 min	Cold temperatures	Ice exposure (∼0 °C) for 30min	Reduced chill-coma recovery time	26% decrease	-	Red flour beetle *T. castaneum*	Scharf et al., 2016
	Heat stress (37°C) for 2 h	Desiccation	Desiccation stress (<10% RH)	Increased desiccation resistance (survival)	67% increase	Changes in energy budget (trehalose, proline, and body lipids)	African fig fly *Z. indianus*	Kalra et al., 2017
	Heat stress (35°C) for 2 h	Ammonia	Ammonia (0.69 mg-N/L)	Increased ammonia tolerance (survival %)	37% increase	Increased aquaporin gene (PmAQP1) expression	Giant tiger prawn *Penaeus monodon*	Peaydee et al., 2014
	Heat stress (39°C) for 3 h	Propoxur (insecticide)	0.625mg/L propoxur for 6 h	Increased survival following propoxur exposure	56% increase	-	Yellow fever mosquito *Aedes aegypti*	Patil et al., 1996
	Elevated temperature (30°C) for 5–12 d	Viruses	St. Louis encephalitis virus	Tolerate higher virus loads	89% increase	-	Southern house mosquito *C. quinquefasciatus*	Hurlbut 1973
	+14°C (39°C) for 1 h	Bacteria (*Bacillus thuringiensis*, Bti)	1–1.5 ppm Bti solution	Reduced larval mortality	50%–160%	-	Southern house mosquito *C. quinquefasciatus*	Barik et al., 2018
Cold temperatures	Cool temperature (22°C) for 21 generations	Starvation	No food provided (water provided)	Increased starvation resistance (survival)	13–17% increase	-	Common fruit fly *D. melanogaster*	Bauerfeind et al., 2014

Continued

Table 2: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Cold temperatures	−4°C (26°C) throughout development	Starvation	No food (or water) provided	Increased starvation resistance (survival)	61% increase	-	Red flour beetle *T. castaneum*	Scharf et al., 2015
	Cold shock- Ice exposure (∼0 °C) for 1.5 h over 5 successive days	Starvation	No food (or water) provided	Increased starvation resistance (survival)	19% increase	-	Red flour beetle *T. castaneum*	Scharf et al., 2019
	Cool temperature (22°C) for 21 generations	Desiccation	Humidity of 0–5%	Increased desiccation resistance (survival)	13%–30% increase	-	Common fruit fly *D. melanogaster*	Bauerfeind et al., 2014
	20 °C for 5 days	Desiccation	RH of 15–30% for 36h	Increased desiccation resistance (survival)	17% increase	-	African fruit fly *C. rosa*	Gotcha et al., 2018
	Cooled to −5 °C	Desiccation	RH of ∼4%	Lower cryoprotectants in haemolymph	35% decrease	Movement of cryoprotectants to intracellular compartment	Goldenrod gall fly *E. solidaginis*	Williams and Lee, 2011
	0 °C for 3 weeks	Elevated temperatures	33.5 °C for 2 h	Increased survival at elevated temperature	58%–78% increase	-	Kelp fly *Paractora dreuxi*	Marais et al., 2009
	Cold shock (0 °C for 15 min)	Elevated temperatures	HS (43°C) exposure	Extended heat knockdown time	4% increase	-	Silkworm *B. mori*	Mir and Qamar 2018
	Cold shock (ice exposure; ∼0 °C) for 30min	Elevated temperatures	HS (42.5 °C) exposure	Extended heat knockdown time	28% increase	-	Red flour beetle *T. castaneum*	Scharf et al., 2016
	Cold pre-treatment (0 °C for 60 min) twice over 5 day	Elevated temperatures	Resistance to heat (37°C)	Increased resistance (survival) to heat	2%–13% increase	-	Common fruit fly *D. melanogaster*	Le Bourg 2016

Continued

Table 2: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
	Cold pre-treatment (0 °C for 60 min) twice over 5 day	Pathogens	Fungal infection (*B. bassiana*)	Increase longevity (days)	7%–38% increase	-	Common fruit fly *D. melanogaster*	Le Bourg et al., 2009
Desiccation stress	Desiccation at 98.5% RH for 7 days	Cold temperatures	Cold shock (+1.6 to −4 °C)	Increased tolerance (survival) to cold temperatures	50%–488% increase	Increase in membrane fatty acids; HSP70 synthesis	Collembola sp. *Folsomia candida*	Bayley et al., 2001
	Desiccation at 0, 75, or 98% RH	Cold temperatures	Cold shock (−10 or − 15 °C for 3 h)	Increased tolerance (survival) of cold temperatures	23%–206% increase	Increased trehalose concentrations	Antarctic midge *B. antarctica*	Benoit et al., 2009
	Desiccation at 7–30% RH for 11 h	Cold temperatures	Cold shock (−0 °C for 3 h)	Reduced chill-coma recovery time	18% decrease	-	Common fruit fly *D. melanogaster*	Bubliy et al., 2012
	Desiccation at 0–75% RH for 2 h	Cold temperatures	Cold shock (−18°C for 24 h)	Increased tolerance (survival) of cold temperatures	386%–444% increase	-	Goldenrod gall fly *E. solidaginis*	Gantz and Lee 2015
	Desiccation at RH of 98.5% for 24–192 h	Cold temperatures	Cold tolerance (ice exposure; ∼0 °C) for 48 h	Increased tolerance (survival) of cold temperatures	10%–82% increase	Membrane phospholipid fatty acids desaturation, accumulation of cryoprotectives	Collembola sp. *Folsomia candida*	Holmstrup et al., 2002
	Desiccation at 0–99% RH for 2 h	Cold temperatures	Cold shock (−14°C for 2 h)	Increased tolerance (survival) of cold temperatures	284%–409% increase	-	Antarctic midge *B. antarctica*	Kawarasaki et al., 2019
	Desiccation at 20% RH for 24 h	Cold temperatures	CTmin cooling rate (0.25°C/min)	Decreased CTmin	29% increase 59% increase 46% increase	-	Maize stalk borer *B. fusca,* African pink stem borer *Sesamia calamistis,* Spotted stalk borer *C. partellus*	Mutamiswa et al., 2018

Continued

Table 2: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Desiccation stress	Desiccation at 3% RH for 2 weeks	Cold temperatures	Cold tolerance (−10 °C for 1–28 d)	Increased tolerance (survival) of cold temperatures	260% increase	-	Khapra beetle *Trogoderma granarium*	Shivananjappa et al., 2020
	Desiccation for 3 h	Cold temperatures	Cold shock (−9 °C for 2 h)	Increased tolerance (survival) of cold temperatures	18%–51% increase	-	Flesh fly *S. bullata*	Yi et al., 2017
	Dehydrated at 0, 75, or 98% RH	Elevated temperatures	HS (20 or 30°C for 3 h)	Increased tolerance (survival) of elevated temperatures	8%–257% increase	-	Antarctic midge *B. antarctica*	Benoit et al., 2009
	Desiccation at 7–30% RH for 11 h	Elevated temperatures	HS (36°C for 1 h)	Increased tolerance (survival) of elevated temperatures	16% increase	-	Common fruit fly *D. melanogaster*	Bubliy et al., 2012
	Desiccation at 20% RH for 16 h	Elevated temperatures	HS (38 °C)	Increased tolerance (survival) of elevated temperatures	35% increase	-	Fly sp. *Drosophila simulans*	Bubliy et al., 2013
	Desiccation at < 10% RH for 16 h	Elevated temperature	HS (38°C) for 2 h	Increased tolerance (survival) of elevated temperatures	59% increase	Changes in energy budget (trehalose, proline levels)	African fig fly *Z. indianus*	Kalra et al., 2017
	Desiccation at < 7% RH for 4.5 d	Elevated temperature	HS (38 °C) exposure	Increased tolerance (survival) of elevated temperatures	157%–335% increase	-	Lesser mealworm *A. diaperinus*	Renault et al., 2015
Anoxia	Anoxia	Elevated temperature	HS (53°C for 2 h)	Increased tolerance (survival) of elevated temperatures	100% increase		Migratory locust *L. migratoria*	Wu et al., 2002

Continued

Table 2: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Anoxia	Anoxia for 12–36 h	Cold temperatures	Cold shock (0 °C for 12–36 h)	Increased tolerance (survival) of cold temperatures	5%–216% increase	Increased membrane fluidity, HSP70 expression	Codling moth *Thaumatotibia leucotreta*	Boardman et al., 2015
	Anoxia for 10–60 min	Cold temperatures	Cold shock (0 °C for 2 h)	Increased tolerance (survival) of cold temperatures	123%–271% increase		Housefly *M. domestica*	Coulson and Bale, 1991
	Anoxia for 1 h	Irradiation	Irradiation dose of 70 Gy at rate of 8.95 Gy/min	Improved flight performance Increased mating success	24% increase 56% increase	Upregulation of antioxidant enzymes	Caribbean fruit fly *Anastrepha suspensa*	López-Martínez and Hahn, 2014
Fasting/food limitation	Fasting for 24 h	Cold temperatures	Cold shock (2 h at −4 °C)	Reduced chill-coma recovery time	5%–13% decrease	-	Migratory locust *L. migratoria*	Andersen et al., 2013
	Fasting for 18 h	Cold temperature	Cold shock (0 °C for 3 h)	Reduced chill-coma recovery time	5% decrease	-	Common fruit fly *D. melanogaster*	Bubliy et al., 2012
	Fasting for 24 h	Cold temperatures	Ice exposure (∼0 °C) for 1 h	Reduced chill-coma recovery time	19% decrease	-	Silkworm *B. mori*	Mir and Qamar 2018
	Fasting for 4 d	Cold temperatures	CTmin cooling rate (0.25°C/min)	Decreased CTmin	40% decrease 17% decrease 45% decrease	-	Maize stalk borer *B. fusca,* African pink stem borer *Sesamia calamistis,* Spotted stalk borer *C. partellus*	Mutamiswa et al., 2018
	Fasting for 18 h	Elevated temperatures	HS (38 °C)	Increased tolerance (survival) of elevated temperatures	7% increase	-	Common fruit fly *D. melanogaster*	Bubliy et al., 2012
	Fasting for 10 d	Elevated temperatures	CTmax heating rate (0.25°C/min)	Increased CTmax	2% increase	-	African fruit fly *C. rosa*	Gotcha et al., 2018

Continued

Table 2: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Fasting/food limitation	Fasting for 2 d	Elevated temperatures	HS (38 °C) for 2 h	Increased tolerance (survival) of elevated temperatures	78% increase	-	African fig fly *Z. indianus*	Kalra et al., 2017
	Fasting for 4 d	Elevated temperatures	CTmax heating rate (0.25°C/min)	Increased CTmax	2% increase	-	Spotted stalk borer *C. partellus*	Mutamiswa et al., 2018
	Fasting for 14 d	Elevated temperatures		Increased tolerance (survival) of elevated temperatures	24% increase	Changes in energy metabolites, downregulation of metabolism, increased HSP70 expression	Amphipod sp. *G. fossarum*	Semsar-kazer-ouni et al., 2020
	Fasting for 18 h	Desiccation	17–30% RH for 15 h	Increased tolerance (survival) under desiccation stress	21% increase	-	Common fruit fly *D. melanogaster*	Bubliy et al., 2012
Photoperiod	light: dark cycle 18:06	Desiccation	RH of 0–5%	Increased desiccation resistance (days)	5%–13% increase	-	Common fruit fly *D. melanogaster*	Bauerfeind et al., 2014
Cadmium	Cadmium exposure (5 µg Cd/L) for 20 generations	Metals (zinc, silver)	Median lethal concentrations (µg/L)	Increased tolerance (lethal concentration) to other metals	Zinc: 118% increase Silver: 474% increase	Expression of metal response gene (metallothionein 1)	*Water flea Daphnia pulex*	Shaw et al., 2019
Chlorpyrifos	Chlorpyrifos exposure (1 µg/L) for 7 days	Predation risk	Dragonfly *Anax imperator* larvae	Reduced oxidative damage (Malon-dialdehyde, O_2^-, H_2O_2)	27%–67% decrease	Increased antioxidant (superoxide dismutase, catalyse) levels	Common blue damselfly *E. cyathigerum*	Janssens and Stoks, 2017

Continued

Table 2: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Immune challenge	Bacterial exposure (*Staphylococcus aureus* and *Pseudomonas aeruginosa*: 10^{10}, 10^{9} or 10^{8} cells/ml)	Temperature (cold and warm)	Cold shock (0 °C for 5 h) HS (39°C)	Reduced chill coma recovery time Increased heat knockdown time	2%–12% decrease in chill coma recovery time 6%–14% increase heat knockdown time	-	Common fruit fly *D. melanogaster*	Hector et al., 2020
Crowding stress	Medium (60 eggs/ml) or high (300 eggs/ml) density	Temperature (cold and warm)	Cold shock (0 °C) or HS (38 °C)	Increased tolerance (survival time) of cold and heat	32%–164% increase in cold tolerance 33%–55% increase in heat tolerance	-	Common fruit fly *D. melanogaster*	Henry et al., 2018
	High density (1000+ larvae) for 30 generations	Starvation	Starvation resistance (time to death)	Increased starvation tolerance	73% increase	-	Common fruit fly *D. melanogaster*	Mueller et al., 1993

RH, relative humidity; CTmin, critical thermal minima; Gy, gray; CTMax, critical thermal maxima; HSP, heat shock protein. Cross-protection can occur when exposure to a priming stressor increases tolerance to a secondary stressor. Where identified, physiological changes associated with cross-protection are presented.

Table 3: List of studies identified through a systematic search showing cross-protection interactions in other taxonomic groups

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Elevated temperatures	+15 °C (35°C) for 1.5–2 h	Cadmium (Cd)	1–5 mM Cd up to 120 min	Reduced mortality	17%–34% decrease	Increased HSP- 16.2 expression	Nematode *C. elegans*	Wang et al., 2020
	+10 °C (30 °C) for 4 h	Phosphine fumigation (PH_3)	50–6400 ppm for 24 h	Increased PH_3 tolerance (LC_{50})	173% increase	HS response regulator (HSF-1)	Nematode, wild-type *C. elegans*	Alzahrani and Ebert, 2018
	+5 °C (32 + 14 °C) for 2–7 days	Injured coral branches	3 injured branches	Enhanced constituent immunity	-	-	Hump coral *P. cylindrical*	Palmer 2018
	+1.7 °C (39.5 °C) for 21 days (embryonic period)	Lipopolysaccharide (LPS) challenge for 6 h	0.3 µg LPS 6–24 h	Reduce febrile response	23% decrease	Reduced expression of pro-inflammatory genes Increased expression of anti-inflammatory genes 10–11 translocation family enzymes	Chicken *Gallus gallus domesticus*	Rosenberg et al., 2020
Food limitation	60% feed restriction for 3 days	Heat stress	+14 °C (38 °C) for 2 h/day for 6 days	Reduced heterophil/lymphocyte ratios Improved growth Improved survival	43% decrease 4% increase 20% increase	Increased HSP70 expression	Chicken *Gallus gallus domesticus*	Zulkifli et al., 1994, 2000, 2003
Desiccation	75% RH for 3 or 7 days	Freezing	Cooling from 4 to −10 °C (1 °C/h)	Increased freezing tolerance (survival)	72%–135% increase	Increased transcription of genes encoding trehalose	Antarctic nematode *Plectus murray*	Adhikari et al., 2010
Air exposure	Air exposure for 24 h	Tetrabromobisphenol A (TBBPA)	100 µg/L TBBPA for 1 day	Reduced TBBPA accumulation in gill and digestive gland tissue	24%–28% decrease	Upregulation of CAT, HSP70; increased GST activity and p-glycoprotein levels	Manila clam *Ruditapes philippinarum*	Hu et al., 2020
	Air exposure for 4.25 h at 25–35°C	HS	Lethal temperature ramp (6 °C/h)	Increased thermal limits of cardiac performance	0%–16% increase	-	Fingered limpet *Lottia digitalis*	Pasparakis et al., 2016
Selenite	0.01 µM Selenite, Se(IV) for 40 h	Lead (Pb(II))	100 µM Pb(II) for 24 h	Restored locomotion behaviours	-	Lower ROS levels, protects sensory neurons	Nematode, wild-type *C. elegans*	Li et al., 2013

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Table 3: Continued.

Priming stressor	Magnitude and duration of priming stressor	Secondary stressor	Magnitude of secondary stressor	Biological effect	Magnitude of cross tolerance conferred	Associated physiological changes	Species	Reference
Insecticide	1 mg/L of carbaryl throughout development (Gosner stage 4–19)	Malathion	15 mg/L of malathion for 120 h	Increased tolerance to malathion	-	-	Wood frog *Lithobates sylvaticus*	Hua et al., 2014
	0.5 or 1 mg/L of carbaryl throughout development (Gosner stage 4–19)	Cypermethrin	0.03 mg/L of cyperme-thrin for 120 h	Increased tolerance to cypermethrin	-	-	Wood frog *Lithobates sylvaticus*	Hua et al., 2014
Predation	Crayfish + crushed snail for 12 weeks	Cadmium	300 µg/L for 120 h	Increased cadmium tolerance (survival) in offspring	108% increase	Transgenerational cross-protection	Freshwater snail *B. glabrata*	Plautz et al., 2013
Pathogen	Fed pathogenic bacteria (*E. coli*)	HS	+10 °C (35°C) for 10 h	Increased survival during HS	20% increase	Increased expression of HSP-16.2 gene	Nematode *C. elegans*	Leroy et al., 2012

HSP = heat shock protein; LPS = lipopolysaccharide; CAT = catalase; GST = Glutathione S-Transferases; RH = relative humidity; ROS = reactive oxygen species. Cross-protection can occur when exposure to a priming stressor increases tolerance to a secondary stressor. Where identified, physiological changes associated with cross-protection are presented.

habitats. Warming temperatures can even act as an important cue for the development of a desiccation-resistant phenotype in salamanders (*Plethodon metcalfi*) (Riddell *et al*., 2019). Moreover, heat resistance can be boosted by desiccation acclimation (<10% RH for 16 h) in a tropical drosophilid (*Zaprionus indianus*) (Kalra *et al*., 2017). This cross-protection interaction was linked to an accumulation of trehalose, which is an osmoprotectant implicated in heightened tolerance to cold, desiccation, and even hypoxia in several insects (Benoit *et al*., 2009, Chen and Haddad, 2004). In a similar study, desiccation exposure (7% RH, for 4.5 d) in the lesser mealworm (*Alphitobius diaperinus*) extended survival times at elevated temperatures by 4 days compared to controls (Renault *et al*., 2015). Similarly, critical thermal maxima also increased following desiccation stress in the natal fruit fly (*Ceratitis rosa*; Gotcha *et al*., 2018). Understanding cross-protection interactions between desiccation and heat stress is becoming increasingly important as climate change disrupts precipitation patterns, causing more intense droughts (Trenberth *et al*., 2014, Williams *et al*., 2013).

Hypoxic and anoxic stress

Almost all organisms require oxygen to support cellular metabolism. Consequently, low-oxygen conditions can be tremendously stressful and often result in oxidative stress [i.e. the over-accumulation of reactive oxygen species (ROS), which can damage nucleic acids, proteins, and lipids; Majmundar *et al*., 2010]. However, ROS production is also essential for cellular communication and reinstating homeostasis following stress in a range of species (Görlach *et al*., 2015). Indeed, low levels of oxidative damage may be critical for the development of cross-protection. The preparation for oxidative stress (POS) hypothesis predicts that, in cases of cross-protection, the priming stressor stimulates a beneficial level of ROS, which serve as signalling molecules to activate cellular defences (Giraud-Billoud *et al*., 2019, Hermes-Lima *et al*., 2001, Hermes-Lima and Zenteno-Savin, 2002). Therefore, it is unsurprising that exposure to hypoxic or anoxic conditions can sometimes provide organisms with cross-protection to other stressors (Boardman *et al*., 2015, Dolci *et al*., 2014, López-Martínez and Hahn, 2014, López-Martínez and Hahn, 2012). Moving forward, hypoxic conditions are projected to intensify in aquatic habitats due to the progression of climate change and continued eutrophication from agricultural, urban and sewage runoff (Breitburg *et al*., 2018, Diaz, 2001). Therefore, understanding how exposure to hypoxia influences an organism's capacity to cope with additional stress is an essential consideration in species management plans.

Hypoxic waters are frequently contaminated with a range of chemicals, deeming the interactions between these stressors particularly relevant. Exposure to low oxygen can sometimes provide cross-protection against contaminants. For example, Fitzgerald *et al*. (2016) found that copper (Cu) toxicity was lowered by more than 2-fold when zebrafish embryos (*Danio rerio*) were reared under hypoxia compared to normoxia. The suppression of Cu toxicity stemmed from the activation of the hypoxia inducible factor (HIF, HIF-1α), which is a transcriptional activator. Once the embryos hatched, however, hypoxia exposure had the opposite effect and Cu toxicity was enhanced by hypoxia, showing that the cross-protection interaction is highly specific to life-stage. Similarly, hypoxia acclimation can protect silver catfish (*Rhamdia quelen*) from manganese pollution coming from oil and gas extraction operations (Dolci *et al*., 2013, Dolci *et al*., 2017, Dolci *et al*., 2014). Dolci *et al*. (2014) acclimated silver catfish to hypoxic (36% oxygen saturation) or normoxic (97% air saturation) conditions for 10 days and subsequently exposed fish to manganese for an additional 10 days. Hypoxia-acclimated fish showed reduced manganese accumulation in their kidneys, brain and plasma. Moreover, the usual toxic actions of manganese (reduced haematocrit, hormonal disruptions and reduced Na^+K^+– ATPase activity) were reduced in hypoxia-acclimated fish. Lending support to the POS hypothesis, the protective role of hypoxia was linked to its capacity to ameliorate oxidative damage by increasing catalase enzyme activity, which plays a key role in detoxifying the renal system. Although these cases of cross-protection exist, hypoxia-induced protection from contaminants cannot be generalized. These interactions are highly variable among pollutant types, species and life-stage, and several studies report an increase in contaminant toxicity/sensitivity under low-oxygen conditions (Hattink *et al*., 2005, Hattink *et al*., 2006, Mustafa *et al*., 2012).

Hypoxia and heat stress are frequently paired in natural habitats, as the solubility of oxygen decreases as water temperatures increase (Keeling *et al*., 2010). The links between hypoxia and heat stress have captured the attention of many ecophysiologists because both stressors impact aerobic metabolism in ectotherms and both stressors are projected to intensify under climate change. Hypoxia directly limits the availability of oxygen in the environment; as hypoxia intensifies it becomes increasingly difficult to meet metabolic demands. Whereas, heat increases resting metabolic demands in ectotherms, so that more oxygen is required as temperatures rise. Many ecophysiologists have, therefore, hypothesized that organismal heat tolerance should be reduced under hypoxic conditions (McBryan *et al*., 2013, Pörtner, 2001), but this hypothesis overlooks the potential for overlapping compensatory responses between the two stressors. Acclimation to hypoxia may induce physiological changes that lower an organism's sensitivity to elevated temperatures. Hypoxia acclimation in fish typically involves adjustments that increase oxygen uptake efficiency (e.g. increased gill surface area), improve blood oxygen carrying capacity (e.g. increased haematocrit) and lower metabolic rates (Polymeropoulos *et al*., 2017, Richards, 2009). Since heat tolerance is linked to oxygen supply and demand, the physiological changes induced by hypoxia acclimation may also improve heat tolerance. Indeed, hypoxia acclimation has resulted in improved heat tolerance in several fishes. For example,

channel catfish (*Ictalurus punctatus*) acclimated to hypoxic conditions (50% air saturation) for 7 days, showed increased heat tolerance compared to fish maintained under normoxic conditions (Burleson and Silva, 2011). This increased heat tolerance was linked to hypoxia-induced remodelling of the cardiovascular system, where fish were able to maintain heart rate and blood pressure at higher temperatures compared to controls. Similarly, Chinook salmon (*Oncorhynchus tshawytscha*) reared under hypoxic conditions (50% air saturation) experienced improved heat tolerance in later life, but this came at the cost of reduced survival and growth rates (Del Rio *et al*., 2020). In general, chronic exposure to hypoxic conditions is required before cross-protection can develop, likely reflecting the time required to remodel underlying physiology. In support of this idea, numerous studies have shown that acute hypoxia exposure has a depressive effect on heat tolerance in ectotherms (Ellisa *et al*., 2013, Ern *et al*., 2015, Ern *et al*., 2017, Ern *et al*., 2016, Klok *et al*., 2004, Verberk *et al*., 2016).

At the extreme end of oxygen limitation, anoxia can also provide cross-protection to additional stressors. For instance, anoxia exposure can boost both heat and cold tolerance in insects. Brief (1 h) exposure to anoxia increased survival times at high temperatures (53°C) in the locust (*Locusta migratoria*) (Wu *et al*., 2002), and this interaction is thought to be connected to *L. migratoria* naturally experiencing oxygen limitation (from intense aerobic workload) in combination with high temperatures during long-distance migrations. Similarly, house flies (*Musca domestica*) experienced improved survival at −7°C following brief exposure to anoxia (Coulson and Bale, 1991). Preconditioning with anoxia can also protect insects against radiation, by stimulating the upregulation of antioxidant enzymes (López-Martínez and Hahn, 2014, López-Martínez and Hahn, 2012, López-Martínez *et al*., 2014); however, the ecological relevance of radiation protection is limited.

Cross-protection among biotic stressors

Organisms frequently face a complex range of biotic stressors, including pathogens, introduced species, predation pressure and resource competition. Yet, far less research has been conducted on cross-protection interactions involving biotic stressors compared to abiotic stressors. This may be due to biotic stressors being more difficult to manipulate experimentally, or because of the complex, often interlinked nature of biotic stressors. Conspecific crowding, for example, is a complex stressor that may decrease food availability, increase competitive interactions, facilitate disease spread and lead to an accumulation of toxic wastes. Despite these negative effects, crowding stress can sometimes enhance starvation tolerance (Mueller *et al*., 1993), promote greater resistance to fungal growth and increase heat and cold tolerance (Henry *et al*., 2018). For example, Henry *et al*. (2018) reared larval *D. melanogaster* under low (5 eggs ml^{-1} of food), medium (60 eggs ml^{-1} of food) and high densities (300 eggs ml^{-1} of food) and found that both heat and cold tolerance was higher in larvae raised under medium and high densities compared to larvae raised under low densities. Predation pressure can also induce cross-protection in some cases. For example, pesticide-induced oxidative damage was reduced in damselflies (*Enallagma cyathigerum*) when they were exposed to predator cues (Janssens and Stoks, 2017). Similarly, parental exposure to predator cues in freshwater snails (*Biomphalaria glabrata*) resulted in offspring that had greater resistance to cadmium pollution (Plautz *et al*., 2013).

Pathogen stress

Pathogens (e.g. viruses, bacteria, fungi, parasites, etc.) are the most well investigated biotic stressor studied within a cross-protection context. Interactions between pathogen stress and thermal stress have received a great deal of attention, likely because both stressors are predicted to shift under climate change (Metcalf *et al*., 2017). Moreover, since pathogen stress and thermal stress often share common pathways, cross-protection interactions are expected (Sinclair *et al*., 2013). For example, exposure to infectious disease in *Drosophila* increases the expression of heat shock proteins (HSPs; Merkling *et al*., 2015) and exposure to thermal stress can upregulate the expression of immune-related genes (Sinclair *et al*., 2013, Zhang *et al*., 2011). Pathogens are frequently used as either the priming or the secondary stressor in cross-protection studies. For example, Leroy *et al*. (2012) fed nematode larvae (*C. elegans*) with either pathogenic or innocuous (control) bacterial strains and measured heat tolerance and resistance to different pathogens in adults. Nematodes fed the pathogenic bacterial strain showed higher levels of HSP (*HSP-16.2*) expression, increased heat tolerance and greater resistance to other pathogens (Leroy *et al*., 2012). Similarly, the immune system of *D. melanogaster* was activated by exposing individuals to heat-killed bacteria, and this activation improved knockdown times during HS (Hector *et al*., 2020). However, this response was not generalizable as it was only observed in certain populations (Hector *et al*., 2020). The links between temperature-related stress and pathogen resistance remain when pathogen exposure is the secondary stressor (see Cold stress). For example, heat-shocked (39°C for 60, 90, and 120 min) brown mosquitoes (*Culex quinquefasciatus*) showed a 2.6- and 1.5-fold increase in survival when exposed to toxins produced by *Bacillus thuringiensis israelensis*, compared to non-heat-shocked controls (Barik *et al*., 2018). Similarly, corals (*Porites cylindrical*) exposed to an elevated water temperature (32°C compared to a control temperature of 27°C) had heighted constituent immunity compared to controls (Palmer, 2018).

Cross-protection interactions involving pathogens have also been examined within aquaculture and poultry farming contexts. High-density aquaculture operations have increased

the need to protect animals from the spread of diseases, and vaccines are often administered. Huising *et al.* (2003) found that the efficacy of an immersion vaccine can be enhanced in common carp (*Cyprinus carpio*) by exposing fish to an osmotic challenge before vaccination. The osmotic challenge increased the uptake of the vaccine in fish by temporarily disrupting the gill epithelium, and immune system activation was also more pronounced in fish primed with an osmotic shock. Similarly, resistance to a lipopolysaccharide challenge can be heighted in chickens (*Gallus domesticus*) by exposing embryos to heat stress (Rosenberg *et al.*, 2020). Chickens that had experienced heat stress as embryos exhibited substantial reductions in hypothalamic inflammation when exposed to the lipopolysaccharide challenge.

Starvation and feed restriction

Starvation stress can occur when an animal fails to consume food or consumes insufficient food to cover minimum energetic requirements. Most species experience periods of intermittent food limitation during their lifetime. Periods of starvation can occur predictably (e.g. tidal, seasonal) or be caused by unpredictable forces (e.g. stochastic events such as fires, floods or by inter- and intra-specific competition; McCue *et al.*, 2017). To cope with the stress of starvation, many species respond physiologically by undergoing periods of metabolic rate suppression (McCue, 2010, Semsar-kazerouni *et al.*, 2020), upregulate cellular responses (e.g. HSPs; Cara *et al.*, 2005, Yengkokpam *et al.*, 2008) and exploit stored body reserves (primarily lipids, glycogen) to maintain homeostasis and fuel vital metabolic pathways necessary for survival (De Boeck *et al.*, 2013, Hervant, 2013). When starved, animals also alter their behaviour (e.g. starvation-induced hyperactivity, selection of cooler microhabitat by ectotherms, periods of hibernation and torpor in birds and mammals; Geiser, 1988, Killen, 2014, Yang *et al.*, 2015) in an attempt to conserve mass and energy. Such mechanisms used to cope with starvation can confer cross-protection to other stressors (Table 1 and 2). For instance, De Boeck *et al.* (2013) found that oscars (*Astronotus ocellatus*) are more tolerant of low oxygen levels (as measured by the critical oxygen tension, P_{CRIT}) when previously starved for 10–14 days. Similarly, during starvation, *D. melanogaster* conserve glycogen stores and subsequently retain large amounts of metabolic water (Djawdan *et al.*, 1998), which increases their capacity to resist desiccation (Bubliy *et al.*, 2012). This capacity to redirect energy stores during periods of starvation can sometimes prime organisms against the threat of other stressors.

Paradoxically, periods of starvation can improve tolerance to elevated temperatures. Studies on various invertebrate species have found that starvation (of varying degrees) can induce cross-protection to elevated temperatures by increasing upper thermal tolerance limits (c.f. Bubliy *et al.*, 2012, Scharf *et al.*, 2016). For example, starved amphipods (*Gammarus fossarum*) showed improved survival when exposed to an acute, high-intensity heat treatment (Semsar-kazerouni *et al.*, 2020). Similarly, African fruit flies (*C. rosa*) that were starved for 10 days tolerated significantly warmer temperatures than their recently fed counterparts (Gotcha *et al.*, 2018), a result attributed to the accumulation of lipids that occurs during starvation in insects (Djawdan *et al.*, 1998). This accumulation of energy reserves may have benefitted starved flies during subsequent heat stress by allowing them to redirect energy reserves towards energetically demanding processes, such as the production of HSPs (Sokolova, 2013). Cross-protection between starvation and heat stress has also been documented among endothermic animals. Broiler chickens fed on a 60% (but not 80% or 40%) food ration experienced improved heat tolerance; an effect that was correlated with an enhanced ability to express HSP70 in the brain (Zulkifli *et al.*, 2003). Feed-restricted chickens also had smaller increases in heterophil/lymphocyte (H/L) ratios (an indicator of perceived stress in birds; Gross and Siegel, 1983), were more resistant to infection (marble spleen disease), and grew better than counterparts fed *ad libitum* under heat stress (7 days at 35°C; Zulkifli *et al.*, 1994).

Starvation may also be a protective strategy to survive under cold stress. Ectothermic animals can succumb to cold temperatures due to depressive effects on enzyme activity levels, reduced fluidity of membranes, reduced neuromuscular function and an overall energy supply shortage causing cell damage (Andersen *et al.*, 2013, Lu *et al.*, 2019). Yet, when starved, several incidences of cross-protection to acute cold temperatures have been documented in the literature. For example, following 4 days of starvation, cold tolerance was increased by ~1°C in two species of moth (*Busseola fusca* and *Sesamia calamistis*) and increased by a remarkable ~3.5°C in the spotted stalk borer (*Chilo partellus*; Mutamiswa *et al.*, 2018). Similarly, starvation decreased the chill coma recovery time, a measure of cold tolerance in insects, of silkworm (*Bombyx mori*; Mir *et al.*, 2018) and of migratory locust *(L. migratoria*; Andersen *et al.*, 2013). The mechanism for cross-protection between starvation and cold temperature tolerance among insects is likely associated with lipid metabolism (Sinclair *et al.*, 2015) and a faster recovery of muscle potassium concentrations, muscle water content and haemolymph ion equilibria (Na^+ and K^+) of fasted compared to fed animals (Andersen *et al.*, 2013). Cross-protection between starvation and cold temperatures has also been detected among fishes. Resistance to an acute cold shock, for example, was enhanced in zebrafish (*D. rerio*) fasted for 3 days (Lu *et al.*, 2019). This increased tolerance to cold temperatures was correlated with lipid catabolism and cell damage attenuation. Overall, starvation often confers cross-protection to cold temperatures in ectotherms.

Cross-protection in conservation

As stressors continue to multiply in ecosystems, it is essential that we understand the interactions among them so that informed conservation and management actions can be

developed. Complete eradication of stressors is an unrealistic goal, because it requires the removal of stressor drivers (e.g. ceasing water extraction for agricultural purposes), which often conflict with human demands. Conservation funds are also limited, highlighting the importance of directing funds towards the mitigation of stressors that provide the greatest ecosystem benefit. The majority of conservation plans target stressors in isolation and overlook potential interactions, which may lead to less effective conservation outcomes. However, many organizations are moving towards developing multi-stressor frameworks. For example, the Ontario Ministry of Natural Resources and Forestry developed a framework (i.e. Driver-Pressure-State-Impact-Response, DPSIR framework) for freshwater lakes and rivers, which is a conceptual tool that aids in identifying appropriate management options depending on stressor interactions (Chu *et al*., 2018). The DPSIR framework is one of the first decision-making tools to explicitly acknowledge cross-protection interactions (termed 'ecological surprises' in the tool) and suggests interaction-specific management actions. For example, where synergistic interactions (i.e. when stressors amplify each other's negative effects) are identified, the DPSIR framework recommends prioritizing the dominant (exacerbating) stressor for mitigation. In contrast, where protective interactions are identified, the DPSIR framework recommends monitoring the stressor effects rather than mitigating the stressors.

Multi-stressor research is integral to the development of decision-making tools for species conservation. However, synergisms have been overrepresented in ecological and conservation literature, despite other interaction types (antagonisms, additive) being just as common (Côté *et al*., 2016). Due to their nature, synergistic interactions are particularly threatening to species persistence, but focusing exclusively on these interactions may discourage policymakers from taking action and overlook opportunities inherent to cross-protection interactions. Identifying and understanding cross-protection interactions allows managers to avoid costly and unrealistic 'blanket plans' that aim to eliminate all forms of stress. Instead, management plans could aim to conserve the synchronicity of natural stress cycles (e.g. heat and desiccation coupling), where cross-protection has evolved naturally. Cases of natural cross-protection may be disrupted by climate change processes, particularly if co-occurring stressors are decoupled. Phenological shifts may disrupt the temporal coupling of stressors, potentially leaving species less prepared for subsequent stress. Climate change may also alter the intensity of stressors, by for example, extending dry seasons or increasing the severity of droughts. A change in stressor severity is likely to alter the nature of stressor interactions, where mild stress is generally conducive to the development of cross-protection, but severe stress is not (e.g. Gantz and Lee 2015, Smallbone *et al*., 2016, Todgham *et al*., 2005). For example, a +12°C HS proved beneficial in ameliorating the effects (survival) of salinity stress (90 ppt) in tidepool sculpins, but a +15°C HS was too strong and increased mortality (Todgham et al., 2005). Similarly, short-term desiccation stress (2–4 h at 0% relative humidity) improved the survival of Goldenrod gall fly (*E. solidaginis*) when exposed to a subsequent cold shock (−18°C for 24 h), but 12 h of desiccation (0% relative humidity) did not provide cross-protection benefits (Gantz and Lee, 2015). Therefore, conserving natural cross-protection interactions may prevent stress-driven episodes of selection, and the attrition of genetic variation in vulnerable populations (Brévault *et al*., 2011, Coors *et al*., 2009).

Cross-protection interactions may also be taken advantage of more directly. For example, where the use of insecticides is necessary to meet food production demands, non-target species may be preconditioned with mild stress so they are more resilient (e.g. Box 2). Similarly, mass mortalities of aquaculture species are increasing due to heatwaves becoming more intense and frequent. But, cross-protection studies suggest there is potential to prime some species with a mild stressor so they are better prepared for heat stress (Table 1). Aquaculture practices could also be refined to benefit from cross-protection interactions. Aquaculture is set to play a pivotal role in species' conservation (e.g. by enhancing wild fisheries, restoring endangered populations and replacing wild species on the food market; Diana, 2009, Froehlich *et al*., 2017), with the term 'conservation aquaculture' being coined in recent decades (Anders, 1998). Yet, aquaculture species face an unprecedented number of stressors due to the intensification of operations and the challenges arising from climate change (Froehlich *et al*., 2018, Stewart-Sinclair *et al*., 2020). Refining aquaculture practices so that cross-protection interactions are taken advantage of is a promising strategy. For example, stress-priming salmon in freshwater facilities before they are transported to seawater pens can increase survival rates during this osmotic challenge (Box 1; Dubeau *et al*., 1998).

Cross-protection interactions may also be pivotal when considering stress mitigation at both local and global scales. Global stressors, like climate warming and ocean acidification, require the cooperation of several countries for effective mitigation. Contrarily, local stressors, like heavy metal contamination in a lake, are easier to ameliorate by on-the-ground actions. For this reason, local stressors should be managed in a way that increases species resilience to global stressors. For example, a myriad of mild stressors can provide heightened heat tolerance in ectotherms (Tables 1–3), and allowing these stressors to persist in habitats may protect species from episodic heatwaves. However, key to the successful implementation of such a strategy is the inclusion of stressor intensity thresholds into management plans. Cross-protection interactions are highly sensitive to the intensity of the priming stressor; above a critical threshold, stress exposure is detrimental, but below the critical threshold cross-protection develops (e.g. Todgham *et al*., 2005). It might be difficult for management action plans to dial in on exact levels of exposure to a priming stressor to promote cross-protection to secondary stressors. However, as we gain increasing control over the environment (physical control, e.g. water mixing, artificial aeration, water removal, vegetation control;

Box 2. Cross-protection to pesticides in the wood frog (*Lithobates sylvaticus*)

Pesticide use is integral to many agricultural operations. However, pesticides not only impact pest species but also impact non-target species. Amphibian populations are particularly sensitive to pesticide use and global declines in amphibian numbers have been linked to pesticide exposure (Wake, 2012). In an effort to find a solution to this conservation problem, Hua *et al.* (2014) investigated whether cross-protection to pesticides could be induced in wood frogs (*L. sylvaticus*). As embryos, wood frogs were exposed to a sub-lethal dose of an insecticide (carbaryl) as a priming stressor and the control group was not exposed to insecticides. Tolerance to other insecticides (chlorpyrifos, malathion, permethrin, cypermethrin) was subsequently measured in both treatment groups as tadpoles. Carbaryl priming induced cross-protection in the tadpoles, where their tolerance to two of the four insecticides (malathion and cypermethrin) was heightened. Pesticide use is projected to increase in the future, to meet the demands of a continually growing human population. Thus, using cross-protection interactions to heighten the resilience of nontarget species to pesticides is a promising conservation action. *Images by Jessica Hua (left) and Christopher E. Smith (right).*

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chemical control, e.g. nutrient precipitation, sediment dredging; biological control, e.g. re/introduction of species, removal of species, pesticides/herbicides), controlling stressor intensity and duration may become more feasible. Adding further complexity is the importance of the RP between the priming stressor and secondary stressor that is sometimes required before cross-protection develops. Cases where cross-protection is instantaneous may therefore be better suited to conservation actions. The longevity of cross-protection benefits have not been characterized for most stressor combinations, reflecting a pressing knowledge gap. Protective benefits may be brief (hours), last throughout a lifetime (Le Bourg, 2016), or even persist between generations (Plautz *et al.*, 2013). For example, freshwater snails (*B. glabrata*) raised in the presence of predators produced offspring that were more tolerant of cadmium contamination (Plautz *et al.*, 2013). Cases of transgenerational cross-protection are particularly promising for conservation actions because they represent an avenue for rapid, non-genetic compensation to changing conditions. However, very little is known about cross-tolerance within a trans- and multi-generational context.

Although cross-protection interactions provide obvious benefits, the potential costs associated with these interactions must be considered. Most studies have overlooked the costs that cross-protection may incur, but some studies have observed fitness trade-offs. For example, harsh cold stress in the red flour beetle (*T. castaneum*) led to improved starvation tolerance, but these beetles were also less active and suffered from a reduced probability of mating (Scharf *et al.*, 2019). Similarly, although freshwater snails (*B. glabrata*) exposed to predation stress produced offspring with higher contamination tolerance, this came at the cost of producing fewer offspring compared to non-stressed snails (Plautz *et al.*, 2013). Understanding the costs associated with cross-protection interactions is a large research gap, and further work is required so that cost–benefit analyses can be performed before the integration into management plans.

Conclusion and research gaps

Cross-protection may act as a pre-adaptation to a changing world (Sinclair *et al.*, 2013), and here we have highlighted many cases of cross-protection among novel/human-driven stressors. These protective interactions occur across a diverse range of taxonomic groups, and among both abiotic and biotic stressors. However, research efforts have been biased towards assessing the effects of abiotic stressors in insects and fishes, and increasing our understanding of cross-protection interactions in other taxa (e.g. mammals, birds, amphibians, reptiles, arthropods) and among biotic stressors is a priority. While the recent increase in studying cross-protection within a global change context is encouraging, many interactions among emerging or recently recognized stressors (e.g. noise pollution, microplastic pollution and the spread of invasive species) are yet to be characterized. Efforts should focus on understanding if stressors currently present in habitats can provide cross-protection to novel threats predicted to emerge with climate change. Moreover, evidence for cross-protection

has arisen primarily from laboratory-based studies that often use extreme or unrealistic stressor treatments. Field validation studies are therefore necessary to determine if cross-protection interactions can be observed among free-ranging animals exposed to realistic stressor treatments. Moving forward, we also require a greater understanding of how long cross-protection lasts for, and if there are any costs associated with the expression of cross-tolerant phenotypes. Elucidating the costs associated with cross-protection will allow for a greater understanding of the selection pressures potentially driving protective interactions, and how these interactions may play out between generations. Understanding the costs of cross-protection will also allow managers to weigh up protection benefits against any trade-offs. Harnessing the power of cross-protection interactions will become increasingly necessary if atmospheric carbon dioxide concentrations exceed 'tipping points' (Schneider *et al*., 2019), and the management of local stressors is the last line of defence. The studies outlined in this review highlight the promise of cross-protection interactions in a changing world and reinforce the need for additional investigation. Improving our understanding of cross-protection interactions and the underlying mechanisms is key in projecting how species will cope with a changing world and concurrently developing conservation solutions that provide the best chance of success.

Glossary

Stress/stressor: changes in an organism's habitat that compromise fitness or performance.

Cross-protection: a phenomenon where exposure to an initial stressor elicits a beneficial response that protects the organism from a subsequent stressor of a different nature.

Cross-tolerance: a type of cross-protection where stressors share protective mechanisms.

Cross-talk: a type of cross-protection where stressors share signalling/regulatory pathways that activate independent protective mechanisms.

Priming stressor: the initial, often mild, stressor organisms experience before exposure to a subsequent stressor of a different nature.

Secondary stressor: the second stressor an organism experiences following exposure to a priming stressor.

Supplementary material

Supplementary material is available at *Conservation Physiology* online.

Funding

This work was supported by the University of Canterbury.

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