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COMMENTARY

CENTENARY ARTICLE

The mechanistic basis and adaptive significance of cross-tolerance: a 'pre-adaptation' to a changing world?

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ABSTRACT

Protective responses are pivotal in aiding organismal persistence in complex, multi-stressor environments. Multiple-stressor research has traditionally focused on the deleterious effects of exposure to concurrent stressors. However, encountering one stressor can sometimes confer heightened tolerance to a second stressor, a phenomenon termed 'cross-protection'. Cross-protection has been documented in a wide diversity of taxa (spanning the bacteria, fungi, plant and animal kingdoms) and habitats (intertidal, freshwater, rainforests and polar zones) in response to many stressors (e.g. hypoxia, predation, desiccation, pathogens, crowding, salinity, food limitation). Remarkably, cross-protection benefits have also been shown among emerging, anthropogenic stressors, such as heatwaves and microplastics. In this Commentary, we discuss the mechanistic basis and adaptive significance of cross-protection, and put forth the idea that cross-protection will act as a 'pre-adaptation' to a changing world. We highlight the critical role that experimental biology has played in disentangling stressor interactions and provide advice for enhancing the ecological realism of laboratory studies. Moving forward, research will benefit from a greater focus on quantifying the longevity of cross-protection responses and the costs associated with this protective response. This approach will enable us to make robust predictions of species' responses to complex environments, without making the erroneous assumption that all stress is deleterious.

KEY WORDS: Cross-protection, Cross-talk, Inducible stress tolerance, Pre-conditioning, Multiple stressors, Stressor interactions

Introduction

Sometimes a little bit of stress is good, and to be forewarned is to be forearmed. Cross-protection (see Glossary) is a phenomenon where exposure to a stressor, be it biotic or abiotic, heightens organismal resilience to a second stressor of a different nature (Rodgers and Gomez Isaza, 2021). Here, we define stressors (and stress) as any alteration in an organism's environment that compromises performance or fitness (Schulte, 2014). Comparative physiologists have long been fascinated with how organisms tolerate and respond to environmental stressors, allowing us to uncover how physiological systems acclimatize and adapt to challenging environments (e.g. Beadle, 1939; Bentley et al., 1958; Brijs et al., 2020; Rodgers and Franklin, 2017; Storz et al., 2010; Wright et al., 1990). Many of these investigations have involved quantifying organismal responses to a stressor in isolation but, to better reflect nature, recent focus has shifted to quantifying interactions among multiple stressors (Blewett et al., 2022; Gomez Isaza et al., 2020; Opinion et al., 2020; Sokolova, 2021; Todgham and Stillman, 2013). It is now widely accepted that organisms rarely face one stressor at a time, and instead contend with a complex suite of stressors simultaneously (Todgham and Stillman, 2013).

Experimental biology has been pivotal in disentangling complex stressor interactions with the use of tightly controlled factorial experiments, through which the isolated and combined effects of stressors can be elucidated (e.g. Dezetter et al., 2022; Rodgers et al., 2019). This work has revealed that stressor interactions frequently result in 'ecological surprises', where the combined effect of stressors is non-additive, with either synergistic or antagonistic effects whereby stressors amplify or dampen each other's negative effects, respectively (Côté et al., 2016; Piggott et al., 2015). Stressors sometimes activate shared protective mechanisms (termed 'cross-tolerance'; see Glossary) or shared signalling pathways that activate independent protective mechanisms (termed 'cross-talk'; see Glossary) (Rodgers and Gomez Isaza, 2021; Sinclair et al., 2013). When stressors share protective mechanisms or signalling pathways, exposure to one stressor results in increased tolerance to the other stressor. For example, exposure to cold shock often increases desiccation resistance in polar insects because these stressors can be countered through shared mechanisms (e.g. upregulation of cryoprotectants, osmoprotectants and molecular chaperones; Hayward et al., 2007; Sinclair et al., 2013). Similarly, heat acclimation can increase hypoxia resistance in rats (*Rattus norvegicus*) as a result of higher hypoxia-inducible factor-1 (HIF-1) protein levels and a concomitant increase in erythropoietin expression (Maloyan et al., 2005).

Cross-protection (encompassing both cross-tolerance and cross-talk) has been documented across a wide diversity of taxa, from the bacteria, fungi, plant and animal kingdoms (Brown et al., 2014; Bueno et al., 2023; Foyer et al., 2016; Hůla et al., 2022; Rodgers and Gomez Isaza, 2021). In the animal kingdom alone, cross-protection has been documented in over 50 species, spanning insects, arthropods, fishes, amphibians, birds and mammals from a diversity of habitats (e.g. intertidal, freshwater, rainforests and polar zones) in response to a wide range of stressors (Fig. 1). From an eco-physiological perspective, the concept of cross-protection provides a basis for evolutionary adaptation of organisms exposed to multiple stressors in nature. Cross-protection is frequently observed between stressor pairs that co-occur or co-vary predictably in nature, such as cold and desiccation (Hůla et al., 2022) or heat and hypoxia (Del Rio et al., 2019), as discussed above, and also between cold and food limitation (Rodgers et al., 2019), and heat and salinity (Denny and Dowd, 2022; Song et al., 2005). Intertidal species, for example, are exposed to a series of stressors that co-vary with tidal changes and, unsurprisingly, cross-protection

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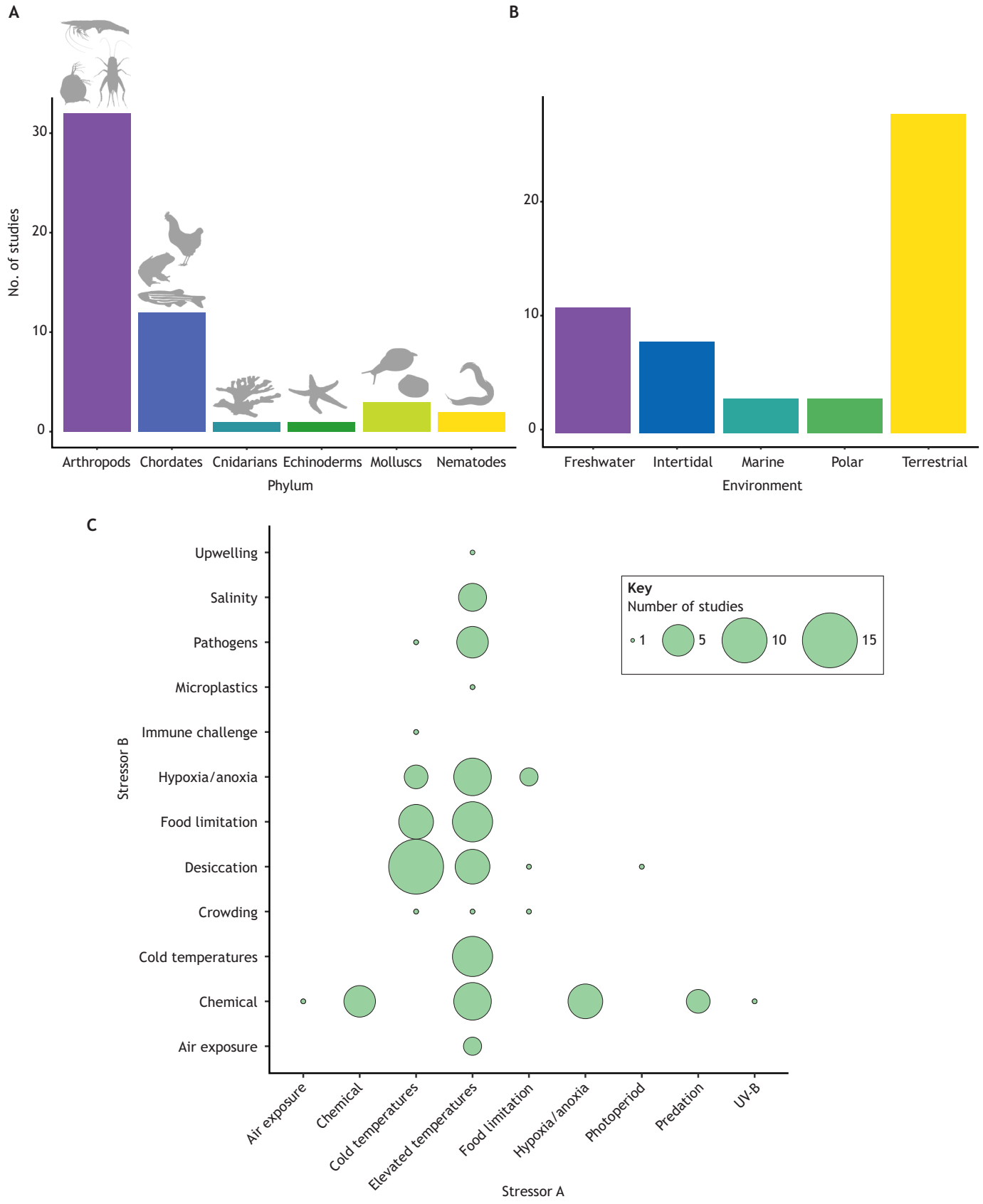

Fig. 1. Summary of cross-protection across studies and systems. (A,B) The number of studies documenting cross-protection (A) across animal phyla (arthropods, chordates, cnidarians, echinoderms, molluscs and nematodes) and (B) across environments. (C) Bubble-plot of cross-protection among pairs of stressors (stressor A and stressor B), with larger circles representing a greater number of studies conducted on that stressor pair. The data were identified through a Web of Science using search terms from Rodgers and Gomez Isaza (2021). Animal silhouettes were sourced from PhyloPic (www.phylopic.org).

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Glossary

Acclimation cross-protection
Long-term (days–months) cross-protection based on physiological remodelling following chronic exposure to a priming stressor in a laboratory setting. Also known as cross-acclimation.

Acclimatisation cross-protection
Long-term (days–months) cross-protection based on physiological remodelling following chronic exposure to a priming stressor in nature.

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

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

Heterologous stressor
A stressor that is different from the original or primary stressor that caused a stress response in an organism.

Priming stressor
The initial, often mild, stressor that an organism experiences before exposure to a subsequent stressor of a different nature.

Secondary stressor
The second stressor that an organism experiences following exposure to a priming stressor.

Transgenerational cross-protection
A phenomenon where parental exposure to a priming stressor elicits heightened tolerance to a heterologous stressor in offspring.

Transient cross-protection
Short-lived (hours–days) cross-protection induced by the upregulation of a cellular stress response.

is well documented among salinity spikes, elevated temperatures, desiccation and hypoxia (Denny and Dowd, 2022; Pallarés et al., 2017; Todgham et al., 2005).

Robust forecasting of species persistence in multi-stressor environments requires a deep mechanistic understanding of how physiology responds to current and future levels of stress. However, the road to mechanistic enlightenment is laden with complexity. Temporal patterns of covariation in stressors are accompanied by extreme climatic events and emerging threats. Forecasts based on single stressor studies, or studies where stressors are held constant, are likely to overinflate effect sizes because the potential for cross-protection has been overlooked. In this Commentary, we discuss the mechanistic drivers behind cross-protection and the adaptive significance of cross-protection, and provide advice for enhancing ecological realism in cross-protection experiments. We also put forward the idea that cross-protection may act as a 'pre-adaptation' to a changing world in which organisms face a growing number of anthropogenic threats.

Mechanistic drivers of cross-protection

Experimental biology has been pivotal in disentangling stressor interactions and in identifying the mechanistic underpinnings of these interactions. A reductionist approach has proved invaluable in determining both the isolated and combined effects of stressors, whereby a factorial experimental design is used (Dezetter et al., 2022; Rodgers et al., 2019). Factorial experimental designs allow for the classification of stressor interactions as additive, synergistic or antagonistic (Piggott et al., 2015). Synergistic interactions are overrepresented in the literature, despite antagonisms being just as common (Côté et al., 2016). Cross-protection underpins antagonistic interactions, but specific experimental designs are required to determine which stressor is responsible for inducing a cross-protective phenotype. In cross-protection experiments, organisms are first exposed to a priming stressor (see Glossary) either acutely or chronically, and tolerance to a second, heterologous stressor (see Glossary) is subsequently measured and compared with that of unstressed control organisms. If tolerance to the secondary stressor (see Glossary) is enhanced, cross-protection has occurred.

Investigating the mechanisms underlying cross-protection is critical to understanding the how and why behind protective stressor interactions. Exposure to stressors can trigger an organism's endocrine stress response, which involves the activation of the hypothalamic-pituitary–adrenal axis in mammals, birds and reptiles, and the hypothalamic-pituitary–interrenal axis in fishes (Pankhurst, 2011; Romero and Butler, 2007). In response, vertebrates produce catecholamines and glucocorticoids, while most invertebrates produce peptide proteins (such as adipokinetic hormone) to mobilize energy substrates and restore homeostasis (Orchard et al., 1993; Romero and Butler, 2007). A cellular stress response also occurs, leading to the upregulation of various heat shock proteins (HSPs) and antioxidant defences (Kültz, 2005). The preparation for oxidative stress hypothesis suggests that cross-protection occurs when a priming stressor stimulates the production of a helpful level of reactive oxygen species (Giraud-Billoud et al., 2019; Hermes-Lima et al., 2001; Hermes-Lima and Zenteno-Savín, 2002). These molecules act as signalling molecules, activating the cellular stress response and giving rise to cross-protection. Short-term activation of the stress response can therefore be highly beneficial, leaving organisms better prepared for future stress or an upcoming environmental challenge. This type of cross-protection is typically short-lived and is termed 'transient cross-protection' (see Glossary; Fig. 2A).

The upregulation of HSPs is a commonly proposed cellular mechanism underlying many cross-protection interactions. HSPs are highly conserved and, despite their name, these proteins can be upregulated in response to a wide variety of stressors, often leading to heightened stress tolerance (Basu et al., 2002). The overexpression of HSPs persists long after a stressor is removed, suggesting that these proteins can provide protection against subsequent, heterologous stressors (Bayley et al., 2001; Boardman et al., 2015; Dubeau et al., 1998). For example, nematodes exposed to heat stress (1 h at 35°C) increased the expression of *HSP-16.2* and were subsequently more tolerant of cadmium pollution compared with unstressed controls (Wang et al., 2020). Inducing a *HSP-16.2* loss-of-function mutation removes the protective benefit of heat stress, confirming that the expression of *HSP-16.2* is essential for the development of cross-protection in this case (Wang et al., 2020). A wide variety of stressors (high and low temperatures, and osmotic, anoxic, emersion and pathogenic stressors) can increase the expression or abundance of HSPs and subsequently provide heightened tolerance to a heterologous stressor (Bayley et al., 2001; Boardman et al., 2015; Dubeau et al., 1998; Hu et al., 2020; Leroy et al., 2012; Semsar-kazerouni et al., 2020).

In general, cross-protection interactions between acute stressors are underscored by the upregulation of a cellular stress response. But the mechanisms underlying cross-protection differ when stressors are experienced chronically. When chronic stressors affect shared physiological systems (e.g. the cardiovascular system), an acclimation/acclimatisation response to one stressor often results in heightened tolerance to another stressor (Rodgers and Gomez Isaza, 2021). In aquatic ectotherms, for example, overlap exists in the physiological remodelling underlying acclimation to heat and hypoxia stress (Collins et al., 2021b). Chronic exposure to either stressor typically results in

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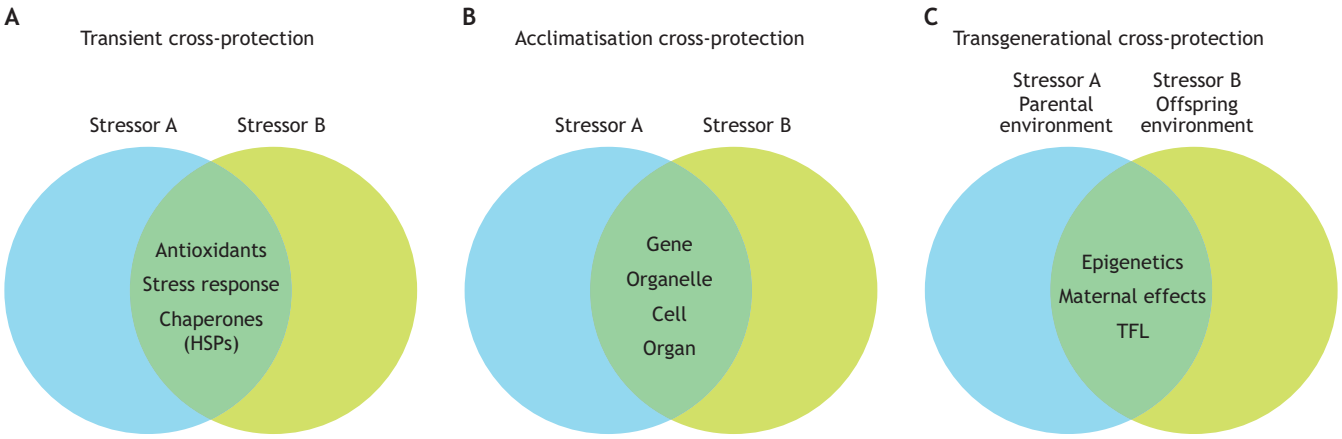

Fig. 2. Mechanistic basis for cross-protection interactions. Circles represent two heterologous stressors that provide cross-protective benefits when they share overlapping protective mechanisms or signalling pathways. (A) Transient cross-protection can arise from short-term exposure to a priming stressor (stressor A) that activates a generalised stress response and confers protection to a second stressor of a different nature (stressor B). HSPs, heat shock proteins. (B) Acclimatisation (or acclimation) cross-protection can occur when long-term exposure to one stressor induces physiological changes (from gene to organismal levels) that provide overlapping protection to a second, heterologous stressor. (C) Transgenerational cross-protection occurs when parental exposure to a priming stressor elicits heightened tolerance to a different stressor in offspring through genetic and non-genetic mechanisms. TFL, transcriptional frontloading. Ecological realism can be enhanced in cross-protection experiments by mimicking natural stressor variation and dynamics.

similar changes to the cardiorespiratory system (e.g. larger respiratory surface areas, altered ventricle size and morphology), giving rise to a cross-protective phenotype (Collins et al., 2021b). For example, when channel catfish (*Ictalurus punctatus*) are acclimated to hypoxia (50% air saturation), remodelling of the cardiovascular system enables fish to maintain heart rate and blood pressure at higher temperatures compared with controls; this translates to heightened heat tolerance (Burleson and Silva, 2011). Here, we refer to this type of cross-protection as 'acclimation cross-protection' (see Glossary; when observed in a laboratory setting) or 'acclimatisation cross-protection' (see Glossary; when observed in nature; Fig. 2B). Acclimatisation/acclimation cross-protection may also involve 'transcriptional frontloading', where long-term changes to constituent gene expression (typically cellular defence and metabolic genes) occur in response to stress exposure (Barshis et al., 2013; Palumbi et al., 2014). For example, Collins et al. (2021a) recently found that cross-protection between chronic warming and chronic hypoxia was underscored by changes in the expression of hundreds of genes, leading to a hypometabolic phenotype. Transcriptional frontloading may be a key mechanism underlying cross-protection among chronic stressors, and this newly proposed mechanism is a promising avenue for future work.

Cross-protection interactions can also operate across generations, where parental stress exposure gives rise to offspring with heightened tolerance to a different stressor. For example, parental exposure to predator stress in freshwater snails (*Biomphalaria glabrata*) results in juvenile offspring that are more tolerant of a contaminant stressor, cadmium (Plautz et al., 2013). Parental stress exposure, in some cases, allows parents to 'prepare' offspring for future stressful conditions through non-genetic inheritance or epigenetic processes, termed 'transgenerational plasticity' (Badyaev and Uller, 2009; Bonduriansky et al., 2012; Ho and Burggren, 2010; Yin et al., 2019). Cross-protection operating across generations is termed 'transgenerational cross-protection' (see Glossary) and is thought to occur when stressors in parental and offspring environments share protective mechanisms/stress responses (Fig. 2C; Chang et al., 2023; Plautz et al., 2013). Although transgenerational plasticity is an area of intense investigation, very little is known about transgenerational cross-protection because most studies expose parents and offspring to the same stressor.

Adaptive significance of cross-protection

Individuals with heightened levels of cross-protection may be afforded considerable fitness advantages in highly heterogeneous environments (e.g. tidepools), during extreme climatic events (e.g. heatwaves, cold snaps) and in response to novel anthropogenic stressors (e.g. microplastics). Numerous studies show that cross-protection can translate to increased survival during episodic selection events under challenging environmental conditions (Adhikari et al., 2010; Chidawanyika and Terblanche, 2011; Dubeau et al., 1998; Gotcha et al., 2018; Lu et al., 2019). For example, the capacity of tidepool sculpins (*Oligocottus maculosus*) to withstand osmotic stress (90 ppt for 2 h) greatly increases following a +12°C heat shock, with survival rates increasing from 68% in control fish to 96% in heat-primed fish (Todgham et al., 2005). However, it remains unknown whether these fitness advantages hold in nature because most studies have been lab based.

Overall, the adaptive potential of cross-protection is hypothesised to be mediated by the longevity of these interactions (Fig. 3), coupled with the severity, timing and predictability of the priming stressor. Transient cross-protection offers heightened stress resilience for hours to days, generally reflecting the time span of cellular stress responses, leaving a narrow time window for protective interactions to arise (Fig. 3). The fitness advantages of transient cross-protection may only be realised in habitats with stressors that regularly co-vary in a predictable pattern on an hourly or daily time scales, such as the changing conditions in tidepools. In contrast, acclimatisation/acclimation and transgenerational cross-protection may offer greater protection against novel or unpredictable stressors because these responses can be long lasting, and the occurrence of stressors does not need to align in a predictable sequence (Fig. 3). The probability of cross-protection occurring is also strongly tied to the severity (i.e. magnitude and duration) of the priming stressor. In general, mild levels of stress induce cross-protective phenotypes, whereas more severe stress loads can have the opposite effect, where organismal susceptibility to future stress increases (i.e. cross-susceptibility) (Rodgers and Gomez Isaza, 2021). The development of cross-protection can also be non-linear with stressor intensity (Rodgers and Gomez Isaza, 2022). Despite the nuanced nature of cross-

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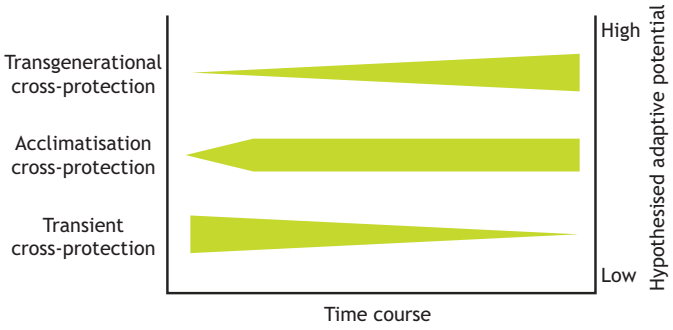

Unknowns:
- Longevity of the stress response
- Costs and trade-offs of cross-protection
- Heritability of cross-protection
- Field observations (e.g. using data loggers or biologgers)
- Natural stressor dynamics

Fig. 3. adaptive potential of cross-protection interactions. The adaptive potential of cross-protection interactions is predicted to be related to the time course of protective mechanisms. Transient cross-protection provides rapid, but short-lived (hours–days) protection, whereas acclimatisation (or acclimation) and transgenerational cross-protection operate over longer time courses (weeks–generations). Our understanding of the adaptive potential of each type of cross-protection is hindered by several knowledge gaps and unknowns, including the longevity of the stress response and cross-tolerance benefits, the potential costs and trade-offs associated with cross-tolerant phenotypes, the heritability of cross-tolerance, and how cross-tolerance operates under field conditions with natural stressor dynamics.

protection, experimental evidence offers a solid basis for continued exploration of the adaptive potential of these interactions.

Cross-protection: a 'pre-adaptation' to a changing world?

The conserved nature of the stress response suggests that exposure to natural stressors, currently present in habitats, may shield species from novel, anthropogenic stressors (e.g. heatwaves, metal pollution, microplastics). In this sense, cross-protection may be viewed as a 'pre-adaptation' to global change stressors. For example, several species can increase their heat tolerance when primed with a natural stressor. Exposure to desiccation stress (e.g. Benoit et al., 2009), food limitation (e.g. Semsar-kazerouni et al., 2020), crowding (e.g. Henry et al., 2018), hypoxia (e.g. Del Rio et al., 2019) and cold shock (e.g. Scharf et al., 2016) has been shown to elicit protection against high temperatures, with upper thermal limits increasing by 2–28% and survival rates at elevated temperatures increasing by 8–335% (Rodgers and Gomez Isaza, 2021). The presence of these stressors, at the right level, may therefore prepare species for abrupt temperature spikes, such as heatwaves. Cross-protection can also hold in the opposite direction, with heat stress being the priming stressor. For instance, exposure to elevated temperatures can induce cross-protection to a number of heterologous stressors (e.g. osmotic stress, heavy metal pollution) in both endotherms and ectotherms (Kalra et al., 2017; Peaydee et al., 2014; Rosenberg et al., 2020), suggesting that habitat warming, in some cases, may buffer species from additional threats.

Observations of cross-protection have recently led researchers to explore the possibility of engineering cultured agricultural/aquaculture species that are resistant to warmer environments (Foyer et al., 2016; Gomez Isaza and Rodgers, 2022; Pettinau et al., 2022; Rodgers and Gomez Isaza, 2022). Cross-protection studies suggest that economically valuable species could potentially be primed with a mild stressor, so they are better prepared for future heat stress. For example, upper thermal limits are increased by 0.6°C in Chinook salmon (*Oncorhynchus tshawytscha*) exposed to salinity stress, and by 3.6°C in rainbow trout (*Oncorhynchus mykiss*) exposed to exercise stress (Pettinau et al., 2022). This work is in its infancy, but it represents a promising avenue for sustainably culturing species that are resilient to a warmer world.

Remarkably, cross-protection is also proving effective in combating a number of emerging, anthropogenic stressors (Rodgers and Gomez Isaza, 2021). For example, exposure to heat, hypoxia and ultraviolet-B radiation stress can heighten pesticide and pollutant resistance in a range of species, from nematodes to fishes (Fig. 1C; Alzahrani and Ebert, 2018; Dolci et al., 2013, 2017, 2014; Fitzgerald et al., 2016; Schunck and Liess, 2022; Wang et al., 2020). Similarly, exposure to polystyrene microplastics over two generations can increase heat tolerance in *Daphnia magna* (Chang et al., 2023). Cross-protection to emerging stressors is likely to occur when the priming stressor and the emerging stressor have overlapping protective mechanisms. Thus, once we understand the protective mechanisms associated with an emerging stressor, we may be able to predict which stressors will be effective in conferring cross-protection. Although there has been a recent increase in studying cross-protection within a global change framework, these interactions remain uncharacterised for many emerging threats, such as ocean acidification and noise pollution.

Increasing ecological realism in cross-protection experiments

Hypervariable environments lend themselves well to revealing the origins and adaptive potential of cross-protection interactions. Species inhabiting dynamic environments such as intertidal zones, alpine environments and arid zones are likely to show cross-protection amongst the many co-varying stressors in their habitat. If cross-protection has arisen from the co-evolution of response mechanisms to multiple, co-occurring stressors, we can hypothesise that we will observe higher frequencies of cross-protection in species living in hypervariable environments. But this hypothesis is yet to be tested. The source of experimental organisms is therefore another important consideration. Much of what we know about the eco-physiological limits of species is based on experiments where organisms have been held under constant, benign conditions for several generations prior to testing. However, this approach drastically oversimplifies how stressors operate in nature, with organisms often being faced with several episodes of stress, sometimes in close succession. This issue can be overcome by collecting 'fresh' experimental specimens from the field (e.g. von Weissenberg et al., 2022) or by simulating multiple, sequential stressor events in laboratory experiments. This approach can begin to answer questions about the cumulative effects of multiple stressor exposure, and how cross-protection may operate across a lifetime of stressful events.

Designing ecologically relevant experiments is challenging but greater value needs to be placed on realistic laboratory experiments. Capturing the natural interplay of stressors in space and time can be achieved by deploying data loggers at field sites (e.g. Denny and Dowd, 2022; Kern et al., 2015) or by attaching biologgers to study organisms. For example, Denny and Dowd (2022) recorded the temporal patterns of temperature and salinity in splash-pools inhabited by a copepod species (*Tigriopus californicus*), finding these variables to covary such that when salinity is high, temperature is also high. Laboratory experiments were subsequently designed using ecologically relevant levels and timings of salinity and temperature spikes, finding that the splash-pool copepod is well adapted to these conditions, with temperature spikes rapidly inducing cross-protection to salinity spikes (Denny and Dowd, 2022). Moving forward, research

will benefit from greater focus on designing treatments that mimic stressor dynamics in nature. Stressors are sometimes experienced sequentially in nature (Rodgers, 2021), leaving a window for preparatory mechanisms to occur. But multi-stressor studies typically expose organisms to stressors simultaneously, making it difficult to identify cross-protection interactions that take time to develop. In eutrophic habitats, for example, aquatic species are typically exposed to nutrient pollution prior to algal bloom development and associated stressors (which include increased turbidity, nightly hypoxia and low light; Rodgers, 2021). Temporal separation of stressors can be key because it provides organisms with a period during which a stress response is mounted or physiological remodelling occurs (Todgham et al., 2005).

Designing studies with realistic temporal patterns of stressor exposure will be an important next step in this field, and emerging technology shows great promise in this regard. Multi-stressor experiments are logistically challenging and time consuming because they require the careful maintenance of conditions across many tanks or enclosures. These challenges have restricted researchers to simplified study designs, typically limited to stressor pairs held at constant levels. The advent of new technology – for example, computer-controlled aquatic systems where water characteristics such as temperature, dissolved oxygen and pH can be carefully manipulated (e.g. using Loligo's omniCTRL system) – will allow for more complex study designs, with fine-scale control over stressor variability, temporal dynamics and the addition of stochastic climatic events. This level of automated control will enable the playback of stressor dynamics recorded in the field. Innovative multi-sensor biologgers also offer new opportunities for multi-stressor research. These biologgers can be attached to both aquatic and terrestrial species to collect high-resolution data on how individuals experience the interplay of several environmental variables (e.g. temperature, light levels, conductivity, dissolved oxygen) in natural habitats, while factoring in critical elements of animal behaviour, such as microclimate selection and changes in phenology (Chmura et al., 2018; Hounslow et al., 2022). These biologgers have the potential to provide unparalleled insight into how organisms experience stress in nature, and this level of detail will allow experimental biologists to bring greater realism into experiments.

Conclusions and new directions

Although cross-protection acting as a 'pre-adaptation' to climate change and emerging anthropogenic stressors is a compelling idea, many questions remain. For example, are there fitness trade-offs associated with cross-protection? Fitness trade-offs may arise owing to the energetic costs associated with expressing a cross-protective phenotype, trade-offs in trait optimisation or overcompensation in stress responses (Fadhlaoui and Couture, 2016; Loughland and Seebacher, 2020; Morgan et al., 1997). Very few studies have quantified the costs associated with cross-protection, but those that have report lower fecundity, higher mortality rates, smaller body sizes and reduced activity levels (Del Rio et al., 2019; Plautz et al., 2013; Scharf et al., 2019). For instance, transgenerational cross-protection in freshwater snails (*B. glabrata*) comes at the cost of producing fewer offspring (Plautz et al., 2013). Similarly, exposure to cold stress in the red flour beetle (*Tribolium castaneum*) induces cross-protection to starvation stress, but these beetles suffer reduced mating probability (Scharf et al., 2019). Future investigations should prioritise the investigation of potential trade-offs associated with cross-protection, by assessing energetic costs (e.g. metabolic rates and growth trajectories), performance trade-offs (e.g. locomotor performance) or reproductive costs (e.g. mating success, fecundity, offspring size). Elucidating the costs of cross-protection may shed light on the selection pressures driving protective interactions, particularly with respect to how these interactions play out between generations. The costs of cross-protection may also differ depending on stressor type and severity, making it essential that we continue to explore cross-protection for a range of stressors (including emerging threats) and severity scenarios.

To build on our current understanding of cross-protection, future experiments need to be designed to test the longevity of cross-protection benefits. Cross-protection may be transient, chronic or even transgenerational, but studies typically assess stressor tolerance at a single time point, leaving a large knowledge gap. Short-lived cross-protection may have limited adaptive potential, but we do not know which stressor combinations fall into this category. Experimental approaches can be easily modified to address this deficiency. Assessing tolerance to a secondary stressor at multiple, independent time points following exposure to a priming stressor will provide insight into the time course of cross-protection. The epigenetic and heritability processes underlying transgenerational cross-protection are another large unknown. Understanding how stress tolerance operates across several generations, with each generation experiencing different stressors, will be vitally important to generating robust forecasts of how organisms will cope in increasingly variable and unpredictable environments. Potentially, cross-protection may act as a form of bet hedging, where the probability of producing offspring that can cope with future, more stressful conditions is increased. However, this idea remains unexplored.

Field measurements of stressor dynamics will be key in designing laboratory experiments with realistic intensities and time frames between stressors. This new approach will meet the call for enhanced ecological realism within experimental biology. Studies assessing cross-protection interactions in the field, along stress gradients (homogeneous–hypervariable habitats, predictable–unpredictable stressor dynamics) may provide compelling evidence for the prevalence of cross-protection in natural environments. However, carefully designed laboratory experiments will continue to be vital in revealing the mechanistic basis of cross-protection, along with the intricacies of stressor interactions. For example, in laboratory experiments, it is important to reverse the order of stressor exposure, because cross-protection interactions do not always hold in both sequences. Exposure to salinity stress (priming stressor), for instance, increases desiccation resistance (secondary stressor) in water beetles (*Enochrus jesusarribasi* and *Nebrioporus baeticus*), indicating cross-protection, but this interaction does not hold when the stress sequence is reversed (i.e. desiccation prior to salinity stress; Pallarés et al., 2017).

Recognising that not all combinations of stress are deleterious is an important step forward in understanding how organisms cope in complex environments. The studies overviewed here highlight the promise of cross-protection acting as a 'pre-adaptation' to global change stressors and reinforce the need for further investigation. Experimental biology will continue to play a pivotal role in disentangling the complex interplay of stressors and revealing the mechanisms underlying cross-protection. Moving forward, designing experiments with ecological realism at their core will be critical in progressing our understanding of the adaptive significance of cross-protection in a changing world.

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Competing interests
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