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INSIDE JEB

Stress: from cells to ecosystems

If there is something that we all know about in the 21st century it is stress, whether it's the stress of work, financial stress or the stress of getting the next grant funded; we are all familiar with that heart-pounding, race-against-time feeling. But this is a very modern perspective on stress. As far as physiologists are concerned, stress is a well-known factor that has driven evolution and moulded the planet's ecosystems since life began. 'Stress is a hot topic', says Shireen Davies, from the University of Glasgow, UK, one of the editors of this collection of reviews, adding that the relevance of stress at a strategic level is becoming more apparent, with global concerns about climate change and food security high on the political agenda. Explaining that responses to stress can be studied at almost every biological level, from the molecular mechanisms of cellular stress responses to stress in entire populations, Davies explains that she defines stress as the loss of homeostasis – an organism's ability to maintain a stable internal environment.

Given the pressing nature of the environmental changes that we are currently experiencing and the ubiquitous nature of stress, Davies joined with two of *The Journal of Experimental Biology*'s Editors, Julian Dow from the University of Glasgow, UK, and Ken Lukowiak from the University of Calgary, Canada, to collate one of the most comprehensive collections of reviews dedicated to the topic to date. Bringing together specialists from disparate fields, Davies, Dow and Lukowiak present reviews covering stress in organisms ranging from yeast and plants to fish, birds and mammals, encompassing the molecular mechanisms that drive cellular responses to stress through to the epigenetic factors that regulate stress responses across generations.

Environmental stress

Launching the collection of reviews, Andrew Cossins, from the University of Liverpool, UK, outlines the molecular basis of cold stress in poikilothermic organisms (p. 6). Discussing what is known about the damaging effects of cold exposure at the molecular level, Cossins describes how cell membranes and protein structures are affected by low temperatures. He goes on to explain how organisms protect themselves from cold damage through a suite of protective mechanisms including: altering the ratio of unsaturated to saturated lipids to increase the fluidity of membrane structures at lower temperatures; the production of metabolites, such as glycerol, that depress the freezing point of cellular fluids and stabilise protein structures; and the expression of heat shock proteins to protect proteins from damage that can lead to cell death. Presenting work from his own laboratory, which takes a multi-omics approach to map the genetic components that underpin physiological responses to cold stress in *Caenorhabditis elegans*, Cossins describes three gene clusters that point to coherent large-scale gene responses, some of which offer new ideas for further exploration of the underpinning mechanisms.

Sea ice Rothera Station, Adelaide Island, Antarctica. Credit: P. Bucktrout (British Antarctic Survey).

Of the many challenging environments provided by our planet, the polar marine environment is amongst the most extreme. Yet the temperatures of the seas around Antarctica are the most stable in the world. Lloyd Peck and colleagues from the British Antarctic Survey, UK, and the European Institute of Marine Studies, France, explain that the Antarctic marine environment has remained virtually unchanged for the last 25 million years, resulting in the evolution of stenothermal species with little thermal tolerance. However, the rapid pace of current climate change now threatens this pristine environment. Peck and colleagues review what is currently known about the abilities of Antarctic marine species to adapt to rising temperatures (p. 16), showing that fish acclimation rates are up to four times slower than those of temperate species, while invertebrates can require as much as 5 months to acclimate to higher temperatures. The team points out that tropical marine environments also have restricted temperature variation compared with the temperate zones, placing tropical and Antarctic species at greater risk from climate change-induced thermal stress than temperate species because they are less resistant to warming.

Continuing the theme of stress in the aquatic environment, Patricia Schulte from the University of British Columbia, Canada, discusses how different populations of Atlantic killifish – which inhabit salt marshes along the length of the US eastern seaboard – have evolved to tolerate the challenges specific to their local environments (p. 23). Defining stressors as 'environmental changes that cause reductions in performance or fitness', Schulte goes on to point out that even though killifish are extremely tolerant of stressful conditions, such as changes in salinity, oxygenation and temperature, the population found at the northern extreme of the range is more tolerant of low temperatures and freshwater, while the southern population is more resistant to high temperatures and less tolerant of freshwater. Schulte adds that these differences are reflected in the levels of the stress hormone cortisol produced by the fish. She also suggests that the stable environment experienced by killifish populations in the lab could represent a stress for the animals, which are used to dealing with variation in the wild.

An organism's ability to tolerate stress is key to survival in environments that change rapidly, and in an intriguing article Art Woods discusses the role of statistical noise in gene networks and its beneficial effects in the production of plastic physiological systems that can adapt to stressful environmental change (p. 35). Woods explains how stochastic effects early in

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development are then amplified through growth to produce 'mosaic physiology' – which he defines as 'sets of diversified phenotypes, within individual organisms, that carry out related functions at the same time, but that are distributed in space'. He suggests that this diversification may better prepare organisms for unpredictable changes in their surroundings, saying, 'Mosaic physiology provides a set of standing, diversified phenotypes, within single organisms, that raise the likelihood of coping well with novel environmental challenges.'

Returning to the marine theme, John Spicer from Plymouth University, UK, discusses how marine organisms deal with the increasing phenomenon of anthropogenic hypoxia (p. 46). Explaining that hypoxia is a common feature of enclosed water systems, Spicer adds that human activities, such as coastal eutrophication and climate change, are increasing the occurrences of hypoxic marine dead zones. Spicer warns that studies of hypoxia tolerance conducted in the lab may not reflect the true physiological responses of species in the wild, and asks, 'What can an ecophysiological approach tell us about the physiological responses of marine invertebrates to hypoxia?' Presenting four case studies of crustacean ecophysiological responses to hypoxia, Spicer shows that many species are able to adapt responses to stress that had been measured in the laboratory in such a way that they are able to tolerate environments in the wild that they were thought unable to survive. Listing factors that allow marine organisms to modify responses discovered in the lab, Spicer also extols the virtues of adopting -omics approaches to gain a better understanding at the molecular level of how animals respond to hypoxia in the wild.

Organismal stress

Moving on from ecophysiology to present an organismal perspective on responses to stress, Pat Monaghan from the University of Glasgow, UK, explains that most vertebrates release glucocorticoid hormones in response to stress. These hormones adjust the animal's physiology to maximise its chances of survival in the short term. However, prolonged exposure to glucocorticoid hormones in response to chronic stressors, such as food shortage or overcrowding, can be detrimental,

Zebra finches ranging in age from a fledgling to an elderly bird. Credit: Paul Jerem, University of Glasgow.

increasing susceptibility to infection, reducing growth and fertility and decreasing life expectancy. Monaghan explains that stress can also affect the length of protective structures at the ends of chromosomes, known as telomeres, which are known to shorten naturally through life and are an indicator of longevity (p. 57). Recent studies have shown that the glucocorticoid hormones and oxidative stress are both factors that lead to telomere loss, and the effects of maternal stress can also be passed on to the next generation in the form of shorter telomeres.

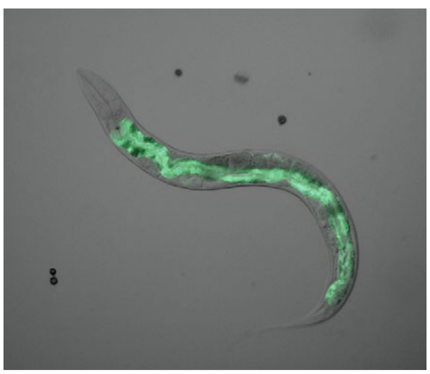
While hormones play a significant role in the stress responses of animals, Peter Hedden and colleagues explain that hormones also regulate plant responses to environmental stressors. Focusing on the gibberellin family of plant growth hormones, the team from Rothamsted Research, UK, explains that stress results in reduced gibberellin production and signal transduction and it is important to understand the mechanisms that bring this about (p. 67). Outlining the mechanisms of gibberellin synthesis and the mechanisms by which the hormone mediates its effects, the Rothamsted scientists list how reductions in gibberellin signalling mediate tolerance to various stressors, including salinity, shading, flooding and drought. They say, 'Gibberellin is clearly involved in a broad spectrum of responses to both mild and severe abiotic stress, and a clearer understanding of the role of gibberellin signalling in these responses would be an important step towards understanding and improving plant growth and stress responses under adverse environmental conditions.'

Environmental stress also affects memory formation and learning, with some stressors enhancing memory formation, while others inhibit it. Ken Lukowiak explains that organisms only invest the energy required to form a long-term memory if the event is perceived to be relevant, and this depends on the severity of the associated stress. While memory formation is an extremely intricate process in complex brains, Lukowiak and his colleagues have focused their attention on the effects of ecologically relevant stressors on memory formation in the simpler *Lymnaea stagnalis* memory (p. 76). Listing temperature, overcrowding, food deprivation and predators as potential stressors, Lukowiak and his colleagues discuss the impacts that these factors have, either blocking or enhancing long-term memory formation. However, organisms rarely experience stressors in isolation and the team describes how a combination of stressors also affects memory formation.

Of all the terrestrial phyla, arthropods are possibly the most stress-resistant group of animals. Found on almost every landmass, they have adapted to most terrestrial conditions, but only a few survive the gruelling conditions on Antarctica. Nicholas Teets and David Denlinger from Ohio State University, USA, describe how the flightless midges, mites and Collembola that are endemic to the continent's maritime regions are adapted to the extreme low temperatures and lack of available water (p. 84). Discussing how some species are freeze tolerant while others supercool to avoid freeze damage, they explain that all are desiccation tolerant and these adaptations require large energy investments. Outlining the molecular mechanisms employed by Antarctic arthropods to survive in a frozen desert, Teets and Denlinger explain that physiological adaptations include accumulation of osmoprotective compounds to protect the animals from dehydration and expression of genes involved in the heat shock response, glucose mobilisation and cytoskeletal proteins. However, none of these adaptations are unique to Antarctic species, as they are also found in temperate species.

Stress clearly has dramatic effects on the organisms that experience it directly, but it is also becoming apparent that the effects of stress at all stages of life can be transmitted down the generations. Isabelle Mansuy, from ETH Zurich, Switzerland, explains that exposure to stress can alter the physiology of an organism through a process known as epigenetics, where alterations are made to the genome – but not the DNA sequence – that modify traits expressed by the organism (p. 94). These genome-wide alterations can also be inherited by the organism's descendants. Mansuy and Bechara Saab describe the epigenetic changes that are transmitted to the offspring of mice and rats that experienced stress during pregnancy, shortly after birth and during adulthood. They discuss the epigenetic legacy of drug and alcohol abuse in humans and go on to explain that the positive effects of a stimulating environment can also be passed on to subsequent generations epigenetically. They conclude by suggesting that an understanding of epigenetic inheritance may lead to improved diagnostics and drugs for the treatment of inherited neurological disorders.

Cellular stress



Transgenic Caenorhabditis elegans that express a HSP-6:GFP reporter revealing the induction of the mitochondrial unfolded protein stress response pathway. Credit: Laurent Mouchiroud.

Having discussed the physiology of stress from the perspective of whole organisms, the collection of reviews now addresses the mechanisms of responses to stress at the cellular level. In the first paper in this section, Laura Senst and Jaideep Bains, from the University of Calgary, Canada, discuss the role of neuromodulators in remodelling circuits in the rat brain in response to stress (p. 102). Explaining that multiple brain nuclei are activated in response to physiological and psychological challenges, the duo says, 'Mounting an appropriate physiological response to such challenges requires the brain to interpret, learn from and then remember the appropriate stimuli'. Describing the synaptic changes that occur in the hypothalamus in response to stress, they also explain that the developing rodent brain responds differently to stress from the adult brain and discuss the role of endocannabinoids in the associated remodelling of the hypothalamus.

The ability to withstand cellular stress is also key to long-term survival and the loss of the ability to withstand cellular damage is a key factor in ageing. Heinrich Jasper and colleagues, Lifen Wang and Jason Karpac, from the Buck Institute for Research on Aging, USA, discuss the effects of ageing on *Drosophila* (p. 109). They report that elderly fruit flies lose the ability to regulate the cellular pathways that maintain cellular growth, metabolism and responses to oxidative stress, adding that it is the loss of regulation of these systems that leads to increased mortality in later life. The team describes how they have been able to prevent or delay the effects of ageing by modulating specific signalling pathways in several tissues, including insulin-producing cells, adipose tissue and the gut, and they are optimistic that such studies will eventually form the basis of novel therapies to treat diseases associated with ageing.

In addition to helping us to unravel the mysteries of the ageing process, *Drosophila* is also teaching us about their remarkable ability to survive a broad array of physiological stresses. Focusing on the insect's Malpighian tubule, which is at the forefront of the insect's defences, Shireen Davies and her team have discovered the molecular signalling cascades that are triggered in the tissue in response to stresses such as infection, salt, oxidative damage and desiccation (p. 119). Importantly, they have discovered that there are overlapping molecular networks which are triggered in response to different stressors. So the key challenge will be to unravel how the organism then mounts specific responses against each stressor. The team concludes by warning that it is essential that we understand the molecular mechanisms of stress tolerance in pollinators and other insects that are crucial for agriculture to ensure their future survival in a changing world.

Good cellular housekeeping is essential for health and the accumulation of degraded proteins in cells is a significant cellular stress that is kept in constant check by the cell's proteostasis network – which governs all stages of protein production, folding and degradation. Patricija van Oosten-Hawle and Richard Morimoto from Northwestern University, USA, discuss how metazoans regulate their response to heat shock through intercellular communication networks that coordinate the response across the entire organism (p. 129). Focusing on the heat shock response in *C. elegans*, the duo discuss recent publications showing that the heat shock response can be centrally controlled by two thermally sensitive neurons as well as transcellular chaperone signalling between non-neuronal cells. The authors discuss emerging concepts of how tissues in an organism communicate their condition of proteostasis *via* intercellular trafficking and cell-to-cell signalling pathways.

Following on, Virginija Jovaisaite, Laurent Mouchiroud and Johan Auwerx from the Ecole Polytechnique Fédérale de Lausanne, Switzerland, focus on proteostasis in the cell's powerhouse – the mitochondrion – through the mitochondrial unfolded protein response (p. 137). As the mitochondrial genome only encodes a fraction of the 1500 proteins required by the organelle, the majority of mitochondrial proteins are encoded by the nucleus, requiring that the mitochondria communicate with the nucleus to trigger production of the proteases and chaperones required for the unfolded protein response, prior to their import across the mitochondrial membrane. Detailing the signalling mechanism that triggers the response in *C. elegans* and mammals, the team concludes by suggesting that the mitochondrial unfolded protein response could be the mechanism that leads to increased longevity in *C. elegans*.

Concluding the section on cellular responses to stress, Alistair Brown and colleagues from the University of Aberdeen, UK, discuss the strategies adopted by the pathogenic fungus *Candida albicans*, which can cause life-threatening infections in immunocompromised patients (p. 144). Outlining the stress tolerance mechanisms that protect the fungus from individual stresses – including heat shock, high salt, oxidative stress, exposure to reactive nitrogen species and pharmacologically weakened cell walls – the team points out that in practice

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Candida rarely experiences these individual stresses in isolation. In addition, they add that these mechanisms were elucidated on fungal strains reared in the lab with glucose as their carbon source. Providing evidence that growth on carbon sources that the fungus is more likely to encounter during infection can modify and increase resistance to certain stresses, the team concludes by saying, ‘Studies of stress adaptation are revealing points of fragility in *C. albicans* that could potentially provide targets for translational research directed towards the development of novel antifungal therapies.’

Concluding remarks

This unique collection of reviews, which have discussed the impact of stress at many different levels of biological organisation, provides new insights into our current understanding of the way that life responds to challenging situations and environments. Presenting viewpoints that are rarely heard together, ranging from the ecological scale to the molecular mechanisms that regulate the stress response and the inheritance of stress-induced traits, the anthology provides an essential introduction to new students while also offering novel perspectives from established authorities.

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