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Translational environmental biology: cell biology informing conservation

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Typically, findings from cell biology have been beneficial for preventing human disease. However, translational applications from cell biology can also be applied to conservation efforts, such as protecting coral reefs. Recent efforts to understand the cell biological mechanisms maintaining coral health such as innate immunity and acclimatization have prompted new developments in conservation. Similar to biomedicine, we urge that future efforts should focus on better frameworks for biomarker development to protect coral reefs.

The current coral health crisis

Similar to humans, organisms in the natural environment face many insults that influence their health. Coral reefs are one of the most diverse, productive, and economically critical ecosystems in the world [1]. Despite this importance, coral reefs are increasingly impacted by local human activities and the threats of climate change [1]. Therefore, there is an urgent need to understand the power of climate change on coral health to plan effectively for conservation.

How can the health of corals be determined? It has been suggested that the symbiotic relationship of corals with their algal partners [2], which contributes to the coral's ability to calcify properly, is a primary physiological determinant of coral health [2]. However, recent evidence from coral cell biology and molecular physiology has suggested two additional molecular-level processes: regulation of the stress response by innate immunity; and acclimatization to physiological stress for an individual colony. By incorporating these processes into the current model of coral health, we will be closer to understanding the mechanisms behind the physiological stress response in corals and will be better able to predict 'unhealthy' corals before it is too late. The hope of translational environmental biology is to use the knowledge of these mechanisms to develop practical biomarkers for use in conservation.

Links between symbiosis, bleaching, and innate immunity

Corals harbor symbiotic algae of the genus *Symbiodinium* that provide photosynthetic nutrients for the coral host and play a critical role in supporting the coral's growth, metabolism, reproduction, and persistence [3]. Maintaining the relationship between symbiont and coral host is critical to the organism's survival. The processes of symbiosis, including bleaching and innate immunity, are tightly coupled to maintain the health of the coral. Indeed, many genes, including Hsp70, nitric oxide, and caspases, have been implicated in both processes [4–7].

The innate immune system plays a critical role during the recognition of bacteria and algae [3]. Although the study of innate immunity in coral biology remains in its infancy, recently discovered immunity genes are suggesting an important role in coral health [8,9]. For example, during recognition, pattern-recognition receptors (PRRs) such as lectins bind to different microbe-associated molecular patterns (MAMPs) found on the surface of bacteria and algal symbionts [3]. Interestingly, many coral lectins are upregulated not only in response to bacterial challenge but also in response to heat shock, indicating that lectins may play a critical role in boosting coral immune response during climate change [3,8,10,11].

The maintenance of algal symbionts in the coral host is an important indicator of coral health and is tightly coupled with immunity. However, this symbiosis is disrupted during the process of coral bleaching, whereby intracellular symbiosis between algae and the coral host cell breaks down culminating in the release of the pigmented symbiotic algae, which gives the coral a 'bleached' appearance due to its white skeleton showing through the translucent tissue. Bleaching is induced by changes in the local environment, including increases in temperature. There are several hypothesized mechanisms for this process, including: exocytosis of the algal cell from host cells; detachment of host cells containing algal cells; apoptosis or necrosis of host cells; and degradation of the symbiont within host cells [3].

Examining the relationship between innate immunity and maintenance of algal symbionts may yield a better understanding of the mechanisms involved in symbiosis and bleaching, which could lead to new conservation efforts.

A new frontier: biomarkers and stress acclimatization in corals

Recent research has shown a surprisingly intricate gene expression network that allows corals to acclimate to changing environments [9]. Due to the availability of transcriptomic data, we know that hundreds of genes react in an environmentally dependent manner in corals [9]. These data sets are valuable tools that should be used to develop new biomarkers and improve current ones. For example,

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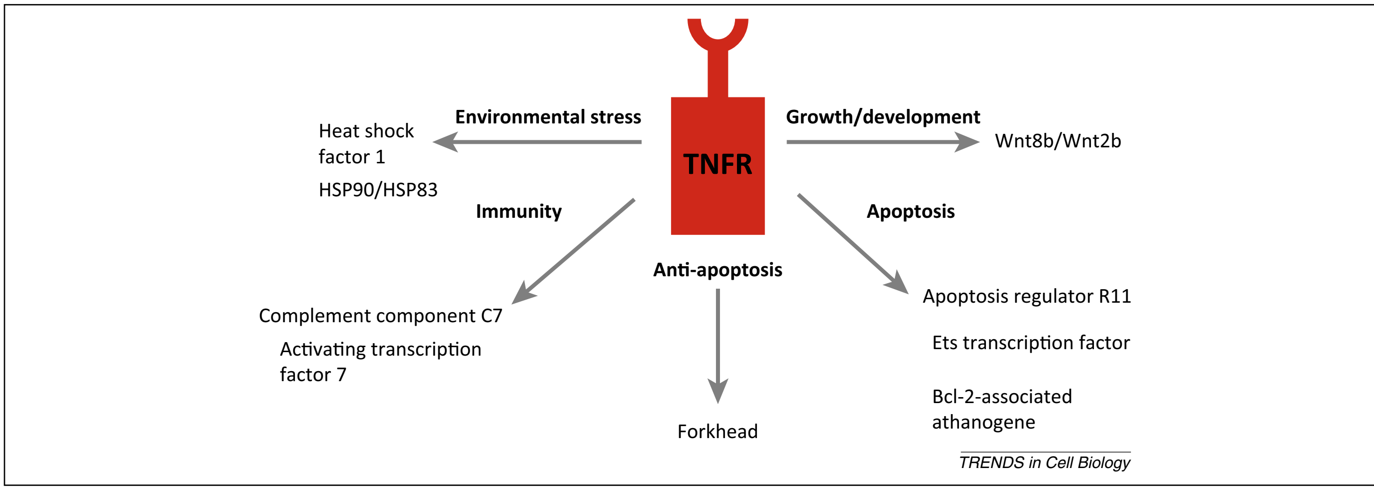

Figure 1. Tumor necrosis factor receptor (TNFR) is a switchboard for many different pathways. In corals, TNFR appears to play a pivotal role in major signaling pathways involved in innate immunity and apoptosis, but also has the potential to be involved in many other pathways including growth and development, environmental stress, and antiapoptosis, similar to what is seen in other organisms [9].

gene expression in orthologs of the tumor necrosis factor receptor (TNFR) were recently shown to change dramatically in corals responding heat stress [9]. Moreover, populations of coral historically known to have been exposed to environmental heat stress displayed constitutively higher expression of TNFR before induction of heat stress [9]. This finding suggests that chronically heat-stressed corals maintain gene expression levels that are primed to react to future heat exposure [9]. Although the role of TNFR is only now being characterized in corals, gene candidates potentially involved in these responses have been discovered (Figure 1). The prominent increase in some TNFR gene expression patterns after chronic heat stress suggests that the gene family may play a pivotal role in the heat stress response of corals, thus providing a set of candidate loci for biomarker development [9].

Translational environmental biology and coral health: linking biomarkers to mechanism

Biomarkers of coral health are key examples linking environmental science to environmental policy – what we call translational environmental biology. As defined by the National Institutes of Health, a 'biomarker' must have the ability to measure accurately and reproducibly the outside-observed medical state of a patient [12]. Biomarkers are different from a 'clinical end point', which in medicine considers the patient's well-being and health [12]. Of course, we cannot ask corals how they feel, but we can take into account their history and therefore their ability to acclimate to a present condition. Incorporating acclimatization into biomarker research will help us to understand variation observed in populations.

Previously, biomarkers have been developed for specific coral species without fully understanding their mechanism or the genotype or acclimatization ability of the coral involved [13,14]. Much of the biomarker development thus far has been challenging, due to high amounts of variation among coral individuals and low repeatability. This challenge may be a product of our lack of understanding of some of the basic mechanisms of the clinical end points involved; that is, the acclimatization ability of the coral. To tackle this issue, techniques in cell biology can lead to a better foundation on which biomarkers can be developed by allowing the development of protocols that are fine-tuned to a coral's innately complex biology.

Improving and developing biomarkers in the context of cell biology

Corals are under threat of extinction in many places and immediate action is needed to understand coral health [15]. Figure 2 summarizes a potential approach to furthering the field of translational environmental biology. Although this discussion is not a complete framework, it does provide a template for future research.

Phase1 – Compilation and Communication – addresses what is currently known about biomarkers and compiles this information into one centralized database. To reach this phase, we need to examine the focus of our past efforts. Has work been conducted on only one type of coral and are there others that could be tested? Are biomarkers disproportionately available for a specific stressor (e.g., heat)? Phase 2 – Biomarker Proof of Concept – requires close examination of the current biomarkers to determine which should be developed further and to explore whether new ones need to be synthesized. Phase 3 – Mechanism – applies knowledge of the first two phases to the biomarker system and aims to determine the mechanism by which the biomarker is functioning. To recognize biomarker variation, we need to understand how the biomarker is being activated and controlled. Without this information, a large amount of variation will be left unexplained, resulting in unstable, and therefore not useful, biomarkers. Phase 4 – Application – culminates in the deployment of biomarker assays to determine the health status of corals in field sites. It will need to be determined whether these biomarkers will be useful to marine park management and how properly to use them.

This framework is a launching point for collaboration and synergy between researchers. By pooling the current resources and understanding the acclimatization history of

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Phase 1 Compilation & communication	Phase 2 Biomarker proof of concept	Phase 3 Mechanism	Phase 4 Application
What biomarkers do we currently have?	Can we work with the biomarkers we have or is the development of new biomarkers necessary?	What is the mechanism behind the reaction?	How do we use these biomarkers?
Compilation of past biomarker studies: • Create a publicly available central repository for antibodies, probes, and primers. • Determine which corals are and should be the continued focus of biomarker work. • What will be the use for these biomarkers?	**Tests for biomarkers:** • How does acclimatization affect biomarker stability? • What is the coral and symbiont genotype? • Is this biomarker found across multiple species or is it species specific? • Does seasonal variation & reproductive phase affect biomarker activity? • Determine if the biomarker is reproducible, specific, and dose dependent?	**Understand the mechanism:** • Does the biomarker act via transcription, translation, or post-translational modifications? • Are there different splice isoforms or paralogs of the biomarker in question? • Is this a species specific biomarker or found in other metazoans? • Are other factors involved?	**Validation & deployment of biomarkers:** • How will the biomarker help in marine park management? • Can the biomarker monitor or reverse/prevent coral health? • Can the biomarker help inform public policy about the growing decline in coral health? • Can the biomarker be used in a field setting?

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Figure 2. Proposed outline for advancing the field of translational environmental biology. This framework is to act as a launching point for discussion and is by no means all-inclusive. By taking the knowledge of current biomarkers and coral health and applying it in a large-scale, collaborative format, progress can be made in our understanding of coral health.

the coral reef that is being studied, we can achieve a better understanding of the biomarkers, leading to progress in translational environmental biology.

Concluding remarks: the future of coral health

In cell biology, developing a biomarker for a particular disease is tied to understanding the disease mechanism and has helped researchers create stable biomarker systems to measure disease states. In coral biology, it is a perfect time to harness the transcriptomic resources available for many different species of corals, in conjunction with previous biomarker studies, to develop mechanistically based tools for conservation. By incorporating the history, genotype, and immunology of corals into the current paradigm, a giant step forward in our understanding of the clinical end points for coral health will be achieved. This framework will help protect the corals that are most vulnerable and assist the scientific community in making predictions for the outcome of the world's future reefs.

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