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Review

Gene expression biomarkers of heat stress in scleractinian corals: Promises and limitations

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Gene expression biomarkers (GEBs) are emerging as powerful diagnostic tools for identifying and characterizing coral stress. Their capacity to detect sublethal stress prior to the onset of signs at the organismal level that might already indicate significant damage makes them more precise and proactive compared to traditional monitoring techniques. A high number of candidate GEBs, including certain heat shock protein genes, metabolic genes, oxidative stress genes, immune response genes, ion transport genes, and structural genes have been investigated, and some genes, including *hsp16*, *Cacna1*, *MnSOD*, *SLC26*, and *Nf-kB*, are already showing excellent potential as reliable indicators of thermal stress in corals. In this mini-review, we synthesize the current state of knowledge of scleractinian coral GEBs and highlight gaps in our understanding that identify directions for future work. We also address the underlying sources of variation that have sometimes led to contrasting results between studies, such as differences in experimental set-up and approach, intrinsic variation in the expression profiles of different experimental organisms (such as between different colonies or their algal symbionts), diel cycles, varying thermal history, and different expression thresholds. Despite advances in our understanding there is still no universally accepted biomarker of thermal stress, the molecular response of corals to heat stress is still unclear, and biomarker research in *Symbiodinium* still lags behind that of the host. These gaps should be addressed in future work.

Contents

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1. Introduction

Scleractinian corals are the principal habitat builders of modern coral reefs. As such, they are critical components of one of the most diverse ecosystems on earth, harboring 32 of the 34 recognized animal phyla, including 800 hard coral species and more than 4000 species of fish (Birkeland, 1997; Spalding et al., 2001). Corals are delicate symbioses between an animal host and diverse dinoflagellate algae in the genus *Symbiodinium*, also commonly referred to as 'zooxanthellae' (Wells, 1957). Climate change, overfishing, nutrient pollution, disease, ocean acidification, and coastal development are among the escalating direct and indirect human pressures contributing to reef decline (Brown, 1997; Hughes, 2003), and many of these varied stressors can result in coral bleaching (the expulsion of algal symbionts, or a reduction in their per-cell pigment concentrations) (Coles and Jokiel, 1977; Falkowski and Muscatine 1981; Lesser et al., 1990; Dove et al., 2000). The breakdown of the cnidarian-*Symbiodinium* partnership results in a significant energy loss for the animal host, leading to reduced growth and reproduction, and increasing the risk of disease and starvation (Bruno and Selig, 2007; Hoegh-Guldberg et al., 2007). Mass coral bleaching events occur when bleaching affects the majority of the zooxanthellate ("symbiont-bearing") hosts on a reef, and typically occurs over large spatial scales (1000s of km^2) (Hoegh-Guldberg, 1998). The occurrence of natural disturbances, such as rising sea surface temperature (SST) and ocean acidification, is increasing as a result of climate change (Hoegh-Guldberg et al., 2007). Sustained periods of elevated SSTs, usually in shallow areas where the incident solar irradiance is also high, are now recognized as the principal factor driving contemporary mass coral bleaching events. Severe episodes of mass coral bleaching usually result in high coral mortality and decreases in coral cover. They also commonly lead to changes in species composition, local extirpation of some reef species, and reductions in species richness (Wilkinson et al., 2008; Alemu and Clement, 2014). Ecological extinction of corals reefs in some regions has been forecast to occur within the next 20 to 50 years if corals are unable to adapt and/or acclimatize sufficiently rapidly to keep pace with warming, and if effective reef management strategies are not quickly implemented (Sheppard, 2003; Hoegh-Guldberg, 1999; Baird et al., 2009; Bhagooli and Sheppard, 2012).

Conservation of coral reefs is a global environmental concern, however the tools for implementing proactive management solutions are currently lacking, particularly for evaluating and predicting the health of corals *in situ* (Aswani et al., 2015). The advent of molecular tools and resources for corals has highlighted the possibility for gene expression biomarker (GEB) development as a means of detecting and quantifying coral stress even before the onset of symptoms (Kenkel et al., 2011; Traylor-Knowles and Palumbi, 2014; Kenkel et al., 2014). Biomarkers are critical tools in biomedical research and clinical practice, where they are used to determine whether patients will benefit from particular treatments (predictive biomarkers), monitor the progression of a disease or efficacy of a prescribed treatment (monitoring biomarkers) and even to predict survival (prognostic biomarkers; Oldenhuis et al., 2008). Such a molecular toolkit for corals could help reef managers identify reefs under stress, pinpoint the causative stressors, and target resilient individuals for restoration. For example, corals from a reef showing stress response biomarkers could be transplanted to a healthier site, or corals showing heat resistance biomarkers could be transplanted or selected for adaptive breeding programs (van Oppen et al., 2015) to prevent collapse of vulnerable reefs.

However, despite more than a decade of research, it is unclear how accurately can we predict the occurrence of stress factors based on changes in the expression of coral and symbiont genes. This is primarily the result of substantial variation in the stress tolerance of different species (Rowan, 2004) and species combinations (Rocker et al., 2012) as well as in gene expression patterns (Granados-Cifuentes et al., 2013). Research into these areas, as well as into ontogenetic changes in gene expression, are emerging as frontiers in the field of GEB development.

This review synthesizes the current state of knowledge in the field of coral GEBs, addresses the potential drivers of variation between studies in results, and highlights gaps in our knowledge to outline a framework for the direction of future research in this area.

2. Gene expression biomarkers of heat stress

In predictive medicine, the term biomarker refers to biological measurements used in the prediction of disease risk and early detection of disease to improve treatment selection and monitor the outcome of therapeutic interventions (Simon, 2011). A "Genomic Biomarker" is therefore a DNA or RNA sequence with similar properties. A gene expression biomarker should reflect the expression of a gene, the function of a gene, and the regulation of a gene (Novelli et al., 2008). In the field of coral biology and conservation, the application of gene expression biomarkers to diagnose heat stress in corals has raised a great deal of interest. Suitable GEB candidates should be able to assess the heat stress of corals rapidly, before onset of visible signs such as bleaching. Expression of genes can be immediate and early, where genes which are expressed immediately after stimulation by external factors and are then downregulated, such as *hsp* 70. Genes can also show delayed and late expression relative to the timing of the stimulus. Expression of 'late' genes is normally induced by early genes (Chambers et al., 1999).

Research on gene expression patterns in coral, with the ultimate aim of informing conservation efforts, started in the early 2000s. During this 'discovery' phase, some genes rose to scientific prominence as they were repeatedly reported to be differentially expressed when the cnidarian host and/or the symbiont were subjected to thermal and/or irradiance stress, well before the onset of visible signs of stress, such as bleaching (Rosic et al., 2014a). These genes included those involved in heat shock response, metabolism, oxidative stress, immune response,