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Prediction of stress induced robustness using molecular biomarkers

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Introduction: Microorganisms are constantly facing changing environmental conditions and have evolved sophisticated stress adaptation mechanisms to be prepared for challenges even before they arise. The stress adaptive response is a crucial survival strategy for a wide spectrum of microorganisms, including food spoilage bacteria, pathogens and organisms used in functional food applications, and can result in increased robustness of microorganisms. Prediction of mild stress induced enhanced robustness will allow to control and/or exploit these stress adaptive traits.

Methods: We designed a framework for identifying molecular biomarkers for mild stress induced microbial robustness towards lethal stresses. Several candidate-biomarkers were selected by comparing the genome-wide transcriptome profiles of our model organism *Bacillus cereus* upon exposure to four mild stress conditions (mild heat, acid, salt and oxidative stress). These candidate-biomarkers – a transcriptional regulator (activating general stress responses), catalases (removing reactive oxygen species), and chaperones and proteases (maintaining protein quality) - were quantitatively determined at transcript, protein and/or activity level upon exposure to mild heat, acid, salt and oxidative stress for various time intervals. Both unstressed and mildly stressed cells were also subsequently exposed to lethal stress conditions (severe heat, acid and oxidative stress) to quantify the robustness advantage provided by mild stress pretreatment. To evaluate whether the candidate-biomarkers could predict the robustness level of mild stress treated cells, their induction upon mild stress treatment was correlated to mild stress induced robustness towards lethal stress and the correlation significance was evaluated using the Pearson correlation coefficient.

Results: Both short- and long-term biomarkers could be identified of which the induction levels upon mild stress treatment were significantly correlated to the induced enhanced robustness towards lethal heat, acid and/or oxidative stress, respectively. The predictive quality of the transcripts differed from that of proteins and activity level, underlining the necessity to measure molecular biomarkers at different functional cell levels (transcript, protein and activity level). The predictive quality of the biomarkers was also stress-dependent, highlighting the significance to evaluate predictive potential of biomarkers for various stress treatments.

Conclusion: The identified molecular biomarkers for mild stress induced enhanced robustness are widely conserved in microorganisms and have indispensable roles in stress responses. Therefore, they might also serve as biomarkers for stress adaptive behaviour in other microorganisms than *B. cereus*. Our study provides a systematic, quantitative approach to search for these biomarkers for adaptive behaviour and to statistically evaluate their predictive potential at different functional cell levels in order to select biomarkers with high predictive quality that can serve to early detect and predict adaptive traits.