PHYSIOLOGICAL AND MOLECULAR EVIDENCE OF HEAT ACCLIMATION
MEMORY ASSOCIATED WITH CHROMATIN MODIFICATION: A LESSON FROM
THE HEART

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Background: Sporadic findings in humans suggest that re-induction of heat acclimation (AC) after its loss occurs markedly faster than during the initial AC session. Animal studies and gene profiling substantiated that the processes underlying acclimation are molecular. Goal: To test the hypothesis that faster re-acclimation (ReAC) involves ‘molecular memory’ linked to epigenetic modifications. Procedure: Using the Rattus norvegicus AC model physiological-integrative, cellular and molecular aspects of deacclimation (DeAC, 30 and 60 d) and subsequent reacclimation (ReAC, 2d) were assessed. Criteria for assessment of DeAC/ReAC were thermoregulatory Tc-plateau at 41°C and AC mediated cross-tolerance in the heart, comprising infarct size following ischemia/reperfusion insult (I/R) and time to rigor contracture in anoxic cardiomyocytes. To assess epigenetic modifications, histones acetylation (H4, H3) and phosphorylation (H3-Ser10) at the regions of the heat shock response element (HSE) in HSP70 and HSP90 promoters were measured using Chromatin immunoprecipitation (ChIP). HSE accessibility was analyzed via HSF1-ChIP at the region of the HSP70 promoter and measuring hsp70 mRNA kinetics following heat stress (HS) using qPCR.

Results: Tc profiles during HS and ex vivo assessment of cross-tolerance to I/R or anoxia demonstrated that ReAC only needs 2d vs. the 30d required for the initial development of AC phenotype. A cluster of transcriptionally activated genes among which HSPs, and chromatin remodeler genes, did not resume pre-acclimation levels after DeAC despite the return of the physiological phenotype to its pre-acclimation state, suggesting a dichotomy between the geno- and the pheno- types. ChIP analyses provided evidence of H4 acetylation during AC, DeAC and ReAC and H3Ser10-P in 2d and ReAC groups. The accessibility of the HSE to HSF1 was validated by elevated binding to HSP70 promoter and by similar acclimatory mRNA kinetics post HS in the AC, DeAC and ReAC groups. Conclusion: We argue that chromatin remodeling emerging with AC and retained during DeAC upon ReAC is an upstream regulator of the transcription state, preconditioning to faster cytoprotective acclimatory-memory.