

Cellular Mechanisms of Stress-Mediated Allostasis Regulate Intercellular Communication by Extracellular Vesicles

Nickole Moon, Christopher Morgan, Aly Jeng, Rachel Johnson, Mary Sammel, Neill Epperson, Tracy L. Bale

University of Colorado Anschutz Medical Campus

Chronic pre-conception parental stress and trauma experiences influence offspring neurodevelopment. In males, mechanistic studies identified lasting changes following chronic stress at epididymal epithelial cells (EECs) that provide sperm with essential maturation signals. However, the molecular mechanisms of cellular allostasis reprogramming EECs and the effects on sperm function are unclear. As stress-responsive modulators of cellular energy, mitochondria are likely mediators of allostasis. Therefore, we utilized this system to examine the hypothesis that prior stress initiates allostatic mechanisms to establish a new metabolic set point. Using cellular respirometry, we found that prior stress decreased EEC energy requirements, oxidative respiration, and altered mitochondrial ultrastructure. Mechanistically, mitochondrial complex I was identified as a key regulator of this new allostatic state by weighted gene co-expression network analysis, respirometry, and enzyme function assays. Furthermore, using CUT&RUN sequencing, a high efficiency epigenetic profiling approach, we revealed that stress significantly increased binding by the ubiquitous transcriptional repressor, H3K27me3, at 7283 regions of the EEC genome. Interestingly, differentially H3K27me3 bound regions were associated with mitochondrial processes by Gene Set Enrichment Analysis revealing that allostasis is balanced by regulation at both the nucleus and the mitochondria. As extracellular vesicles (EVs) secreted by EECs convey cargo altered by stress and necessary for sperm maturation, we assessed the role of EVs as intercellular communicators of energy regulation. Stress-EV exposure increased sperm mitochondrial respiration and motility, supporting a signaling pathway by which a new allostatic state can be communicated to other cells, resulting in changes in critical functions. As prior stress mediated allostatic changes in EECs to influence sperm physiology via EV cargo, we used a multilevel modeling approach in a repeated sampling human cohort study to assess the impact of prior perceived stress score (PSS) on sperm motility. Amazingly, increasing PSS 2-3 months prior but not 1 month or the same month of the sample collection was significantly associated with increased sperm motility, aligning with our previous work demonstrating that stress at the same time points are associated with altered sperm small noncoding RNA profiles. Together, these studies identify cellular mechanisms of allostasis following stress that regulate somatic to germ cell signaling and are important to better understand the enduring pathophysiology of trauma. Further, by identifying the functional roles of EVs following stress, we establish a foundation for the development of future therapeutic interventions.

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