Extracellular Vesicles as Cellular Communicators of Stress-Mediated Allostasis. NR Moon, (MD/Ph.D., GS), J Chan, C Morgan, and TL Bale, Department of Psychiatry, University of Colorado, Aurora, CO.

Cellular reprogramming at reproductive tissues following chronic parental stress influences offspring neurodevelopment. In males, mechanistic studies identified lasting changes following chronic stress at epididymal epithelial cells (EECs) that provide sperm with essential maturation signals. While the mechanisms regulating the cellular allostatic set point following stress are unclear, the glucocorticoid receptor (GR) is a known mediator of stress and key target orchestrating allostasis. To examine the hypothesis that stress initiates GR-dependent programming, we reduced EEC GR expression in our mouse model of chronic paternal stress. To assess GR dependent processes regulating allostasis, we analyzed the active EEC translatome and detected two clusters of co-regulated genes related to chromatin and mitochondrial processes. Moreover, CUT&RUN sequencing revealed that stress increased binding by the transcriptional repressor, H3K27me3, and that associated genes influence mitochondrial processes. As stress-responsive modulators of cellular energy, mitochondria are likely allostatic mediators. Using cell-based respirometry, we found that prior stress decreased basal mitochondrial respiration, and that GR knockdown protected against this effect. Furthermore, extracellular vesicles (EVs) secreted by EECs convey cargo necessary for sperm maturation, and stress alters that content. Therefore, we assessed EVs as coordinators of mitochondrial respiration, and found reduced respiration following EEC incubation with stress EVs. Together, these studies demonstrate a role of GR in programming the chromatin landscape after chronic stress to impact cellular energy requirements, and of EVs to maintain this new set point. These regulatory mechanisms of allostasis broadly apply to stress-vulnerable cells and are important to understand the enduring pathophysiology of trauma and potential interventions.