

EXERCISE-MEDIATED TRAINING OF THE IMMUNE RESPONSE.

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Inflammation, one of the earliest responses of the immune system, protects the host from infections and injury. It plays a crucial role in defending us from invading pathogens and initiating the healing process. However, excessive or prolonged inflammation is the root cause for serious human diseases including cancer, cardiovascular disease, type II diabetes and autoimmune disorders. Trained immunity, a concept adopted recently, occurs when long-lasting functional reprogramming of inflammatory cells due to epigenetic and metabolic rewiring following infection or injury. This project hypothesizes that structured exercise programs cause persistent epigenetic and metabolic changes in inflammatory cells, which could be used to study how exercise can be optimized to achieve a form of trained immunity in healthy animals prior to infection, where one can enhance the capacity to eliminate infection while reducing the damage associated with runaway inflammation. C57/Bl6 mice were subjected to long-term moderate exercise training on a treadmill. Splenic, peritoneal and bone marrow-derived macrophages were stimulated in-vitro with Lipopolysaccharide (LPS). Western blotting, Real-time PCR, Seahorse, Flow-Cytometric and ATAC-Seq (genome-wide chromatin accessibility) analyses were performed to evaluate persistent effects of long-term moderate exercise on inflammatory, metabolic and epigenetic state of inflammatory cells. Data showed that long-term moderate exercise reduces the activation of pro-inflammatory transcription factors (NF- κ B, IRF3) and expression of pro-inflammatory cytokines (IL-1 β , TNF- α , IFN- β) and attenuates inflammatory signaling pathways (iNOS, Hif-1 α , p-P65, p-ERK, p-S6). Conversely, it increases the expression of anti-inflammatory markers (IL-10, Arginase-1, I κ B- α). Furthermore, long-term moderate exercise reduces mitochondrial oxidative stress and sustains mitochondrial membrane potential. Mechanistically, these observations suggest that chronic moderate exercise leads to persistent changes in macrophages such as training macrophages towards anti-inflammatory (M2) phenotype. Additionally, ATAC-seq analysis showed differential chromosome accessibility in immune and metabolism associated regions in exercised compared to sedentary samples. Overall, our data suggest that chronic exercise programs cause long-lasting epigenetic modifications in inflammatory cells that can be targeted in therapies pre-programming the inflammatory responses.