Physical Activity Rescues Immune Homeostasis in Individuals Genetically Predisposed to Obesity-Induced Regulatory Collapse

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Chronic low-grade inflammation is a hallmark of obesity, yet the architectural shifts and genetic factors determining systemic immune resilience remain poorly defined. We aimed to characterize the relationship between adiposity, immune remodeling, and genetic vulnerability. We analyzed a clinical cohort using high-dimensional immunophenotyping (149 immune markers), mediation modeling, *ex vivo* LPS challenge of PBMCs, and genetic risk scores (GRS) for stroke and obesity.

BMI was positively associated with serum IL-6 ($\rho=0.36$, $p=0.0011$) and CRP. Mediation analysis revealed a mechanistic bifurcation where systemic IL-6 primarily drives the inflammatory signaling cascade (defined by CRP and Albumin), whereas metabolic dysfunction (Triglycerides, ALT) followed a direct, BMI-dependent metabolic path. In the cellular compartment, increased BMI drove a profound absolute expansion of the $CD4^+$ memory T-cell pool ($\rho=0.57$, $p<0.0001$) alongside a significant reduction in the homing receptor CXCR3, suggesting a state of premature immune aging and impaired trafficking capacity.

A central feature of this remodeling was the progressive decline in the regulatory T cell (T_{reg})/IL-6 ratio ($\rho=-0.37$, $p<0.001$), signifying a systemic *Regulatory Collapse* where inflammatory pressure disproportionately outpaces regulatory buffering. Functional assays demonstrated that a Stroke-GRS predicted exaggerated inflammatory reactivity (ΔIL-6) upon *ex vivo* challenge of PBMCs with LPS. We have also identified a genetic rescue effect underpinned by physical activity functioning as a targeted stabilizer of the T_{reg}/IL-6 ratio specifically for individuals with high Stroke-GRS ($\rho=0.45$), whereas this restorative relationship was absent in the low-risk group.

We conclude that obesity-associated immune remodeling is defined by an absolute expansion of memory cells and a loss of regulatory stoichiometry. This manifestation of regulatory collapse is modulated by underlying genomic susceptibility, establishing the T_{reg}/IL-6 stoichiometric ratio as an important biomarker for stratified, precision lifestyle interventions.