EXERCISE INDUCED HORMONE IRISIN INHIBITS INTEGRIN αV-TGF-β AXIS IN TUMOR MICROENVIRONMENT TO IMPROVE CD8+ T CELL MEDIATED TUMOR CONTROL

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Background It has been reported multiple times that exercise can prevent cancer development, help anti-tumor therapies, and lower relapse rate after successful cancer treatment. However, an underlying molecular mechanism for these beneficial effects remained elusive. Recent studies revealed that cytotoxic immune cell populations contribute to exercise mediated effects, and exercise induced hormones including insulin, cortisol, testosterone, and epinephrine have been studied in this context, especially related to CD8+ T cell function. Exercise also induces secretion of another myokine irisin, which was originally discovered in 2012. Role of irisin has been primarily studied in metabolic disease including obesity and diabetes. However, the role of irisin in tumor immunology has not been studied.

Methods To address this point, multiple pre-clinical tumor models including colon, skin, bladder, and lung cancer were utilized. After tumor implantation, irisin was intraperitoneally injected for every 2 days starting at day 7. Tumor growth was monitored to check anti-tumoral effect of irisin. To address immunological changes within the tumor microenvironment (TME), high-dimensional flow cytometry panels were applied and analyzed. To confirm our findings, publicly available scRNA-seq data sets were re-analyzed and web-based TCGA database was utilized for further validation.

Results Irisin displayed anti-tumoral activity when tested in multiple pre-clinical models. High-dimensional flow cytometry analysis revealed that irisin treatment reduced accumulation of regulatory T cells (Tregs) in TME. Suppressive marker expressions in Tregs were also decreased and led to better CD8+ T cell function with evidence of less dysfunctional signature. Integrin αv-TGF-β axis was identified for responsible mechanism, and myeloid cell specific knockout of integrin αv further confirmed importance of this pathway. Our findings were validated using publicly available scRNA-seq, spatial-transcriptomics, and TCGA data sets. Integrin αv was specifically expressed in myeloid cells, and TGF-β signaling pathway was higher in integrin αv adjacent spots. Also, overall survival rate and immunotherapy response rate was lower in patients with high expression of integrin complex and TGF-β. This was experimentally validated in pre-clinical model by combining irisin with PD-1 blocking antibody; the combination group exhibited better tumor control.

Conclusions We conclude that irisin treatment reduced tumor growth in multiple tumor models and this outcome was mediated by T cells. Integrin αv-TGF-β axis in the TME was responsible for this effect, and blocking this pathway exhibited better tumor control. Re-analysis of publicly available data sets further validated importance of this signaling pathway, implying therapeutic potential of irisin in treating cancer.