

1083 **FUNCTIONAL IMPACT OF ADRENERGIC SIGNALING ON T AND NK CELLS: WHERE EXERCISE MEETS CANCER**

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Background In several cancer types, tumors are innervated by adrenergic nerves, resulting in sustained levels of noradrenaline that promote tumor growth and support an immunosuppressive tumor microenvironment (TME).¹ In contrast, adrenaline increased during exercise has been shown to enhance mobilization and tumor infiltration of T and natural killer (NK) cells in mice.² This finding suggests using exercise in cancer treatment to improve response to immunotherapies. However, the impact of adrenaline on immune cell function in humans remains unclear. The opposing effects of noradrenaline and adrenaline, both acting through β -adrenergic receptor (β -AR) signaling, could be explained by the duration of exposure. We hypothesize that chronic noradrenaline levels in the TME are detrimental to immune cell function, while acute increases in adrenaline during exercise have no negative impact. Accordingly, we aim to study the impact of β -AR signaling on the function of T and NK cells.

Methods Serum levels of adrenaline and noradrenaline were measured in healthy volunteers before and after exercise to determine the physiological concentrations for *in vitro* experiments. Human T and NK cells were activated in the presence of acute or chronic isoprenaline (a β -AR agonist) *in vitro* and analyzed based on cytokine production and proliferation by flow cytometry. The expression of the β -AR was examined and β -blockers are used to validate whether the observed effect is mediated through β -ARs.

Results Following exercise, healthy volunteers showed increased levels of adrenaline (573 ± 354 pg/mL) and noradrenaline (4006 ± 574 pg/mL). Upon chronic stimulation with repeated doses of isoprenaline, activated T cells showed decreased levels of interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) secretion. In contrast, the cytokine levels were fully recovered 24 h after acute stimulation with a single dose of isoprenaline. Similarly, prolonged treatment with isoprenaline significantly inhibited the proliferation of CD4⁺ T cells for up to 5 days, correlated with β -AR expression. Conversely, acute stimulation showed no long-term negative impact on CD4⁺ T cell proliferation.

Conclusions Our data suggest that chronic but not acute β -AR signaling may hamper cytokine secretion and proliferation of T cells. This finding supports the use of exercise and suggests exploiting this signaling pathway to improve the efficacy of immunotherapies. Further investigations are underway to elucidate additional aspects of β -AR signaling in immune cell functions.

REFERENCES

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