

Estrogen-induced CD8⁺ T cell exhaustion promotes progression of triple-negative breast cancer

Ying Zhou, Qianqian Duan, Guanfeng Chen, Yue Liu, Yuanyuan Li, Tao Zhu, Zhao Liu, Jingshan Tong*, Xueyan Zhou*

Despite remarkable clinical efficacy of immune checkpoint blockade (ICB) in cancer treatment, ICB benefits for triple-negative breast cancer (TNBC) remain limited. To investigate the regulatory mechanisms of the tumor immune microenvironment in TNBC, we analyzed the levels of 15 estrogen metabolites in TNBC patient tissues and identified abnormal accumulation of estradiol (E2) in the tumor microenvironment. Using a syngeneic TNBC mouse model, we demonstrated that E2 treatment promoted tumor growth, reduced the infiltration of CD8⁺ T cells, and induced CD8⁺ T cell dysfunction, exhaustion, and resistance to ICB. Notably, the combination of the selective estrogen receptor degrader (SERD) fulvestrant, which targets ER α , with ICB therapy significantly suppressed tumor growth and enhanced the antitumor efficacy of ICB. Mechanistically, E2 upregulated fibroblast growth factor 2 (FGF2) expression in CD8⁺ T cells, impairing their infiltration into tumors. These findings highlight the critical role of the E2 and FGF2/ERK signaling axis in modulating CD8⁺ T cell function and suggest the potential clinical application of ER-targeting agents to improve ICB efficacy in TNBC.