Patient-derived organoid-immune co-cultures integrated with multi-omics reveal immunotherapy resistance mechanisms in urothelial carcinoma

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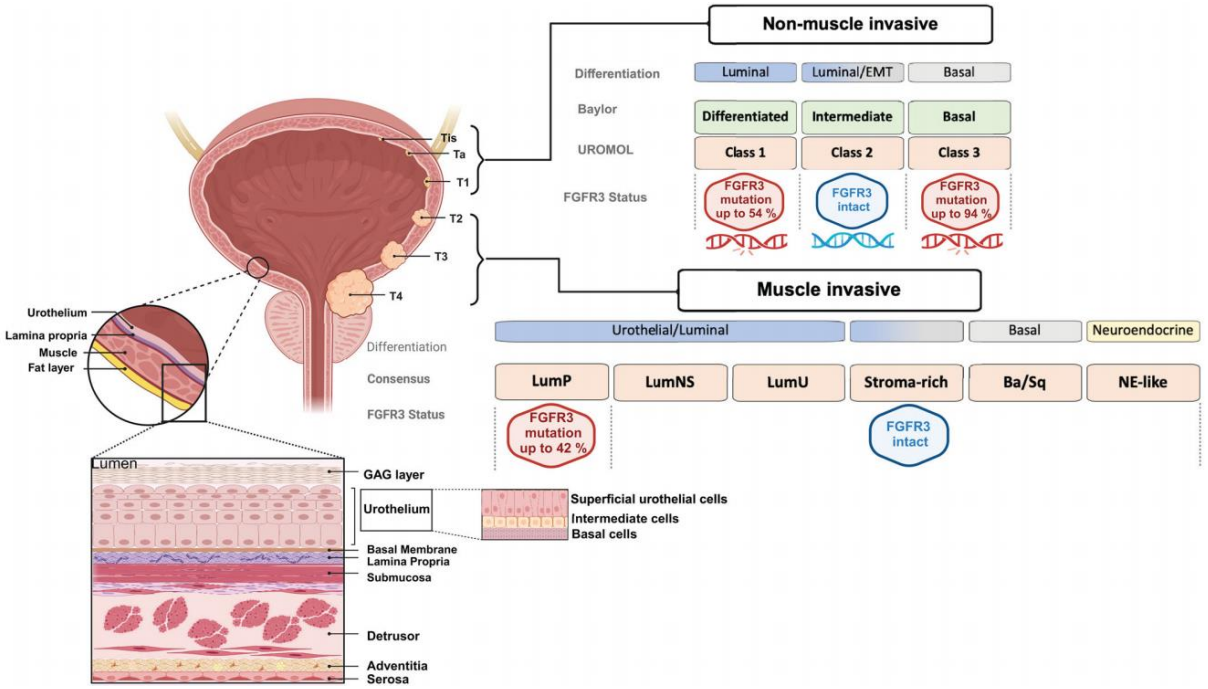
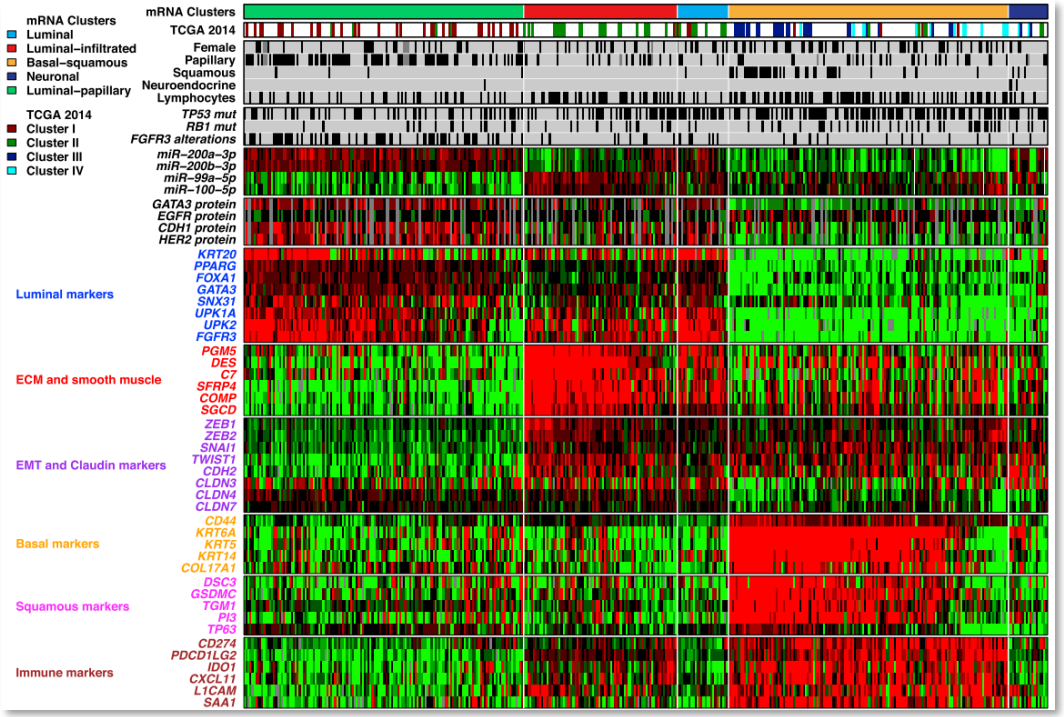
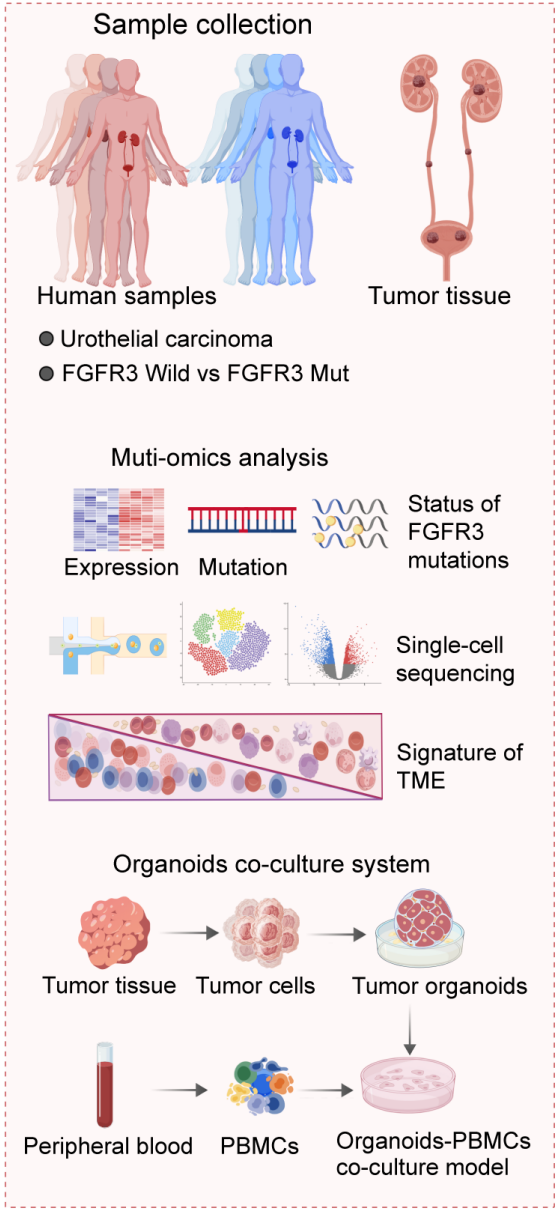
Background

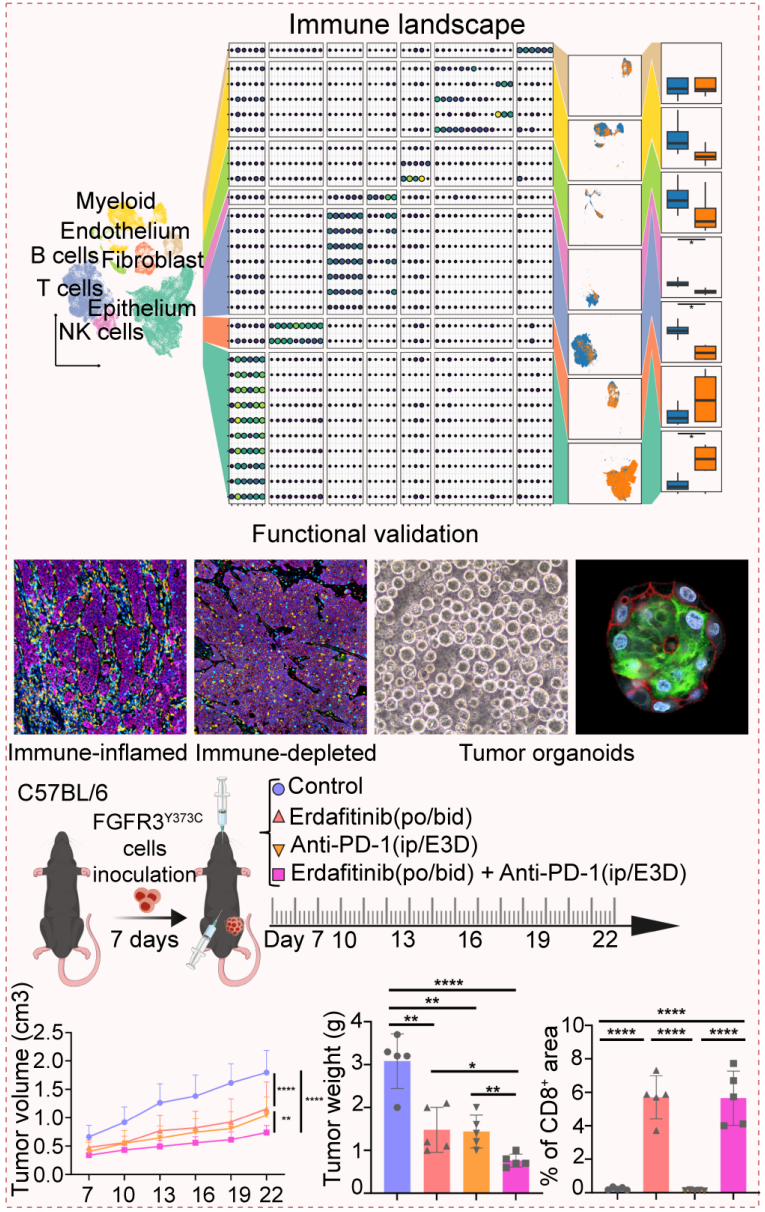


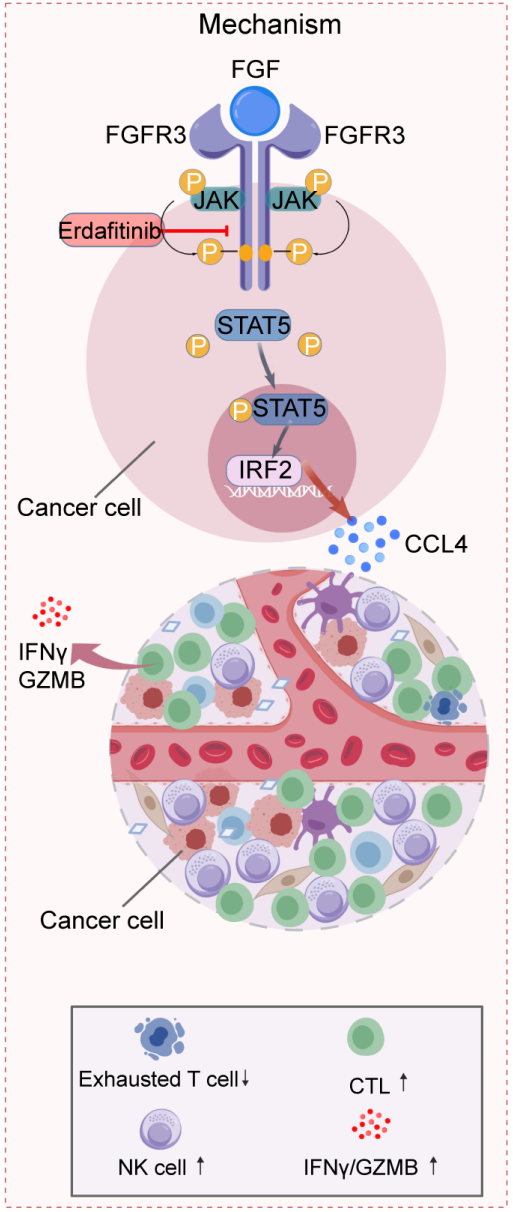


- FGFR3 is one of the most common oncogenic driver mutations in urothelial carcinoma
- FGFR3 activating mutations are associated with tumor immune suppression.
- Previous studies have largely relied on correlative clinical data or cell line models.
- Currently, there is still a lack of patient-derived models to investigate the underlying mechanisms.

Highlights

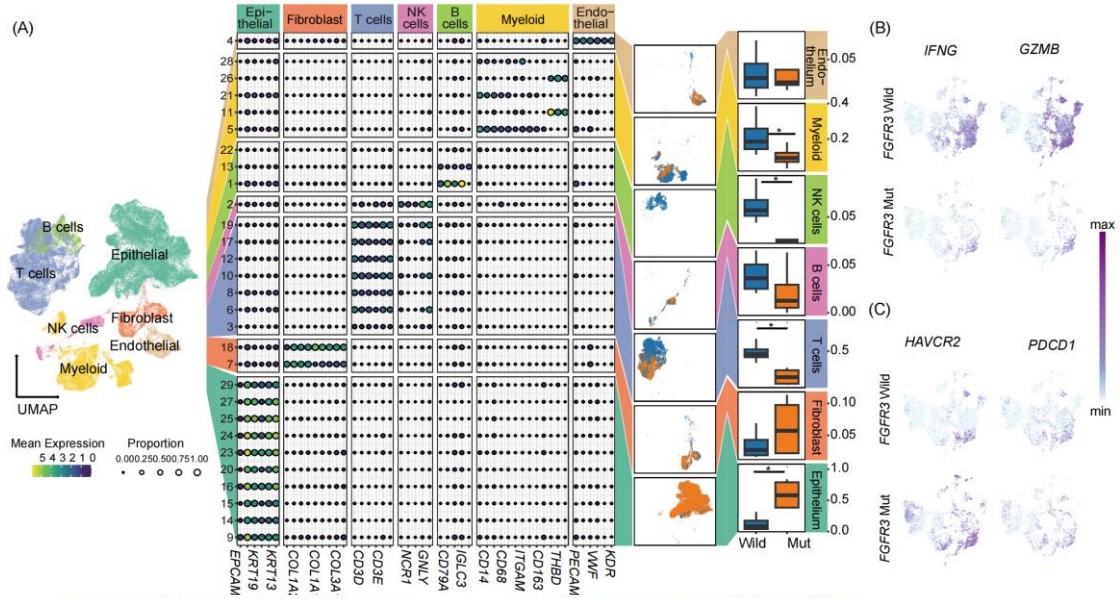


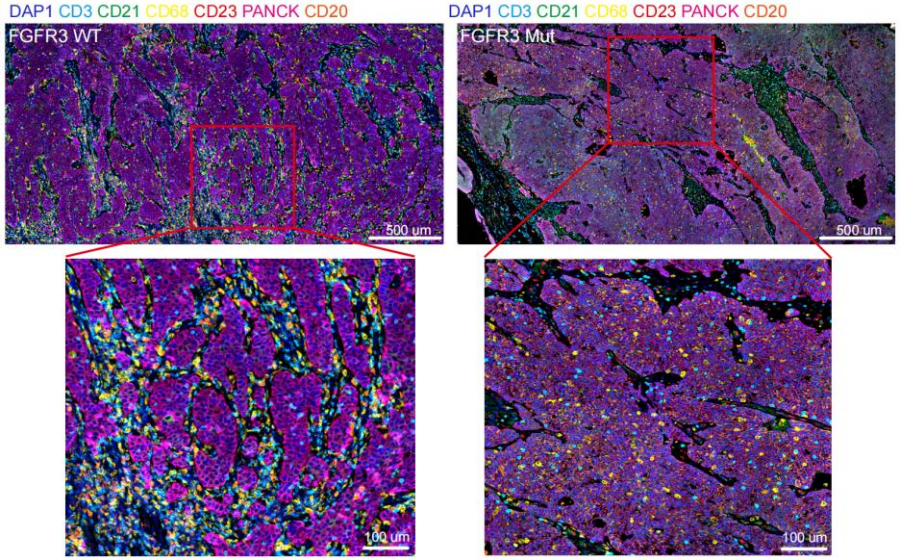


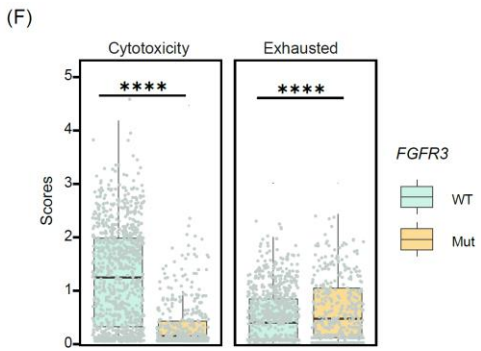


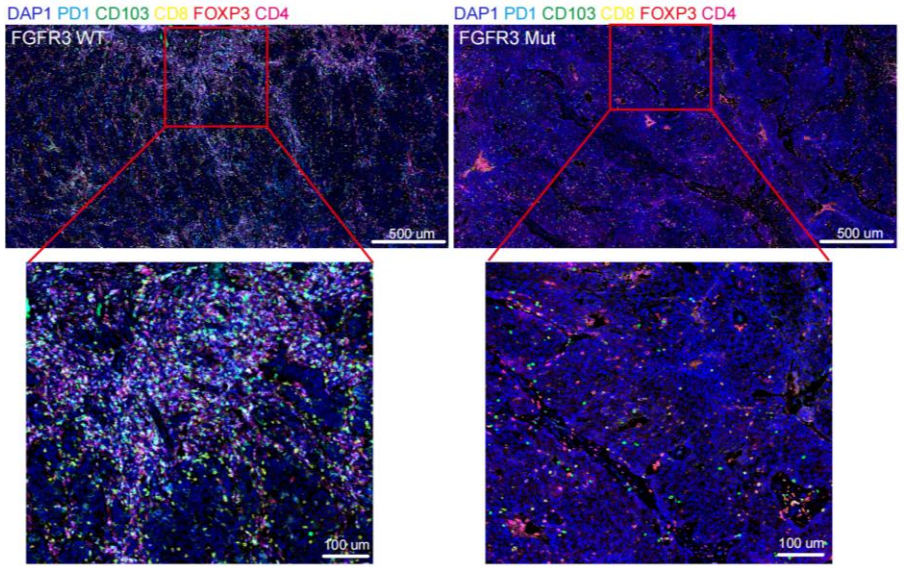
- Organoid co-culture combined with integrated multi-omics analysis enables the dissection of heterogeneous tumor–immune interactions within tumor tissues.
- The FGFR3–STAT5–IRF2 signaling axis suppresses chemokine production, driving an immune-depleted tumor microenvironment accompanied by T-cell exhaustion.
- Targeting the FGFR3 signaling pathway can reprogram an immunosuppressive “cold” tumor microenvironment into an immune-infiltrated state.
- Combination with PD-1 blockade induces synergistic antitumor effects, supporting the clinical translation of FGFR3-targeted therapy plus immunotherapy.

Results: FGFR3 mutations drive an immunosuppressive tumor microenvironment



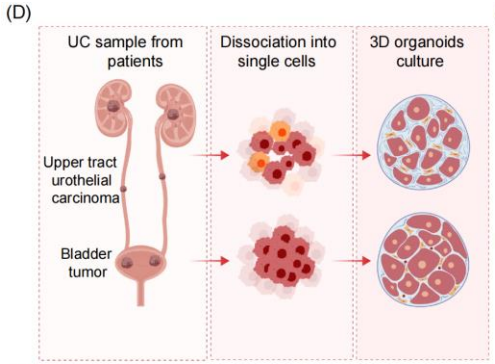


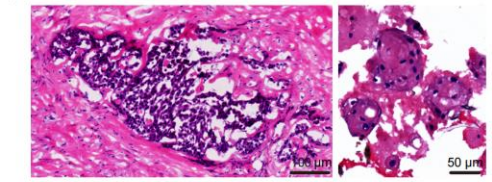


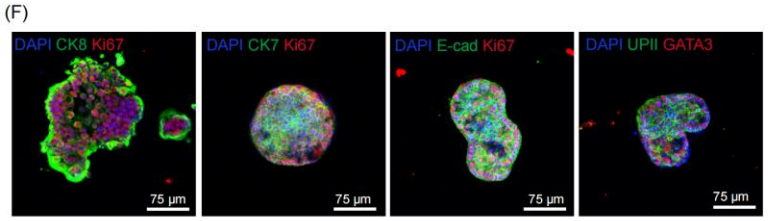


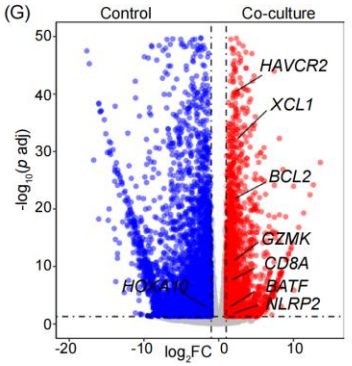
FGFR3 mutations are closely associated with an immune-depleted tumor microenvironment, characterized by reduced infiltration of NK cells, cytotoxic T lymphocytes, B cells, and macrophages, along with decreased T-cell cytotoxicity and increased exhaustion.

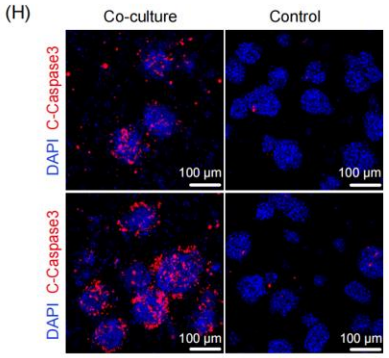
Results: FGFR3 mutations drive an immunosuppressive tumor microenvironment

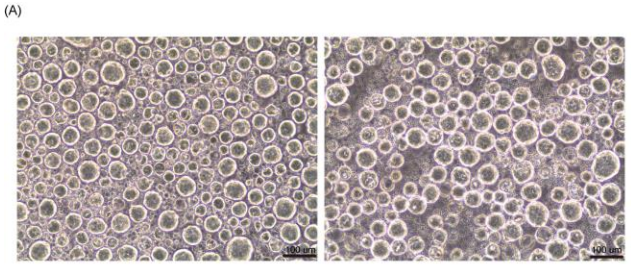


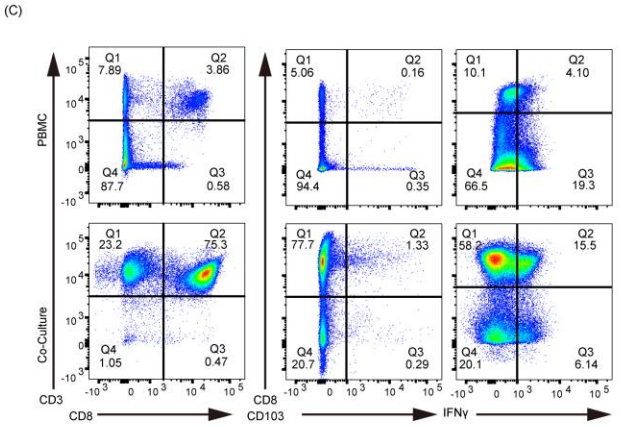


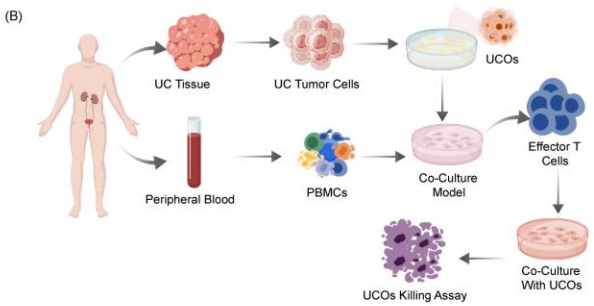


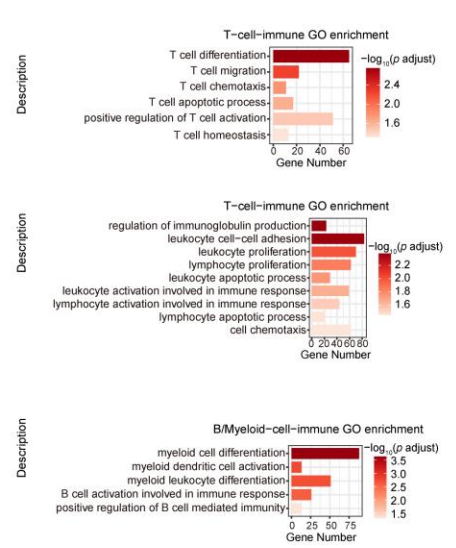






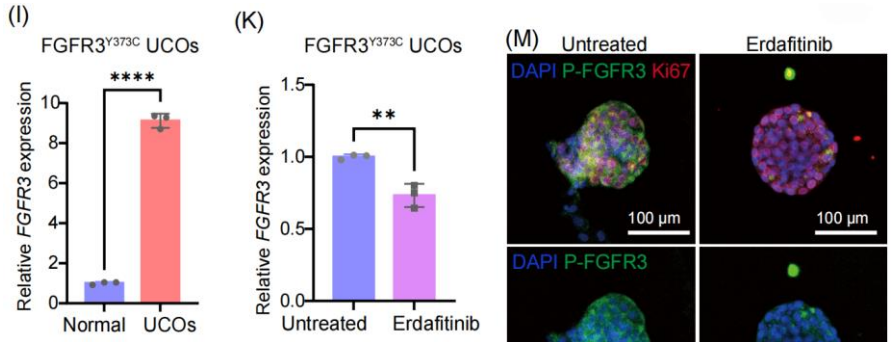


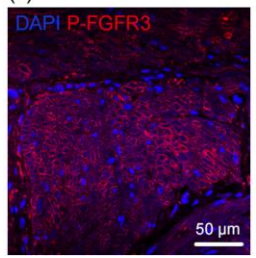


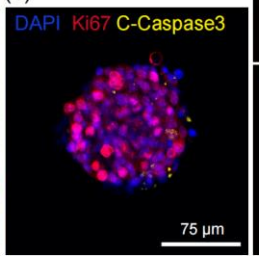


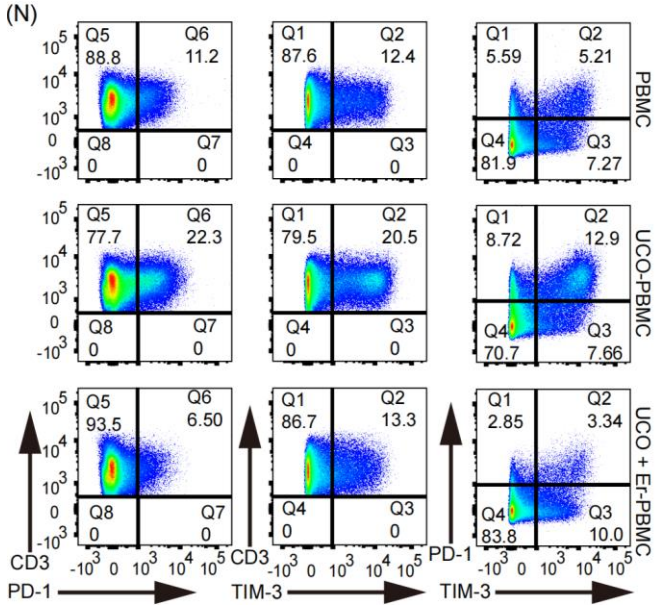
In vitro tumor organoids and immune co-culture systems induce antigen-specific T-cell activation and recapitulate tumor–immune interactions.

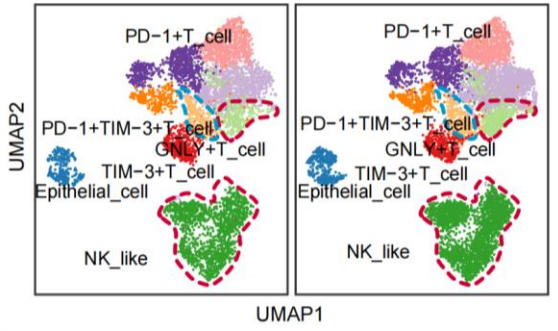
Results: FGFR3 inhibition enhances antitumor immunity

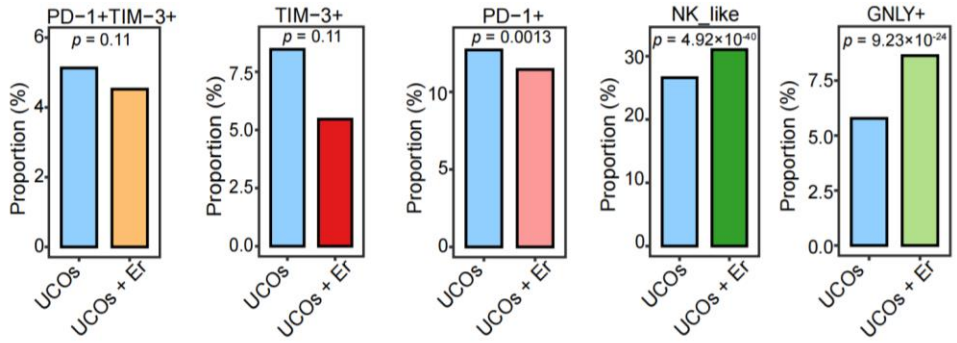


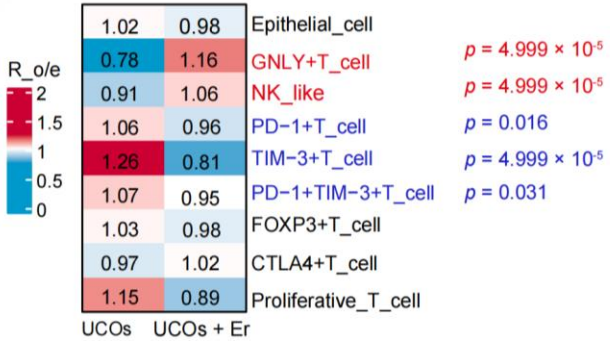


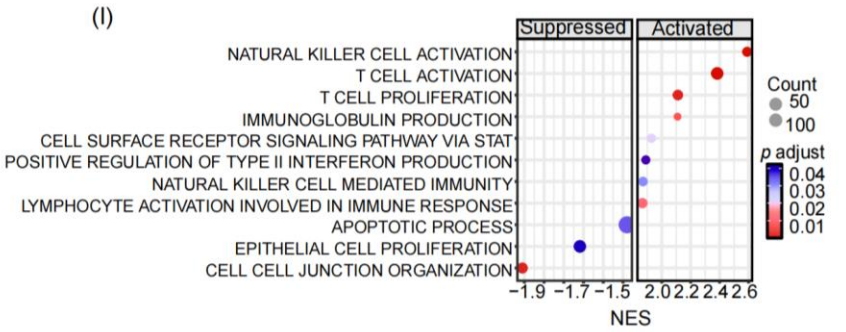






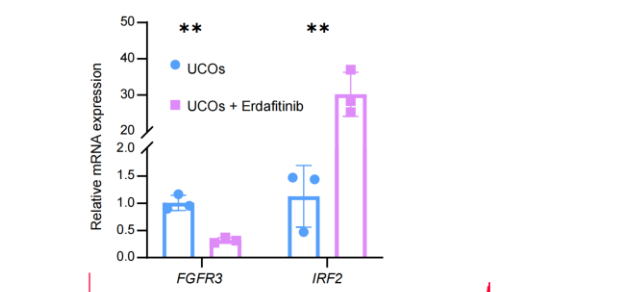


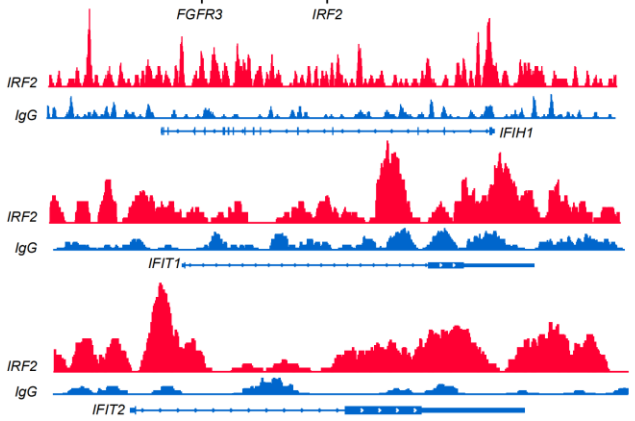


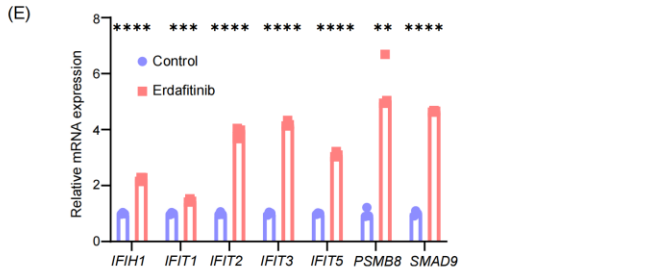


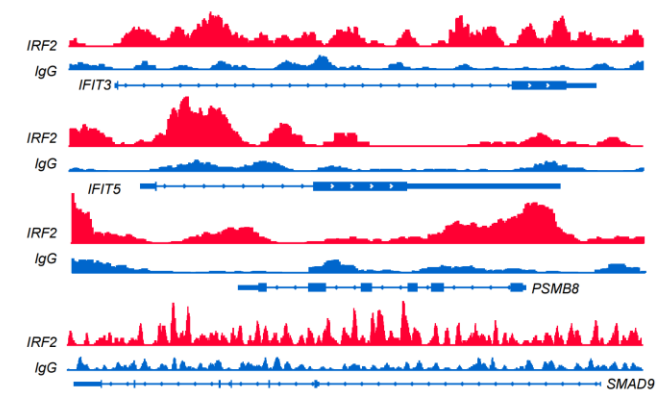
Targeting FGFR3 reduces the proportion of exhausted T-cell subsets, including PD-1⁺, TIM-3⁺, and PD-1⁺TIM-3⁺ cells, while increasing GNLY⁺ cytotoxic T lymphocytes and NK cells. This shift is accompanied by upregulation of key effector molecules, such as GNLY and IFNγ, and enhanced NK cell mediated cytotoxicity.

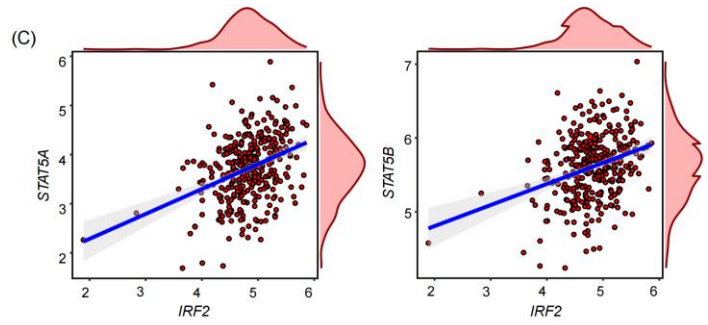
Results: The STAT5–IRF2 axis regulates IFN gene expression

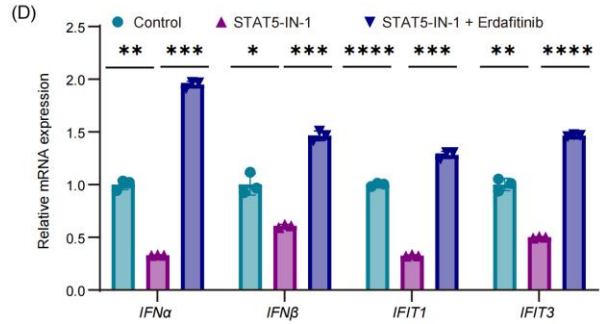


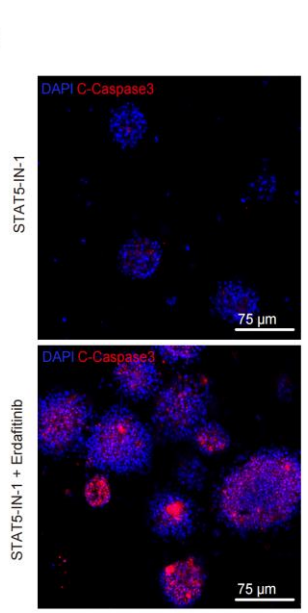


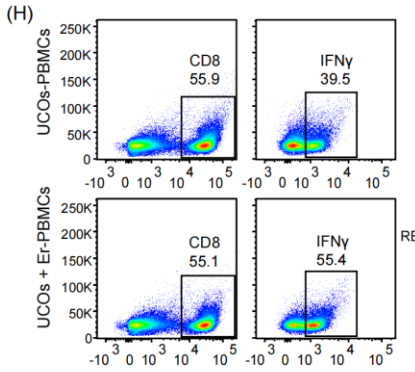


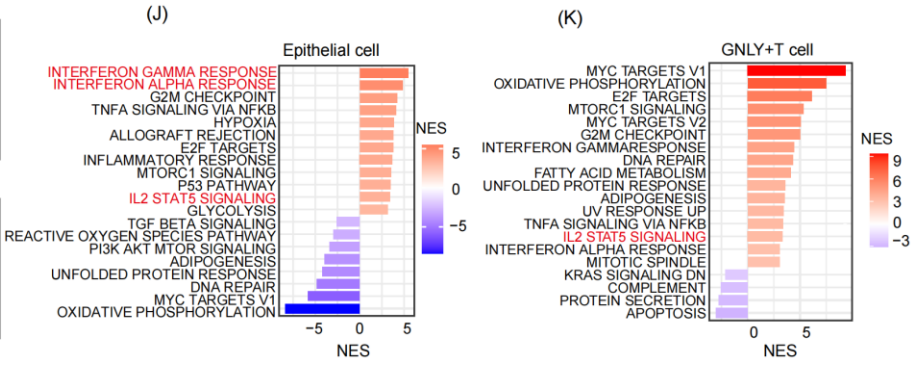


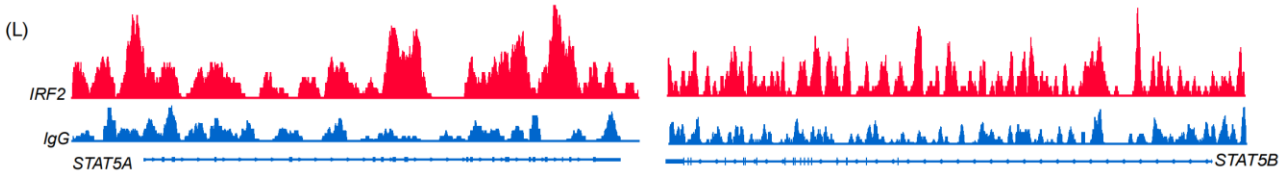






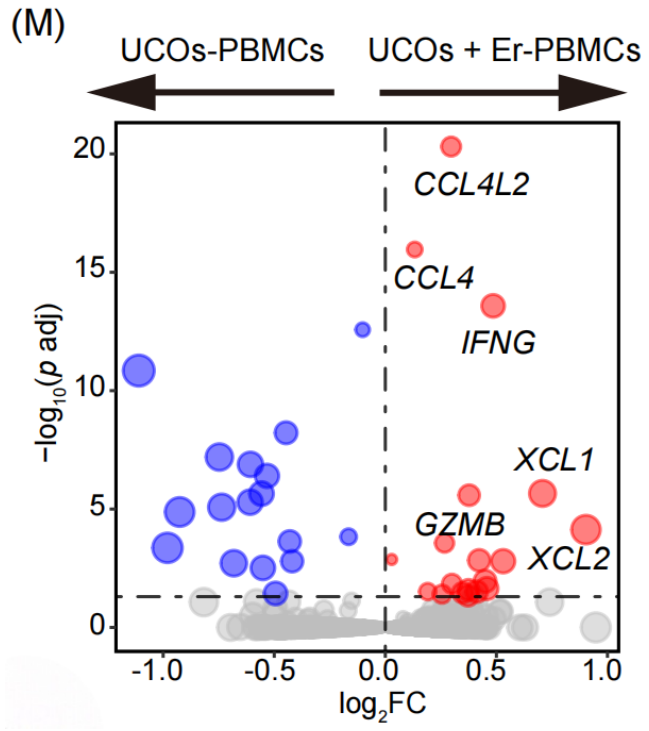


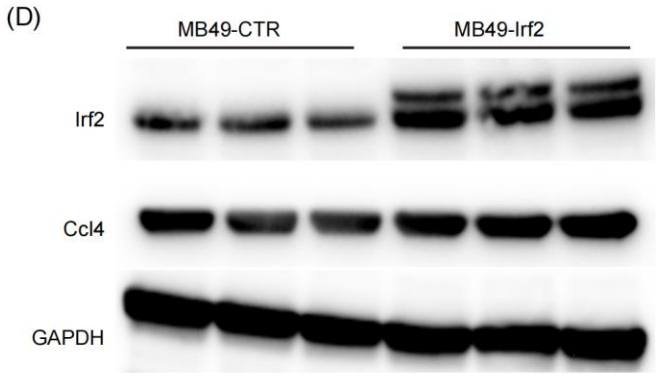


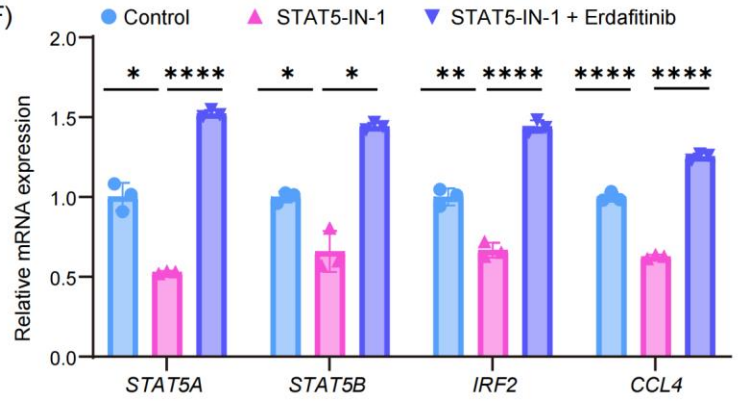


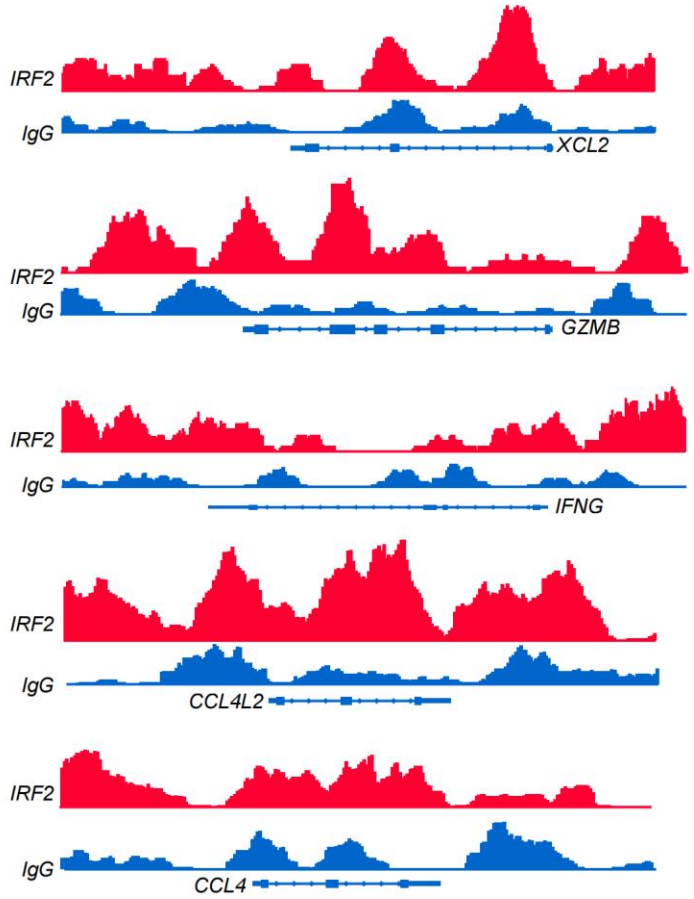
Targeting the FGFR3 signaling pathway enhances inflammatory IFN signaling in tumor cells through the STAT5–IRF2 axis. In the immune co-culture system, this is accompanied by increased secretion of IFNγ and other cytotoxic factors, thereby relieving immunosuppression in FGFR3-mutant urothelial carcinoma, remodeling the tumor microenvironment, and promoting antitumor immune responses.

Results: IRF2 transcriptionally regulates chemokine expression



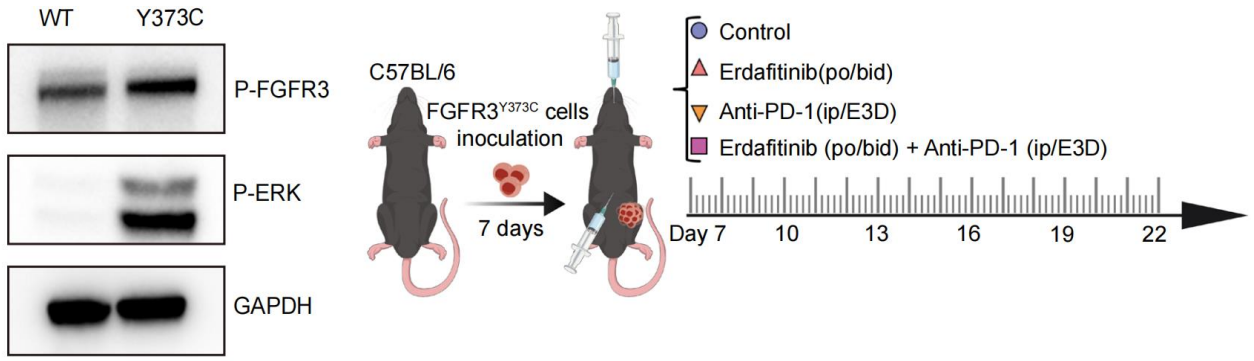


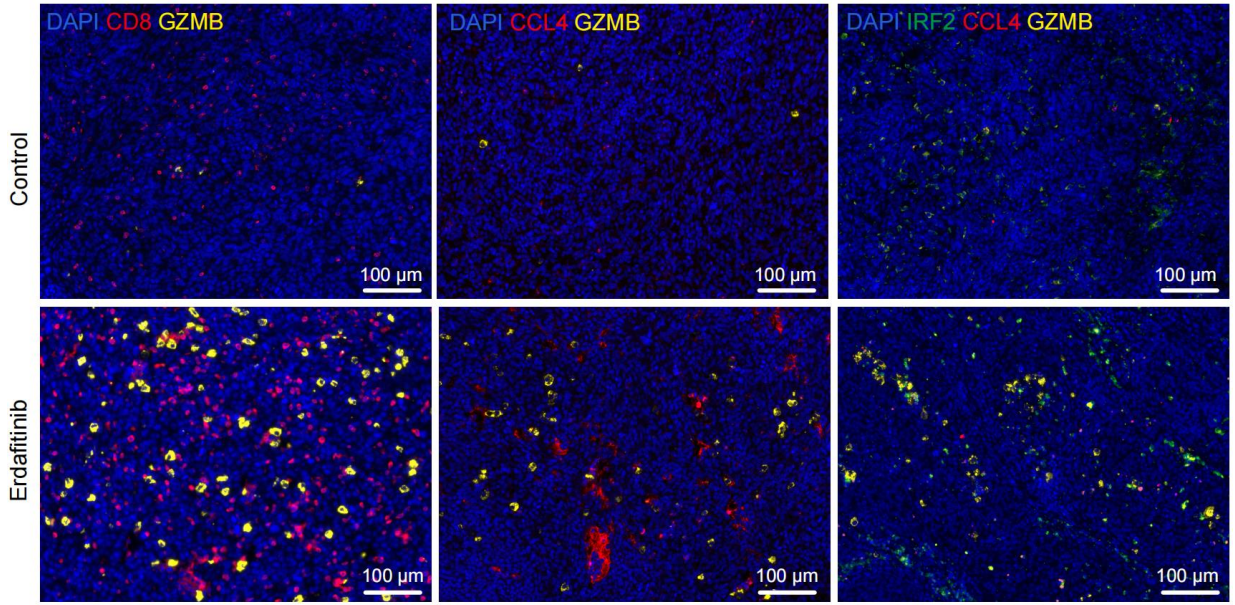


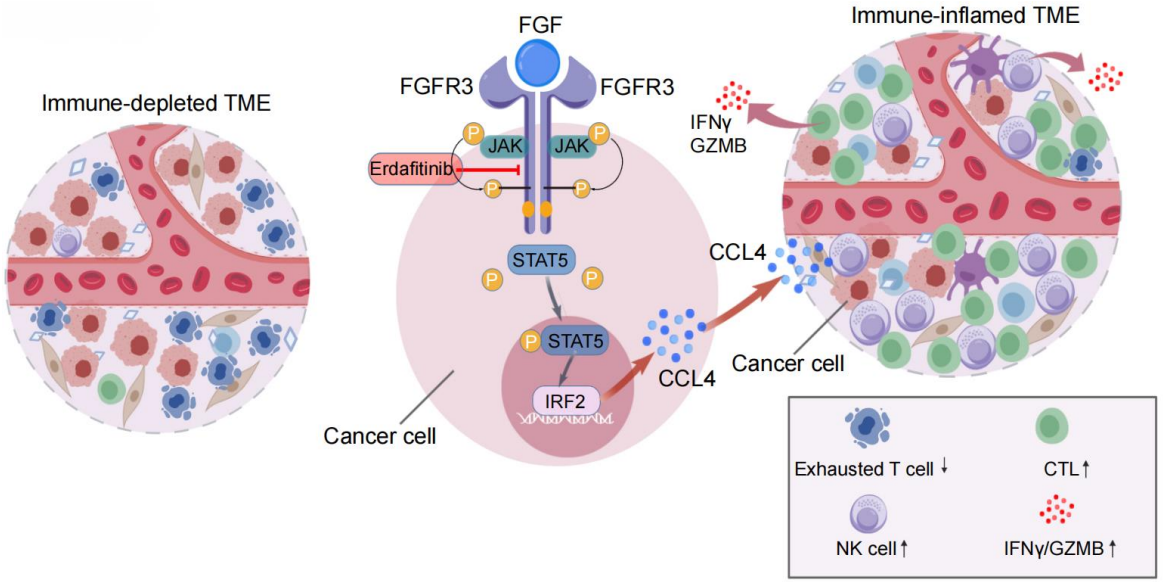


Following FGFR3 inhibition, single-cell RNA sequencing revealed significant upregulation of chemokines, including CCL4L2, CCL4, XCL1, and XCL2, which are known to promote the recruitment of CTLs and NK cells across multiple solid tumors. Overexpression of IRF2 in MB49 cells markedly increased CCL4 expression at both the mRNA and protein levels. CUT&Tag analysis further confirmed that IRF2 directly binds to the promoter regions of these chemokines, indicating transcriptional regulation. In vitro co-culture experiments showed that STAT5 inhibition significantly reduced IRF2 and CCL4 expression, supporting a STAT5–IRF2–mediated regulatory axis controlling CCL4 transcription.

Results: The STAT5–IRF2–CCL4 axis recruits and activates immune cells

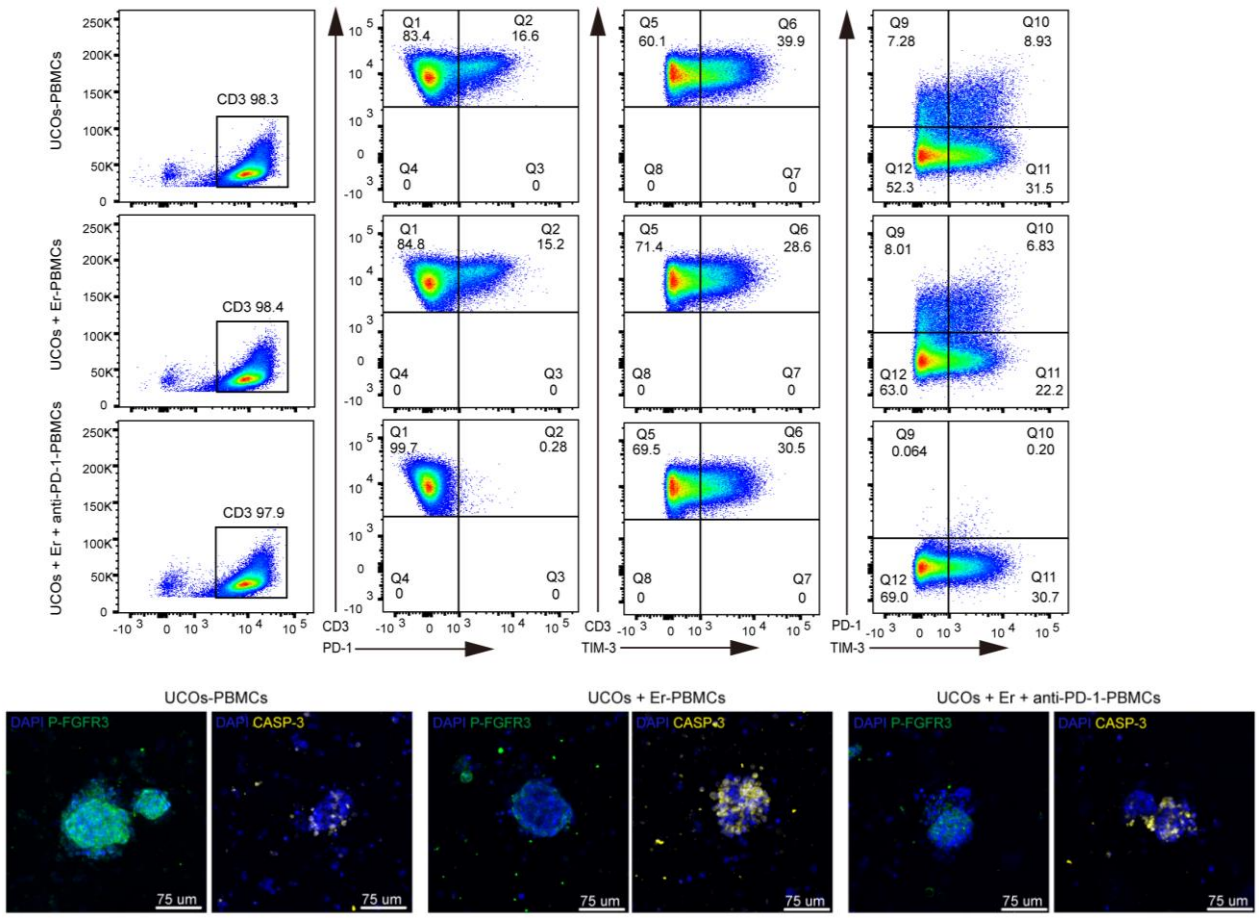


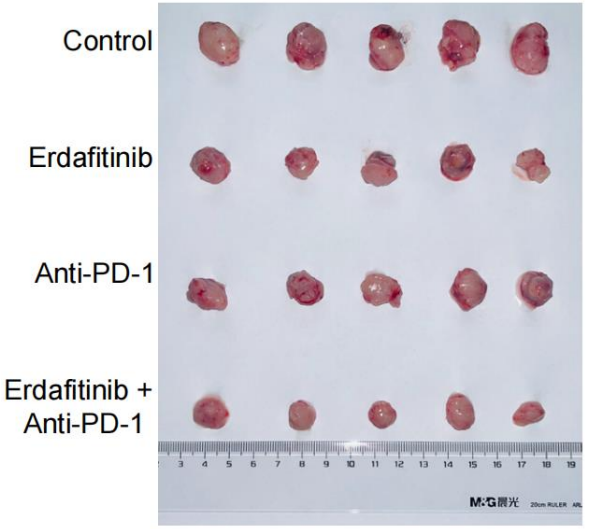


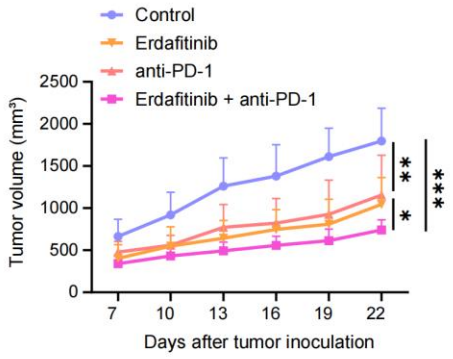


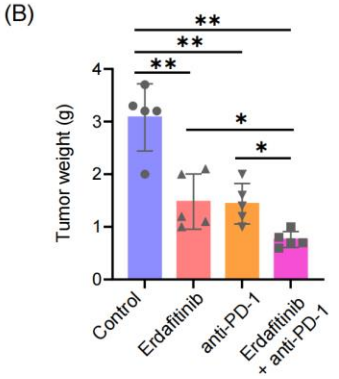
In a syngeneic MB49 mFGFR3^{Y373C} model, erdafitinib increased IRF2 and CCL4 expression and enhanced GZMB^{+} CTLs and NK cells infiltration. These results indicate that FGFR3 inhibition promotes immune cell recruitment and activation via the STAT5–IRF2–CCL4 axis.

Results: Erdafitinib combined with immunotherapy exhibits synergistic antitumor effects









Erdafitinib-induced remodeling of the tumor microenvironment provides a rationale for combination with immune checkpoint blockade. In the co-culture system, combination therapy further reduced terminally exhausted PD-1^{+} TIM-3^{+} T cells and showed greater tumor-killing efficacy than erdafitinib alone. In an MB49 FGFR3^{Y373C} syngeneic model, both monotherapies inhibited tumor growth, while the combination achieved significantly stronger antitumor effects, with improved control of tumor progression and weight loss.

Conclusions

- Activating FGFR3 mutations induce an immunosuppressive microenvironment and limit immune cell infiltration into tumors;
- Targeting the FGFR3 signaling pathway reverses T-cell exhaustion and promotes antitumor immune responses;
- Blocking the FGFR3 signaling pathway promotes the expansion and activation of effector T cells;
- Targeted inhibition of FGFR3 remodels the STAT5–IRF2–CCL4 axis to promote immune cell infiltration and antitumor immunity;
- Combination therapy with an FGFR3 inhibitor and anti–PD-1 exerts synergistic antitumor effects in FGFR3-mutant urothelial carcinoma.

Shan Jiang, Yuxuan Song, Yun Peng, Ran Yan, Yunze Niu, Baoqiang Chen, Jianxing Lin, et al. 2026. Patient-derived organoid-immune co-cultures integrated with multi-omics reveal immunotherapy resistance mechanisms in urothelial carcinoma. ***iMeta*** 5: e70130. https://doi.org/10.1002/imt2.70130

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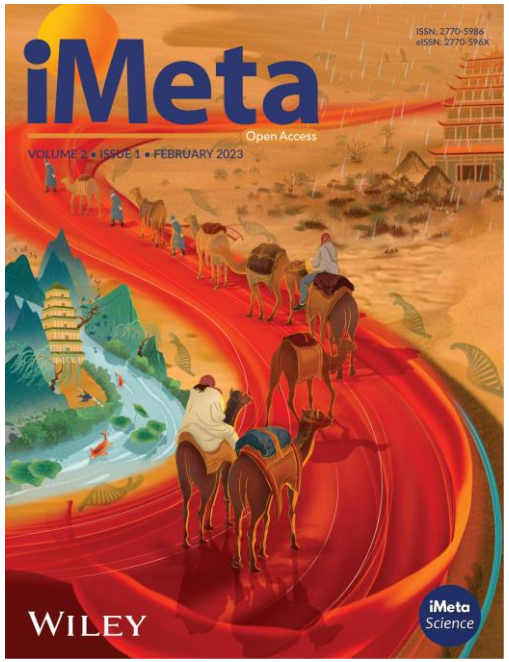

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