Combination of oncolytic vaccinia virus and immune checkpoint blockade overcomes resistance to immunotherapy in renal cell carcinoma

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Introduction

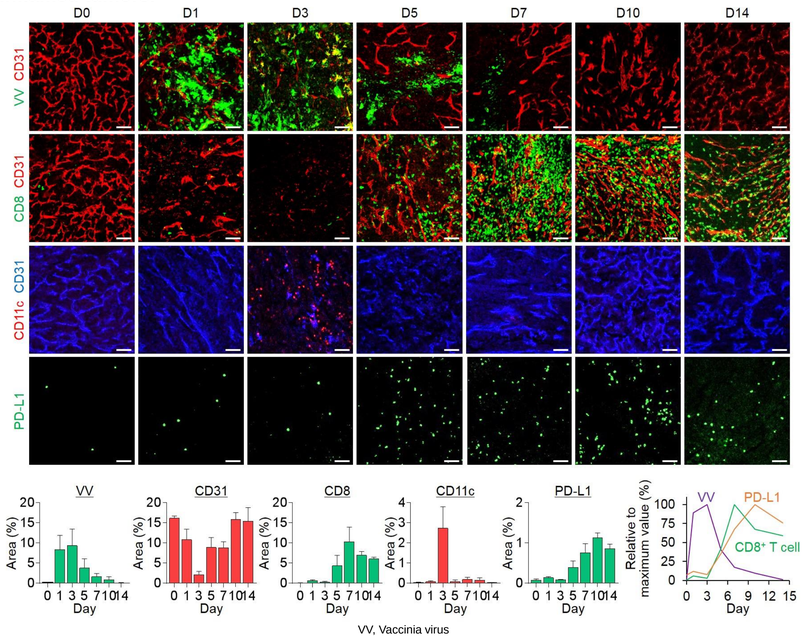
- Recently, immune checkpoint inhibitor (ICI) has emerged as another standard of care in advanced cancer, but response is limited as a monotherapy. To determine the optimal combination strategy for cancer immunotherapy, we employed mJX-594 (hereafter referred to as JX), an oncolytic vaccinia virus, as a combination partner for ICI.
- Here, we comprehensively dissected the changes of tumor microenvironment with mJX-594 virotherapy and investigated its immunotherapeutic potential to provide a rational combinatorial strategy with ICIs in poorly immunogenic tumor models with emphasis on kidney cancer.

Materials and Methods

- **Generation of virus**: mJX-594 was provided by Sillajen, Inc. (Seoul, Korea). Briefly, mJX-594 is a Western Reserve strain of oncolytic vaccinia virus with murine GM-CSF in the vaccinia thymidine kinase gene locus under the control of the p7.5 promoter.
- **Tumor model and treatment regimens**: Tumors were implanted by SC injection of 2 x 10^5 Renca cells into the right flank of mice. When tumor size reached >50 mm^3, mice were treated with 1 x 10^7 pfu of mJX-594 every 3 days. For depletion study, depletion antibodies for $CD4^+$ (200 ug), $CD8^+$ (200 ug) T cells or GM-CSF^+ (200 ug) were injected IP with mJX-594. For immune checkpoint blockade, αPD-1 (10 mg/kg, BioXCell) and/or αCTLA-4 (4 mg/kg, BioXCell) antibodies injected IP every 3 days.

Results

Figure 1. mJX-594 virotherapy converts immunosuppressive non-inflamed tumors into inflamed tumors.



Results

Figure 2. PD-L1 is predominantly expressed in tumor cells after mJX-594 virotherapy.

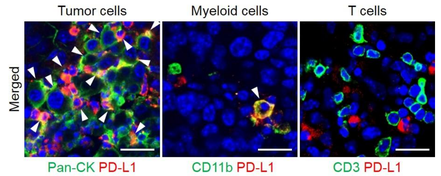


Figure 3. PanCancer Immune Profiling panel shows remarkable differences in immune signatures between mJX-594-treated tumors and control tumors.

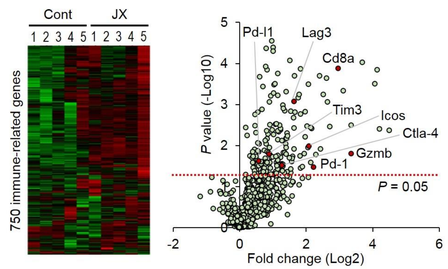


Figure 4. Intratumoral injection of mJX-594 leads to systemic and cancer-specific immune responses.

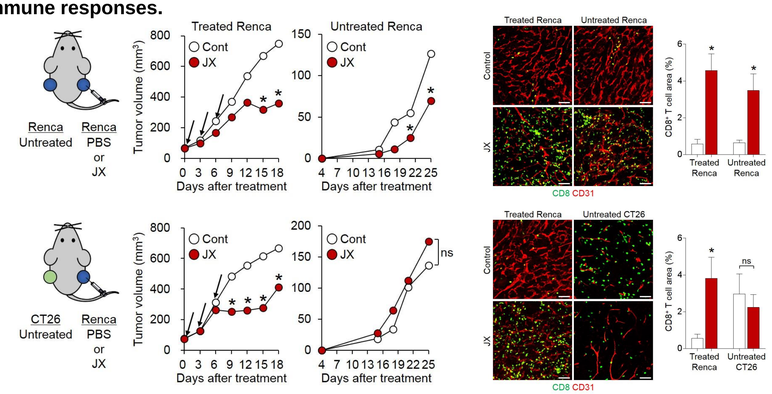
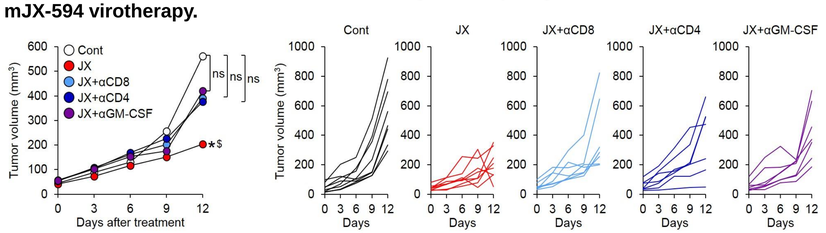
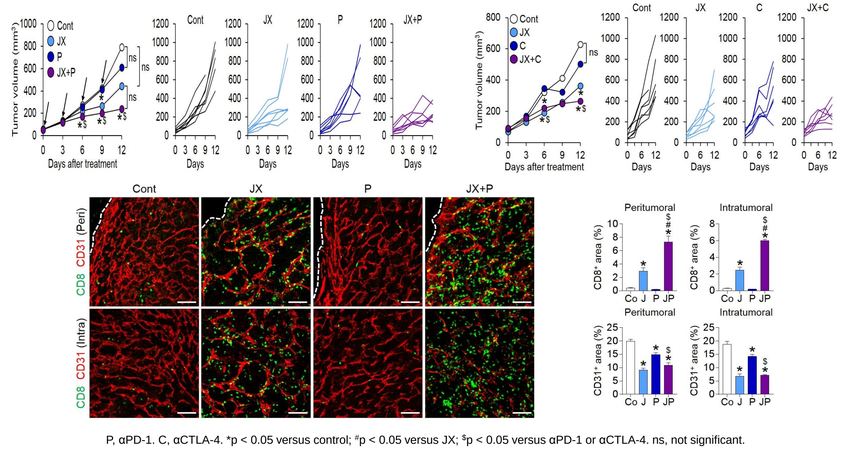


Figure 5. Depletion of T cells or GM-CSF significantly negated the anti-cancer effect of mJX-594 virotherapy.



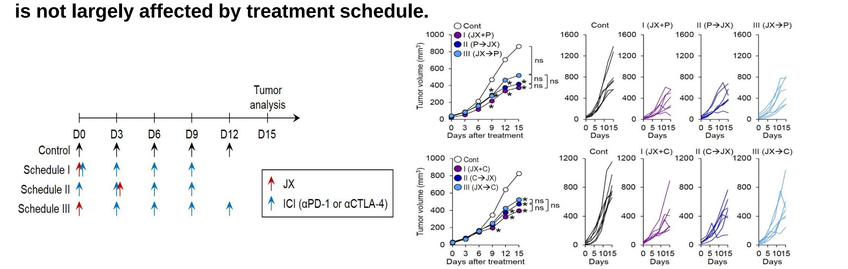
*p < 0.05 versus control; $p < 0.05 versus αGM-CSF. ns, not significant.

Figure 6. Combination of mJX-594 with immune checkpoint blockade elicits a synergistic anti-cancer effect with enhanced infiltration of T lymphocytes into tumor.



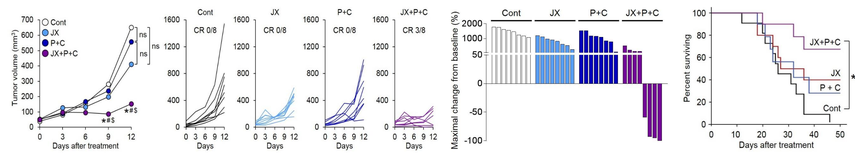
P, αPD-1. C, αCTLA-4. *p < 0.05 versus control; #p < 0.05 versus JX; $p < 0.05 versus αPD-1 or αCTLA-4. ns, not significant.

Figure 7. The efficacy of combination immunotherapy with intratumoral mJX-594 and ICIs is not largely affected by treatment schedule.



P, αPD-1. C, αCTLA-4. *p < 0.05 versus control. ns, not significant.

Figure 8. The triple combination of mJX-594, αPD1, and αCTLA4 can induce complete tumor regression and provides a long-term survival benefit in implanted kidney cancer.



P, αPD-1. C, αCTLA-4. *p < 0.05 versus control; #p < 0.05 versus JX; $p < 0.05 versus αPD-1+ αCTLA-4. ns, not significant.

Introduction

In conclusion, this study indicated that intratumoral injection of mJX-954 induces a profound remodeling of TME from cold to hot state and elicit robust anti-cancer immunity in combination with ICIs, overcoming immunotherapy resistance.