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

Hong Jae Chon1,2, Won Suk Lee1,2, So Jung Kong1,2, Hannah Yang1,2, Na Keum Lee1,2, Intae Park3, Eun Sang Moon4, Ji Won Choi4, Joong Bae Ahn5, Joo Hang Kim1, Gou Young Koh3, Chan Kim1,2

1Medical Oncology and 2Laboratory of Tumor Vasculature and Microenvironment, CHA Bundang Medical Center, CHA University, Seongnam, Korea
3Graduate School of Medical Science and Engineering, KAIST, Daejeon, Korea, 4SillaJen, Inc., Seoul, Korea, 5Yonsei Graduate School, Yonsei University College of Medicine, Seoul, Korea

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 × 106 Renca cells into the right flank of mice. When tumor size reached >50 mm3, mice were treated with 1 × 107 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.

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 immune responses.

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

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

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

Figure 8. The triple combination of mJX-954, αPD1, and αCTLA-4 can induce complete tumor regression and provides a long-term survival benefit in implanted kidney cancer.

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