INDUCTION OF TUMOR CELL AUTOSIS BY MYXOMA VIRUS-INFECTED CAR-T AND TCR-T CELLS TO OVERCOME PRIMARY AND ACQUIRED RESISTANCE IN SOLID TUMORS

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Background: Cytotoxicity of tumor-specific T cells requires tumor-cell-to-T cell contact-dependent induction of classic tumor cell apoptosis and pyroptosis. However, such canonical mechanisms may not trigger sufficient primary responses of solid tumors to adoptive cell therapy (ACT) and prevent tumor antigen escape-mediated acquired resistance.

Methods: One of the candidate oncolytic viruses is myxoma virus (MYXV), a DNA virus, which has a highly restricted host range and is only pathogenic to European rabbits (Stanford et al., 2007). In this study, we investigated the potential to exploit CAR-T and TCR-T cells as myxoma virus (MYXV)-delivery carrier cells by pre-infecting the T cells with MYXV ex vivo by a spin-infection protocol (CAR-T MYXV and TCR-T MYXV).

Results: Here, we demonstrate that myxoma virus (MYXV)-infected tumor-specific T (T MYXV) cells, expressing chimeric-antigen-receptor (CAR) or T-cell-receptor (TCR), which systematically deliver MYXV into solid tumors to overcome primary resistance. In addition to T cell-induced apoptosis and pyroptosis, tumor eradication by CAR/TCR-T MYXV cells is also attributed to tumor cell autosis induction, a special cell death unleashed by this unexpected novel T-cell-cytotoxic machinery. Mechanistically, T cell-derived IFN-γ/AKT signaling synergizes with MYXV-induced M-T5/SKP-1/VPS34 signaling to trigger robust tumor cell autosis. Moreover, CAR/TCR-T MYXV-elicited autosis also functions as a potent bystander killing to restrain antigen escape.

Conclusions: Collectively, our results highlight a pivotal role of CAR-T MYXV cells in improving the efficacy of ACT by: (1) delivering MYXV into tumor beds; (2) recognizing and inducing classic tumor cell apoptosis and pyroptosis to antigen-positive tumor cells accompanied by IFNγ secretion; (3) inducing autosis in antigen-positive and antigen-negative cancer cells; and (4) potentially eliminating ALV cells by autosis and adaptive antitumor immunity. Thus far, our data suggest the existence of a tumor cell autosis-triggering strategy dependent on both MYXV and antigen-programmed CAR-T cells, which strategically incorporates MYXV and tumor-specific T cells to overcome therapeutic resistance in solid tumors (figure 1).

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Graphical Abstract
- CAR-T MYXV cells systemically deliver MYXV into cognate antigen-expressing tumors
- T cell-derived IFNγ synergizes with MYXV-derived M-T5 to trigger tumor cell autosis
- Autosis is a potent bystander killing to eradicate antigen-negative tumor cells
- CAR/TCR-T MYXV induces autosis and adaptive immunity to restrain antigen escape