Peds-ONC Immunotherapy Center:
Targeting M2-like Macrophages and MDSC with Myelolytic-Virotherapy

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Abstract
Cure rates for pediatric patients with relapsed or metastatic solid tumors remain unacceptably low. Cancer immunotherapies hold great promise, but scores of disappointing studies highlight our relative ignorance in understanding the immunosuppressive tumor microenvironment (TME). Tumor associated macrophages (TAMs), typically polarized to a so-called “M2-like” immunosuppressive phenotype, and myeloid-derived suppressor cells (MDSC) are major constituents of the TME and are emerging as important therapeutic targets. We have found a clinically viable strategy that simultaneously reduces TAMs/MDSC in the TME, resulting in significant antitumor efficacy. We found that systemic reduction of macrophages via liposomal bisphosphonate (Clodrosome) augmented the proinflammatory status of intratumoral F4/80+ macrophages induced by oncolytic herpes virus virotherapy (oHSV), resulting in high expression of inflammatory T cell and NK cell chemokines in a mouse xenograft model of Ewing sarcoma.1 The FDA-approved chemotherapy trabectedin showed even more profound effects on tumor regression when combined with virus, with significant reductions of M2-like macrophages and MDSC.1 We hypothesize that targeting TAMs and MDSC by combining “myelolytic” therapies (e.g., trabectedin) with pro-inflammatory therapies (e.g., oHSV) activates innate antitumor mechanisms that cause cancer regression and reshapes the solid tumor microenvironment to be more permissive to cellular immunotherapies.

Background

Methods

Oncolytic Herpes Simplex Virus rRp450
HSV-1
rRp450

Deletion of ICPS (ribonucleotide reductase)
Insertion of CYP2B1 (rat cytochrome p450)

CD47

Fig. 1. Clodrosome depletion of macrophages enhances oHSV efficacy.

Fig. 2. Clodrosome plus virus alters the phenotypes of tumor-associated macrophages.

Fig. 3. Myelolytic-virotherapy alters the immune microenvironment and improves animal survival.

Fig. 4. Ewing sarcoma A673 cells express CD47.

Fig. 5. Tumors grown in CCR2 knock out animals show reduced MDSC.

Fig. 6. Myelolytic-virotherapy improves survival in Ewing sarcoma PDX models.

Fig. 7. Effect of GD2 CAR-T cells on tumor growth and animal survival in LAN-1 human neuroblastoma xenografts. Data were provided by our co-investigator, Dr. R. Wang (member of PI-DDN). We will investigate the effects of myelolytic-virotherapy on CAR-T efficacy.

Fig. 8. oHSV infected Ewing sarcoma cells activate NK cells in co-culture.

Fig. 9. oHSV-infected cells show increased susceptibility to NK-mediated cytotoxicity.

Fig. 10. oHSV infection downregulates HLA class I and upregulates NK activation ligands.

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Conclusion and Project Aims
• The combination of virus infection and trabectedin effectively targets MDSC and tumor-associated M2-like macrophages, depleting some and polarizing the remaining toward an M1-like phenotype.
• Our current aims are:
  1. Determine the mechanism(s) by which combined myelolytic-virotherapy drives tumor regressions.
  2. Determine the effects of myelolytic-virotherapy on T cell-mediated immunotherapies.
  3. Determine whether combined myelolytic-virotherapy enhances the efficacy of NK-based cellular therapies.

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References
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