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Local Lung Targeting of Tumor Associated Macrophages Combined with Cytoreductive Therapy Decrease Tumor Burden in a Secondary Lung Cancer Model

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Background and Purpose

Lung cancer is the leading cause of cancer death among both men and women in the US and worldwide. In spite of recent advances in the treatment of lung cancer including targeted and antibody therapies, 5 year overall survival of lung cancer patients continues to be very low at ca. 19%. The purpose of this work was to evaluate the efficacy of a locally administered small molecule colony stimulating factor 1 receptor inhibitor (CSF-1Ri), PLX3397 (PLX), alone or in combination with cytoreductive therapy (paclitaxel, PTX) in reducing the tumor burden of an in vivo model of secondary lung cancer. CSF-1Ri have been shown to inhibit M2-like (tumorigenic) tumor-associated macrophages (TAMs or M2 Mɸ), and alone or in combination with chemotherapies, to reduce tumor burden in pre-clinical and clinical studies of various types of primary and secondary cancers. Local administration of immunotherapy to the lungs may enhance lung biodistribution of such therapies, and reduce potential unwanted off-target toxicity. In addition, combination of such therapy with low dose standard of care chemotherapy may offer improved anti-tumor effects.

Methods

- Pre-clinical Model of Secondary Lung Cancer
  - 25K 4T1 Luc TdTomato expressing luciferase (Luc), TdT, & puromycin resistant gene
  - Bing mice
  - Intratracheal installation (i.t.)
  - DPI: day post tumor implantation
  - IVIS: in vivo imaging system
  - Terminal day: day 19
  - Vehicle: 1% DMSO, 5% Tween80 in PBS

Results: Effect of Immunochemotherapy on Tumor Burden and Tumor Microenvironment (TME)

- 4T1 Transduced and no Changes in Response to PTX
  - 4T1 Transduction:
    - Transduction of Lentivirus expresses luciferase (Luc), TdTomato (TdT), & puromycin resistant gene
    - WT 4T1Luc TdT
  - MTT Assay:
    - PLX reduced M2 Mɸ

- Combination Immunotherapy: Efficacious and Safe
  -combination PLX, PTX
  - Immunofluorescence and Flow Cytometry:
    - PTX induced cell kill in WT 4T1 and 4T1 Luc TdT cells transduced cells behave as WT

- PLX p.a.: Reaches its Molecular Target in TME
  - Western Blot:
    - PLX p.a.: Decreases M2-like Macrophages in TME
  - PLX p.a.: Decreases M2-like Macrophages in TME

Conclusions

- Local administration of immunotherapy to the lungs (PLX p.a.) supports chemotherapies (PTX i.v.) of breast to lung metastases:
  - PLX + PTX reduced tumor burden (ex vivo IVIS & lung weight)
  - PLX reached its molecular target, M2 Mɸ in TME
  - PLX reduced M2 Mɸ shifted the balance towards anti-tumorigenic Mɸ phenotype

References

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5. NSF (DRR #1508363)
6. Center for Pharmaceutical Engineering and Sciences – School of Pharmacy