Title: Viral Vectors and Photosensitive Drugs as Immunomodulators in Cancer Treatment

Anna Zajakina

Latvian Biomedical Research and Study Centre

Abstract:

Combining oncolytic viruses with photodynamic therapy (PDT) shows potential in treating both primary and metastatic tumors, though limited data is available on the mechanisms driving the efficacy of this approach. PDT relies on the activation of photosensitizing agents, such as chlorin e6 (Ce6), by near-infrared (NIR) light following systemic administration. Upon activation, PDT induces immunogenic cell death in cancer cells and can reprogram macrophages toward anti-tumor phenotypes.

This presentation aims to consolidate recent findings on PDT's application in cancer therapy and report on our pilot study integrating alphavirus-based therapy with PDT in both 2D and 3D in vitro models, specifically in the 4T1 mouse breast cancer line. For the first time, we examine PDT's effect on cancer cell-macrophage co-cultures within a 3D setting, assessing how the sequence of PDT and viral infection influences alphaviral transgene delivery (e.g., IFNγ). Our findings reveal that combined therapy has a synergistic effect, with greater efficacy observed when viral infection precedes PDT. Additionally, we observed enhanced phagocytosis of Ce6/NIR-treated 4T1 cells by both M1 and M2 phenotypes of bone marrow-derived macrophages (BMDMs) in co-culture. Ce6/LED exposure at 3 J/cm² notably reduced macrophage viability (M0, M1, M2) and decreased expression of CD11b and MHCII markers. Importantly, 3D culture conditions maintained macrophage polarization stability post-treatment.

In conclusion, PDT appears effective in 3D models in combination with alphavirus-based therapy. It represents a promising cancer therapy strategy, promoting immunogenic cancer cell death and phagocytosis by macrophages. Given its minimal impact on monocyte polarization, PDT holds significant potential as a complement to virus-mediated immunomodulatory gene delivery.

This research is funded by the project: No. lzp-2021/1-0283 “Programming of breast cancer microenvironment to create a "hot" immune-responsiveness in cancer”.