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Air Pouch Models for Immunotherapy Evaluation of ROS-Enhancing Anticancer Compounds

Galyna Bila [1,2], Andriy Mokhir, [3] Rostyslav Bilyy [1,2]

[1] *Institute of Cellular Biology and Pathology "Nicolae Simionescu", Bucharest, Romania*
[2] *Danylo Halytsky Lviv National Medical University, Department of Histology, Cytology and Embryology,Ukraine*
[3] *Friedrich-Alexander-University of Erlangen-Nürnberg (FAU), Department of Chemistry and Pharmacy, Organic Chemistry II,Erlangen, Germany*

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***Correspondence:** Galyna Bila. *Institute of Cellular Biology and Pathology "Nicolae Simionescu",8 B.P.Hasdeu street, Sector 5, Bucharest, Romania Danylo Halytsky Lviv National Medical University, Department of Histology, Cytology and Embryology, 79010 Lviv, Ukraine*
E-mail: galyna.bila@gmail.com
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Abstract

The air pouch model has emerged as a valuable in vivo platform for investigating the complex interplay between the immune system and tumor development, making it particularly relevant for evaluating novel anticancer immunotherapies. This study highlights the utility of the air pouch model for preclinical assessment of reactive oxygen species (ROS)-enhancing compounds aimed at inducing immunogenic cancer cell death (ICD) and eliciting antitumor immune responses.

The air pouch, an experimentally induced subcutaneous cavity, rapidly becomes infiltrated with diverse immune cells, including neutrophils, macrophages, eosinophils, and mast cells, creating a localized environment conducive to studying cellular interactions with administered agents and tumor cells. Injection of monosodium urate crystals (MSU) into the air pouch cavity stimulate abundant neutrophil infilatration and formation of aggregated neutrophil extracellular traps (NETs). Introduction of cancer cells, such as the Nemeth-Kellner (NK/Ly-RB) myeloblastoma cell line, into the air pouch allows for the observation of tumor growth within an immunocompetent host. Here we for the first time demonstrate the dynamics of tumor solification inside the formed airpouch, tumor growth dynamics and morphological changes. Animal survival was also evaluated. Furthermore, the early interaction of immune cells, notably neutrophils, with the inoculated tumor cells and the formation of NETs, cytokine production can be readily assessed in this model.

We leveraged the air pouch model to evaluate the efficacy of ROS-modulating anticancer agents with immunotherapeutic potential. For instance, the compound NCure50, a reversible thiol binder that increases lysosomal ROS, demonstrated significant antitumor effects in the NK/Ly-RB air pouch model, extending the lifespan of treated mice and even leading to cures in some cases. Activation of lysosomal ROS resulted in formation of oxidized neoadjuvants. Importantly, surviving mice developed anti-tumor antibodies and exhibited neutrophil-mediated tumor targeting, including NET formation, indicating the induction of systemic and local antitumor immunity [1].

These findings underscore the air pouch model's capacity to provide critical insights into the in vivo efficacy of ROS-enhancing anticancer compounds and their ability to stimulate antitumor immunity. The model allows for the evaluation of local immune responses, such as NET formation, and the subsequent development of systemic immunity, paving the way for the identification and optimization of novel immunotherapeutic strategies against various cancers.