Immune Response Modulation by Immune Checkpoint Inhibitors (ICI)-Induced Changes in Lung Cancer

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Location: Department of Molecular Medicine, Cancer Vaccines and Immunotherapy Laboratory

Research theme / topic: Immunotherapy in Lung Cancer

Background

The advent of immunotherapy has changed the therapeutic landscape in NSCLC without “driver" alterations. Nevertheless, many patients still do not experience clinical benefit upon these therapies, and indeed some tumor types appear particularly resistant. Fast progression (FP) has been defined as a ≥ 50% increase in the sum of the longest diameter (SLD) of target lesions within 6 weeks from baseline, and early death (ED) as death as a result of disease progression within 12 weeks from baseline in patients without a response assessment. On the other hand, an exciting component of novel immunotherapeutic strategies is the durability of clinical benefit observed, with some patients achieving disease control for many years. Given the complexity of the tumor–immune system interface, it is likely that PD-L1 expression on tumor cells and/or the tumor-immune infiltrate represent only part of the predictive model necessary for selecting patients predisposed to respond to immunotherapy.

Cancer treatment with anti-PD-1/PD-L1 modulates the immune composition of the tumor microenvironment as well described by CyTOF Mass Cytometer (10.1016/j.cell.2017.07.024; 10.1038/s43856-022-00197-2). Single cell analysis reveals a high level of plasticity of the immune populations with a modulation of the epigenetic scar (10.1016/j.cell.2022.09.020). Nevertheless, very, few it is known about how the ICI treatment affects the plasticity of cancer cells. Primary and secondary resistance to ICI-based therapy have been associated with the presence of epithelial-to-mesenchymal transition (EMT) features and cancer stem cells, but only few authors proved a direct effect of the treatment on the modulation of these factors (10.1111/cas.12406; 10.1073/pnas.1921445117; 10.1038/s41467-023-40745-5) and predictive biomarkers of detrimental effects of ICI therapy have not yet been identified (10.1200/JCO.23.00580; 10.1080/15384047.2024.2308097).

Studying two NSCLC cell line models established from cells lines derived from biopsies of the same patient before treatment initiation with ICI (NSCLC-B) and at the time of hyperprogression (NSCLC-H), we reported differences in cell morphology, in vitro behaviour and transcriptome profiles between the two cell lines. The apparent plastic transformation observed in NSCLC-H was partially reproduced in vitro by treating NSCLC-B cells with interferon (IFN)-gamma or with the anti-PD-L1 monoclonal antibody (mAb) atezolizumab (10.1186/s12967-024-06023-8).

Aims

The goal of this project is to understand how the ICI treatment affects the plasticity of cancer cells and how the plasticity of the cancer cells affects the antitumor immune response.

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Experimental plan

The study will be limited to the analysis of advanced NSCLC patients, candidate to immunotherapy.

1. Characterization of the peripheral immunoscore of long responder and fast progressor patients
2. Dissection of the IFN-gamma, PD-L1, TGFB1 and IL6 pathways to identify the mechanisms involved in the evolution of tumor cell phenotype
3. Analysis of the effects of the ICI-mediated tumor plasticity on the spatial interactions between cancer cells and immune cells of long responders and fast progressors
4. Analysis of the effects of the ICI-mediated plasticity on the functional activity of the immune cells of long responders

Techniques. Cell cultures: 2D and 3D growth tests, transfection, silencing, gene editing, cloning. Molecular analysis: confocal microscopy, immunofluorescence, flow cytometry, sorting, Real-Time PCR, Western Blot, ELISA test, ELISPOT.

Angelicola et al. Cancers 2021
Ruzzi et al. Translational Lung Cancer Research 2022
Di Federico et al. JCO Precision Oncology 2024
Angelicola et al., Journal of Translational Medicine 2025