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Search for immunologic drivers that determine the immunosurveillance capability in lung cancer

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Background: The capability of tumours to avoid immune surveillance has emerged as therapeutically approachable, especially through the blockade of immune checkpoints (ICB) such as PD-L1/PD-1. We previously reported that *B2M* inactivating mutations in lung cancer (LC) impaired immunorecognition through the disruption of the MHC-I complex. Our purpose is to identify additional gene alterations that contribute to escape the immune surveillance checkpoints in LC.

Objectives:

To describe new genetic alterations involved in IFN-g pathway that promote immunoescape.

Material and methods: A panel of 42 NSCLC cell lines (32 from ATCC and 10 ex-*vivo,* derived from patients with metastatic pleural effusions- PE) were tested for response to IFNγ treatment. Genomic data was gathered using whole exome sequencing and RNA-sequencing or, in the case of ATCC cell lines, from public databases (Sanger and Cancer Cell Line Encyclopaedia). The response to IFNγ was evaluated by determining the activation of various downstream targets, including increased in the expression of *CD274* (PD-L1), using western-blot or quantitative PCR. We also evaluated other parameters, such as the correct localization of the of the HLA-1/B2M proteins (HLA-I complex) by immunofluorescence (IF), in selected LC cell lines.

Results: Four adenocarcinomas cell lines (10%) were not able to upregulate PD-L1 expression upon IFNγ exposure. We detected intragenic homozygous deletion in *JAK2* in one cell line (NCI-H2126), and we confirmed *JAK2* homozygous truncating mutations in two other cell lines, already reported in databases (p.R426X in NCI-H1993 and p.S507X in NCI-H1573). Interestingly, these mutations were not mutually exclusive with genetic alterations of main oncodrivers in LC. In another cell line (PE-1), we identified a truncating mutation in a different candidate gene which also impaired the response to IFNγ. IF showed that the four candidate cell lines were not able to increase the levels of HLA-1/B2M proteins in the cell surface, after IFNγ exposure. In addition, we found a homozygous deletion in *B2M* in the PE-2 cells, which impaired the proper localization of HLA1 and B2M in the cell surface.

Conclusions: Immunological drivers in our study include *B2M*, *JAK2* and another IFNγ-pathway related gene. Functional characterization of alterations in these genes is crucial to understand the mechanisms that contribute to tumor's immunoescape. Loss of function

mutations in our candidate genes are likely to facilitate tumour growth by enabling immune tolerance and may affect the response to ICB.

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