ABSTRACT FORM

PRESENTING AUTHOR: Annalisa Tocci, Regina Elena National Cancer Institute, via Elio Chianesi 53, 0144 Rome , UOSD Tumor Immunology and Immunotherapy, 3351571225, annalisa.tocci@ifo.it

OTHER AUTHORS: P. Trono[1,2*], A. Tocci[2*], B. Palermo[2], A. Di Carlo[2], L. D'Ambrosio[2], F. De Nicola[3], L. Ciuffreda[3], G. Corleone[3], I. Sperduti[4], F. Marchesi[5], N. Porciello[2], S. Carpano[6], P. Zucali[5], V. Gregorc[7], F. Di Modugno[2], P. Nisticò[2].

[1]Institute of Biochemistry and Cell Biology, CNR, Rome, Italy. [2]Immunology and Immunotherapy Unit, [3]SAFU Unit, [4]Clinical Trial Center, Biostatistics and Bioinformatic Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [5]IRCCS-Humanitas Clinical and Research Center, Rozzano, Italy. [6]Second Division of Medical Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy. [7]Department of Oncology, IRCCS-San Raffaele, Milan, Italy. * P.T. and A.T. contributed equally to this work.

ABSTRACT TITLE: Cancer specific Type I IFN signaling is regulated by hMENA splicing, affects macrophage polarization and participates at resistance to immune checkpoint blockade

ABSTRACT TEXT

Understanding how cancer signaling pathways participate to an immunosuppressive program, sustaining tumor progression and resistance to immune checkpoint blockade (ICB) is fundamental in improving therapy efficacy. Among the pathways that can affect tumor evolution, acquired resistance and immune evasion, Type I interferons (IFNs-I) recently emerged as key players of ICB resistance when chronically produced by cancer cells.
The actin cytoskeleton regulatory protein hMENA, along with its isoforms, differently participate to NSCLC progression and high overall hMENA expression, with low hMENA^{11a} isoform expression, identifies NSCLC patients with poor prognosis.

NSCLC cells were depleted of total hMENA isoforms or only for hMENA^{11a} by siRNA approach. RNA-Seq, ATAC-Seq, qRT-PCR, WB, immunofluorescence, FACS, ELISA and luciferase assays were employed to analyze the role of hMENA isoforms in the activation of IFN-I signaling and PD-L1 expression. Macrophages were treated with conditioned medium derived from cancer cells and analyzed by FACS. Nanostring Technology was used to perform gene expression analysis of tumor tissues of ICB-treated NSCLC patients by IO 360™ Panel and custom probes for hMENA splicing variants.

NSCLC cell lines, specifically depleted for hMENA^{11a}, secrete inflammatory cytokines and chemokines including IFN-β, mechanistically this occurs *via* the viral sensor RIG-I (retinoic acid-inducible gene I). hMENA^{11a} depletion also sustains the increase of expression of PD-L1 in tumor cells, through JAK/STAT1/IRF-1 axis activation. Conditioned medium obtained from hMENA^{11a} silenced cells affects macrophages polarization towards a unique subset, up-regulating immune-checkpoint ligands such as PDL-1/2 and favoring epithelial mesenchymal transition of cancer cells. Finally, to define the clinical relevance of hMENA^{11a} pattern of expression and IFN-I signaling we profiled tumor tissues of a cohort of Fast Progressors (FP) and Good Responders (GR) ICB-treated NSCLC patients, by Nanostring. Notably, we found that low expression of hMENA^{11a} and high expression of IFN target genes identify fast progressor ICB-treated patients.

Collectively, these data establish a new function for the actin cytoskeleton regulator hMENA^{11a} affecting cancer cell intrinsic IFN-I signaling and in turn favoring the expansion of a unique subset of macrophages and epithelial mesenchymal transition of cancer cells, providing insights into novel mechanisms of resistance to ICB in NSCLC.

Supported by AIRC and ACC WG Immunotherapy.

KEYWORDS: please select 2 of the following keywords

- ☐ Adoptive Cell Therapy
- ☐ Cancer Dormancy
- ☐ Cancer Metabolism
- ☐ Emergency myelopoiesis
- ☐ Engineered Lymphocytes
- ☐ Growth-Arrested State
- x Immunotherapy
- ☐ Melanoma
- ☐ Metabolic Alteration
- ☐ Metastasis
- ☐ Metastasis (clinical)
- ☐ Metastasis Niche
- ☐ Microbioma
- ☐ Myeloid Infiltrate
- ☐ Neoadjuvant therapy
- ☐ Organoids
- ☐ PDX/Preclinical models
- ☐ Personalized medicine
- ☐ Systemic Therapy
- ☐ Tumor and Stromal targeting
- ☐ Tumor stroma and senescence
- x Tumor resistance

In accordance with *General Data Protection Regulation UE 2016/679* we declare that the holder of data processing is Achelois Srl. I authorize Achelois srl to handle my personal data for purposes strictly connected to the present and future registrations.

Achelois srl declares that this data will not be divulged or delivered to third parties that are not strictly involved in the event management.

Signature