ABSTRACT FORM

PRESENTING AUTHOR Arianna Brevi, Cellular Immunology Unit, San Raffaele Scientific Institute, via Olgettina 58, Milan, Italy, Division of Immunology, Transplantation and Infectious Diseases, 3937807567, brevi.arianna@hsr.it

OTHER AUTHORS Sara Caputo[1,#], Matteo Grioni[1], Laura Lucia Cogrossi[1], Vittoria Matafora[2], Anna Sofia Tascini[3], Rossella Galli[4], Angela Bachi[2], Massimo Freschi[5], Francesca Demichelis[6], Massimo Alfano[7], Matteo Bellone[1]

[1]Cellular Immunology Unit, Division of Immunology, Transplantation and Infectious Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; [2]Proteomics Unit, IFOM-FIRC Institute of Molecular Oncology, Milan, Italy; [3]Center for Omics Sciences, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Neural stem cell biology Unit, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milan, Italy; [5]Unità Operativa Anatomia Patologica, IRCCS Ospedale San Raffaele, Milan, Italy; [6]Cellular, Computational and Integrative Biology (CIBIO), University of Trento, Trento, Italy; [7]Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy; [#]Current address: L-Nutra Italia SRL, Milan, Italy

ABSTRACT TITLE - Castration-related remodeling of the tumor microenvironment supports signaling through integrin α2 and progression to neuroendocrine prostate cancer

ABSTRACT TEXT

Background Neuroendocrine (NE) differentiation mostly occurs in prostate cancer (PC) patients because of castration resistance, and associates with metastasis and dismal prognosis. How NEPC acquires its aggressive behavior is still incompletely defined. Goal of this project was to define mechanisms favoring NE progression in PC.
Methods NEPC stem-like/progenitor cells (PNE-SCs) and exocrine prostate cancer stem-like/progenitor cell (PAC-SC), were cultured in CSC medium and into extracellular matrixes (ECM) from the prostate of wild type (WT) and transgenic adenocarcinoma of the mouse prostate (TRAMP) mice. α2 expression was determined by flow cytometry. ECMs were investigated by electron microscopy and proteomics.
Results Here we report that in the absence of androgens, PAC-SCs obtained from TRAMP mice

promoted integrin α2 up-regulation and YAP activation in PNE-SCs, thus supporting their proliferation and invasive behavior. The ECM derived from the prostate of tumor-bearing TRAMP mice also supported PNE-SCs proliferation and α2 up-regulation, whereas M1-polarized macrophages also enhanced the expression of the integrin CD29 and MHC-I in PNE-SCs. Conversely, M2-polarized macrophages endorsed SCA-1 expression. While microenvironment-conditioned PNE-SCs showed a remarkable *in vivo* metastatic behavior, pharmacologic inhibition of YAP reduced metastasis appearance and prevented the development of NEPC without modifying the immune composition of the prostate.

Conclusions Taken together, these findings demonstrate the existence of a crosstalk among PCSCs and the ECM that, especially in the absence of androgens, promotes NEPC and metastasis. Drugs targeting the integrin α2-YAP axis might find application in PC patients that are candidate to androgen deprivation therapy.