IJAE
Vol. 123, n. 1 (Supplement): 207, 2018
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Role of anti-PD-1 antibody-Fc/FcR interaction on macrophages in inducing hyperprogressive disease in non-small cell lung cancer

Michele Sommariva[1], Giuseppe Lo Russo[2], Massimo Moro[3], Valeria Cancila[4], Mattia Boeri[3], Monica Ganzinelli[2], Claudia Proto[2], Diego Signorelli[2], Sabina Sangaletti[3], Chiara Storti[1], Lucia Sfondrini[1], Alberto Bardelli[5], Silvia Marsoni[6], Andrea Anichini[3], Licia Rivoltini[3], Claudio Tripodo[4], Mario Paolo Colombo[3], Andrea Balsari[1], Gabriella Sozzi[3], Marina Chiara Garassino[2]

[1] Università degli Studi di Milano, Dipartimento di Scienze Biomediche per la Salute, Milano, Italia
[2] Fondazione IRCCS – Istituto Nazionale dei Tumori, Dipartimento di Oncologia Medica I, Milano, Italia
[3] Fondazione IRCCS – Istituto Nazionale dei Tumori, Dipartimento di Ricerca, Milano, Italia
[4] Università degli Studi di Paermo, Scienze per la Promozione della Salute e Materno Infantile "G.D'Alessandro", Palermo, Italia
[5] Università degli Studi di Torino, Dipartimento di Oncologia, Torino, Italia
[6] IFOM - The FIRC Institute of Molecular Oncology, Precision Oncology, Milano, Italia

Immune checkpoint inhibitors (ICI) targeting PD-1/PD-L1 axis have made a breakthrough in the treatment of non-small cell lung cancer (NSCLC) [1]. However, a paradoxical boost in tumor growth was reported in a fraction of NSCLC patients after ICI administration; a novel pattern of cancer progression defined "hyperprogression" (HP) [2]. Because the mechanism of HP onset is still unknown, aim of this study was to investigate this phenomenon. Among a cohort of NSCLC patients treated with ICI at Istituto Nazionale dei Tumori in Milan, cases with HP were identified according to clinical and radiological criteria. Among patients evaluable for clinical response (152/187), we identified 4 categories: Responders (21%), Stable Disease (27.7%), Progressors (25.7%) and HP (25.7%). Pre-treatment histological samples were evaluated by immunohistochemistry (IHC) for immune cell infiltrate. Tissue samples from all patients with HP showed tumor-infiltration by M2-like CD163+CD33+PD-L1+ clustered epithelioid macrophages. To validate these findings in preclinical models, we utilized immunocompromised mice that, lacking T-cells that may cloud the results, represent a suitable model to evaluate the role of macrophages in determining HP. Immunodeficient mice were injected with human NSCLC cells and patient-derived xenografts (PDXs), treated with anti-PD-1 antibody and tumor growth was assessed. Anti-PD-1 treated NSCLC-bearing mice showed HP-like tumor growth with dissemination to lung and iliac lymph node metastases, as well as an increase in tumor-associated macrophages (TAMs) aggregating in fibrotic-like areas. Interestingly, in these in vivo models, HP-like growth, triggered by anti-PD-1 treatment, was abrogated by using anti-PD-1 F(ab)2-fragments. These results suggest that FcR engagement by ICI on TAMs may determine a functional reprogramming of these immune cells toward a more aggressive and pro-tumorigenic phenotype, eventually inducing HP.

This work was supported by AIRC and Ricerca Strategica Istituzionale (Istituto Nazionale dei Tumori di Milano)

References

[1] Lievense et al. (2017) Checkpoint Blockade in Lung Cancer and Mesothelioma. Am J Respir Crit Care Med. 196(3):274-282.
[2] Champiat et al. (2016) Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. Clin Cancer Res. 23(8):1920-1928.

Key words

Hyperprogression, PD-1, lung cancer, macrophages.