120P A new biomarker of breast cancer stage and patient response to neoadjuvant chemotherapy: HLA-DR expression in cytotoxic and regulatory T cells

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Background: Neoadjuvant chemotherapy (NACT) is the treatment option for locally advanced breast cancer (BC). However, approximately half of the patients have no response. To promptly direct non-responders to personalized therapies, there is an urgency to find a clinical biomarker that could predict treatment response. Tumor infiltrating lymphocytes, namely CD8+ T cells (CTLs) and regulatory T cells (Tregs) are being appointed as biomarkers of response. Nonetheless, tumor cells can escape the immune system by releasing cytokines or expressing immune checkpoint inhibitors, dampening CTLs and increasing Tregs activation. CTLs and Tregs with HLA-DR, a T cell activation marker, by reflecting the tumor immune status, should be a more reliable biomarker of NACT success.

Methods: Fresh biopsies, surgical specimens and blood were collected from 150 BC patients. Immunophenotype was performed by flow cytometry, ELISA and qRT-PCR. Peripheral blood mononuclear cells (PBMCs) were isolated and cultured under canonical stimuli.

Results: 67.3% of BC analysed were ER+, 15.5% HER2+ and 17.2% triple negative. Prior to treatment and independent of BC type, BC with no metastasis in the lymph nodes (53%) have HLA-DR^{hi} CTLs ($p = 0.003$) and HLA-DR^{lo} Tregs ($p = 0.002$), although the average percentage of lymphocytes and myelocytes are similar between more or less advanced disease. Biopsies from NACT responders also have HLA-DR^{hi} CTLs ($p = 0.0006$) and HLA-DR^{lo} Tregs ($p = 0.0002$). A ROC curve revealed a threshold of HLA-DR in CTLs bellow which patients will not respond to NACT. Moreover, HLA-DR+ CTLs express IFN-g, Granzyme B, Perforin, Eomes and TNF-a, essential for CTLs cytolytic activity. HLA-DR+ CTLs negatively correlate with pro-tumorigenesis molecules, such as TGF-b, PD-L1, IL-6, IL-1b and IL-8 ($p < 0.005$); while HLA-DR+

Tregs positively correlate with them. HLA-DR expression in tumor T cells correlates with its level in systemic T cells (CTLs: $r = 0.58$ $p = 0.001$; Tregs: $r = 0.65$ $p = 0.0002$). PBMCs stimulated in vitro from NACT responders reveal higher IFN-g and lower IL-10 ($p = 0.04$).

Conclusions: We propose HLA-DR levels in T cells as a biomarker of BC stage and response to NACT, with the advantage of being systemically evaluated.

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