

T CELL INTRINSIC DNA DAMAGE AND REPAIR RESPONSE AS A NOVEL MARKER ASSOCIATED WITH CLINICAL RESPONSE TO PD-1 BLOCKADE<http://dx.doi.org/10.1136/jitc-2021-SITC2021.310>

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Background Despite the success of immune checkpoint blockade (ICB), many patients still fail to achieve durable clinical benefit. Previous studies have shown that CD8 T cells are reinvigorated by ICB. However, not all patients with this immunological response experience an effective clinical response, suggesting additional parameters may be relevant. DNA damage and repair (DDR) has been extensively studied in the context of inducing cell death of highly-proliferating tumor cells. However, whether T cell-intrinsic DDR impacts T cell differentiation and function, and how the coordination of DDR affects immunological and clinical response to proliferation-inducing ICBs have been largely unexplored. We hypothesized that the T cell-intrinsic DDR responses to proliferative and genotoxic stress might contribute to the disparity between immunological and clinical response.

Methods To understand the impact of cell-intrinsic DDR on T cell differentiation and responses to cancer therapies, we developed a novel high-dimensional cytometry platform. This DDR-Immune platform enables simultaneous analysis of T cell differentiation state and multiple DDR pathways at single cell resolution. We then investigated immune reinvigoration and its association with DDR, in a cohort of chemotherapy-resistant hypermutated or microsatellite instability-high (MSI-H) uterine cancer patients treated with nivolumab. Peripheral blood samples were examined every 2–4 weeks after initiating anti-PD-1 treatment (N = 21).

Results The DDR-Immune platform revealed consistent T cell subset specific patterns of DDR, as well as specific DDR pathways induced by different types of DNA damage, such as γ -irradiation (IR), UV irradiation (UV) or proliferative stress (i.e. anti-CD3/CD28 stimulation). For example, terminally differentiated effector cells had higher DNA damage accumulation and cell death. In contrast, stem cell memory (TSCM) and regulatory T cells (Treg) displayed high DDR with less cell death, suggesting better cell-intrinsic DDR against genotoxic stress for survival advantage. In hypermutated MSI-H uterine cancer patients, CD8 T cells underwent rapid pharmacodynamic proliferation 2–4 weeks after starting PD-1 blockade, which did not correlate with clinical response. Application of the DDR-Immune platform to this cohort revealed, however, that in clinical responders but not clinical non-responders, Ki67+ CD8 T cells responding to PD-1 blockade had rapid induction of DDR represented as a spike increase of phosphorylated-ATM, presumably adapting T cell 'fitness' in response to proliferative stress induced by PD-1 blockade.

Conclusions Collectively, the new platform reveals previously unrecognized roles for T cell-intrinsic DDR as a novel determinant of immune responsiveness and clinical outcome to ICB and have potential application to other cancer therapies including chemotherapy and radiotherapy.

Ethics Approval The study was approved by MSKCC Ethics Board, approval number 17–180 (NCT03241745).