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Antigen-specific peripheral immune cell dynamics predicting clinical responses to checkpoint blockade in melanoma

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Abstract

Many years ago, we hypothesized that melanoma patients possessing T cells reacting to cancer antigens would do better than those who did not. To test this, we cultured PBMC from conventionally-treated metastatic melanoma patients with short (6 month) vs. long (18 month) survival with mixtures of peptides representing the shared cancer antigens NY-ESO-1, Melan-A, MAGE-A3 and survivin. After 12 days, cultures were restimulated with the same antigens and 24 h later intracellular cytokines measured by flow cytometry. The results were consistent with there being a clinical benefit of possessing T cells reactive to NY-ESO-1 and Melan-A but not MAGE-A3 or survivin, and patients possessing T cells reactive to both NY-ESO-1 and Melan-A did better than those with T cells responding to either alone. A dissection of the nature of the responding cells indicated that the majority of T cells responding to NY-ESO-1 was CD4+ whereas the majority responding to Melan-A was CD8+. Responding cells producing predominantly proinflammatory cytokines (IFN, TNF) were associated with clinical benefit, whereas IL 4 production was associated with poorer survival. Following these results, recent studies have focussed on whether similar findings apply to stage IV melanoma patients treated with anti-PD-1 antibodies, or a combination of anti-PD-1 and anti-CTLA-4 antibodies. Patients´ PBMCs were tested before the start of checkpoint blockade (baseline, BL) and at a mean of 44 days during ICB (follow-up, FU). In the discovery cohort from 3 clinical centers (n=92) and a validation cohort (n=49), it was confirmed that the presence of NY-ESO-1 and Melan-A-reactive T cells at BL before ICB conferred clinical benefit, both in terms of PFS and OS. Intriguingly, it was further shown that a *decrease* of these reactive cells at day 44 FU was associated with better survival than either their retention in the blood or their de novo appearance. This was interpreted to suggest sequestration of the reactive cells in the tumour, for which some limited evidence has accrued. By combining such analyses with other blood biomarkers (of which primarily BL and FU lactate dehydrogenase and myeloid-derived suppressor cell dynamics, along with extraordinarily high titers of IgG specific for human herpesvirus 5 (CMV) were associated with clinical outcome), we may approach more closely to the aim of providing robust individualized immune monitoring methods informative for individual patient outcomes.