

Sarah C. Sasson, Vincent T.F. Cheung, Tarun Gupta, John J. Zaunders, Kazi Nahar, C. Mee-Ling Munier, Anna Olsson-Brown, Golo Ahlenstiel, Umamainthan Palendira, Richard A. Scolyer, Matteo S. Carlino, Georgina V. Long, Alexander M. Menzies, Anthony D. Kelleher, Miranda Payne, Benjamin P. Fairfax, Mark R. Middleton, Paul Klenerman and Oliver Brain.

**Tissue-based activation of mucosal-associated invariant T (MAIT) cells in combination ipilimumab and nivolumab checkpoint inhibitor (CI) colitis.**

**Background:** Up to 44% of patients receiving combination ipilimumab and nivolumab develop checkpoint-inhibitor-(CI) colitis, however its molecular pathogenesis is poorly understood. We aimed to characterise peripheral blood and gut mononuclear cells (PBMC;GMNC) in patients with CI-colitis and controls to gain insights into disease aetiology. We were particularly interested in activated, memory, gut-homing CD8<sup>+</sup> T-cells and also the innate-like mucosal-associated invariant T (MAIT) cells that play important roles in mucosal immunity. **Methods:** In Cohort I PBMC from patients with CI-colitis (N=9) were compared with those from patients who received CI with no adverse-events (CI-controls; N=11), patients with active ulcerative colitis (UC; N=6) and Healthy Volunteers (N=16). PBMC findings were tested in a second cohort (Cohort II; IN-Colitis N=15; IN-NAE=9). GMNC were isolated in Cohort III (IN-colitis N=5; IN-controls N=5; UC N=6; Healthy Volunteers N=6). Flow-cytometric analysis was used throughout. **Results:** CI-colitis patients had low circulating MAIT cells compared with CI-controls at baseline in Cohort I. Low levels of circulating MAIT cells in both CI-colitis and CI-controls (compared to Healthy Volunteers) were found in Cohort II. CI-treated patients had high levels of activated-memory T-cells in peripheral blood (CD8<sup>+</sup>>CD4<sup>+</sup>) that included a gut-homing population, regardless of the development of colitis. However, activation of circulating MAIT cells was not evident. In gut tissue there was elevation of activated, granzyme-B<sup>+</sup> MAIT cells in CI-colitis compared with CI-controls. CI-colitis was characterised by an activated-memory CD8<sup>+</sup> lymphocytosis. **Conclusions:** Melanoma patients can have low baseline circulating MAIT cells. In one cohort this associated with CI-colitis. In tissue, activated MAIT cells were elevated in CI-colitis. Further work is needed to determine which immune populations are useful for the prediction and prognostication of CI-colitis, and if MAIT cells contribute to tissue damage or repair.

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