IMMUNOTHERAPY

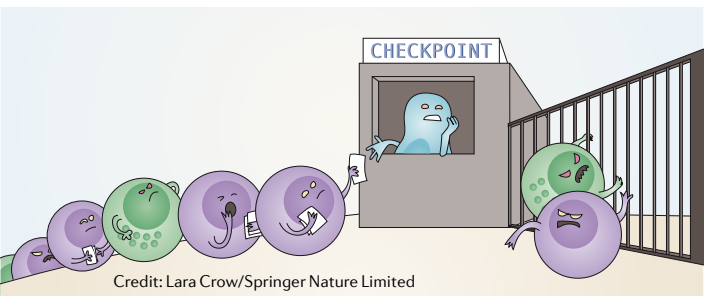
Checkpoint ahead — be prepared to stop!

Immunotherapy has had unprecedented success, yet only a minority of patients exhibit durable benefit. Hence, the challenge at present is to improve clinical responses as well as overcome mechanisms of resistance; blocking other inhibitory immune receptors might be one way to achieve this. Two studies have now characterized the inhibitory receptor NKG2A expressed on cytotoxic lymphocytes, such as natural killer (NK) cells and $CD8^+$ T cells, as a novel checkpoint for cancer immunotherapy.

> “a novel checkpoint for cancer immuno-therapy”

NKG2A forms heterodimers with its co-receptor CD94, transducing inhibitory signals following ligation to its cognate ligand, the non-classical class I molecule human leukocyte antigen E (HLA-E). In several different tumour types, HLA-E is overexpressed relative to normal tissues and represents a mechanism by which cancers present as ‘self’ to the immune system.

Focusing on human head and neck squamous cell carcinomas (HNSCCs), André et al. detected high expression of HLA-E in biopsy tumour samples, along with the presence of $NKG2A^+$ cells. Further analysis revealed high frequencies of $CD8^+$ T cells and NK cells co-expressing programmed cell death protein 1 (PD1) and NKG2A in tumours. Similarly, van Montfoort et al. found NKG2A expression on the majority of NK cells and up to 50% of $CD8^+$ T cells from human HNSCC tissues compared with expression on NK cells only in matched peripheral blood mononuclear cell samples. This selective induction of NKG2A on $CD8^+$ T cells appeared to be the result of their activation in inflammatory tumour microenvironments, as human papillomavirus 16 (HPV16)-positive HNSCCs with T cell immunoreactivity towards HPV antigens had a higher frequency of $NKG2A^+$ $CD8^+$ T cells than HPV16-negative carcinomas. Moreover, these intratumoural $NKG2A^+$ $CD8^+$ T cells were defined as a $CD103^+$ tissue-resident early effector cell subset.



Credit: Lara Crow/Springer Nature Limited

Using a mouse model of HPV16-induced carcinoma (subcutaneous injection of mouse TC-1 tumour cells expressing HPV16 oncoproteins), van Montfoort et al. found that the number of $NKG2A^+$ $CD8^+$ T cells in tumours increased following therapeutic vaccination with previously characterized synthetic long peptides. Vaccination alone results in immune-dependent tumour remissions that rebound at day 20 and beyond. As the percentage of $NKG2A^+$ $CD8^+$ T cells in tumour lesions at relapse was 80% relative to <5% in the spleen of vaccinated mice, the authors reasoned that blocking NKG2A at this time point might improve tumour control. A mouse monoclonal antibody (mAb) against NKG2A doubled progression-free survival in vaccinated mice and increased therapy response rates. In addition, genetic knockout in TC-1 cells of the orthologue of HLA-E, $Qa\text{-}1^b$ — the expression of which increased on tumour cells after vaccination — could potentiate tumour regressions.

André et al. also evaluated the potential of blocking NKG2A to promote antitumour immunity by generating a humanized NKG2A mAb, named monalizumab. To assess the activity of monalizumab, $NKG2A^+$ NK cells were co-cultured with human chronic myeloid leukaemic K562 cells exogenously overexpressing HLA-E. Fewer activated NK cells were observed in the presence of K562-HLA-E^+ cells compared with parental K562 cells. Importantly, addition of monalizumab was sufficient to re-establish the activity of $NKG2A^+$ NK cells to levels seen with parental K562 cells. Monalizumab could also amplify the activation of NK cells against a HNSCC cell line, CAL-27, when used in combination with the epidermal growth factor receptor (EGFR) mAb cetuximab. Thus, monalizumab can relieve the inhibition induced by ligation of NKG2A, consequently augmenting NK cell effector functions.

Last, André et al. took their preclinical findings forward by testing the safety and efficacy of monalizumab in combination with cetuximab in patients with previously treated recurrent or metastatic HNSCC in a phase II clinical trial. Interim results from a total of 31 patients revealed that the combination was well tolerated with only low-grade adverse events. Importantly, the objective response rate (ORR) was 31% with the combination, which exceeded the ORR (13%) for cetuximab alone in this same patient population in earlier undertaken trials.

Together, these findings highlight the promise of blocking alternative inhibitory checkpoints in combination therapies to improve the antitumour activities of NK and $CD8^+$ T cells in patients with cancer.

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ORIGINAL ARTICLES André, P. et al. Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells. *Cell* https://doi.org/10.1016/j.cell.2018.10.014 (2018) | van Montfoort, N. et al. NKG2A blockade potentiates CD8 T cell immunity induced by cancer vaccines. *Cell* https://doi.org/10.1016/j.cell.2018.10.028 (2018)