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IMMUNOTHERAPY

Interferon in anti-CTLA-4 responses

Immune-checkpoint blockade is a breakthrough in anticancer therapy, with dramatic sustained responses observed across a range of tumour types. Nevertheless, response rates are modest and acquired resistance can occur. IFNγ is a hallmark cytokine of an antitumour immune response, and disruption of the IFNγ pathway in tumour cells, particularly loss-of-function mutations in *JAK1*/*JAK2*, has been implicated in acquired resistance to programmed cell-death protein 1 blockade. A new study reveals that loss of IFNγ signalling might also underlie intrinsic resistance to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune-checkpoint inhibition.

Corresponding author Padmanee Sharma explains the rationale for this study: "we previously conducted a pre-surgical study with anti-CTLA-4 antibodies in patients with bladder cancer, and found that treatment with these antibodies increased the abundance of an $ICOS^+$ T-cell subset that produced IFNγ. We hypothesized that tumour cells harbouring mutations in the IFNγ-signalling pathway would not be susceptible to the IFNγ produced by these T cells and, therefore, would be resistant to anti-CTLA-4 therapy."

> "…non-responders had tumour tissues harbouring loss of IFNγ-pathway genes…"

The researchers tested this hypothesis by evaluating genomic alterations of IFNγ-pathway genes in 16 patients with melanoma, four 'responders' and 12 'non-responders' to treatment with the anti-CTLA-4 antibody ipilimumab. "We found that non-responders had tumour tissues harbouring loss of IFNγ-pathway genes at significantly higher frequencies than observed in responders," states Sharma. Indeed, 184 alterations (an average of 15.33) were detected in non-responders, compared with only four (one on average) in responders ($P = 0.015$).

Of note, although no significant enrichment of single-nucleotide variants was observed, 75% of non-responders had copy-number alterations (CNAs) versus 0% of responders ($P = 0.019$). These findings were validated in an independent cohort, using previously published data. The CNAs were mostly gene losses, particularly of *IFNGR1*, *IRF1*, *JAK2*, and *IFNGR2*, but some amplifications involving inhibitors of IFNγ signalling were also observed.

Using The Cancer Genome Atlas data, Sharma and co-workers found that patients with metastatic melanomas harbouring CNAs of IFNγ-pathway genes have shorter overall survival durations than those with tumours lacking such CNAs (40 months versus 48.2 months; $P = 0.0018$). This finding indicates that disruption of IFNγ signalling is associated with a poor prognosis, perhaps owing to reduced responsiveness of tumour cells to host antitumour immune responses.

"We plan to prospectively evaluate patients for responses to immune-checkpoint therapy based on the status of IFNγ-pathway genes in tumour tissues, and to determine whether combination therapy can effectively overcome the loss of IFNγ-pathway genes," Sharma concludes.

David Killock

ORIGINAL ARTICLE Gao, J. *et al.* Loss of IFN-γ pathway genes in tumor cells as a mechanism of resistance to anti-CTLA-4 therapy. *Cell* http://dx.doi.org/10.1016/j.cell.2016.08.069 (2016)
FURTHER READING Hutchinson, L. JAK — opening the door to acquired resistance. *Nat. Rev. Clin. Oncol.* **13**, 528–529 (2016)