

Glioma

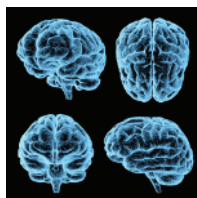
Major finding: Low- and high-grade NF1 gliomas are characterized by distinct genetic and epigenetic features.

Concept: High-grade gliomas harbor *ATRX* mutations, whereas a subset of low-grade gliomas show an immune signature.

Impact: Comparative epigenetic analyses indicate that NF1 gliomas recapitulate a subgroup of sporadic gliomas.

UNIQUE MOLECULAR LANDSCAPES DISTINGUISH LOW- AND HIGH-GRADE NF1 GLIOMAS

Neurofibromatosis type 1 (NF1) is a tumor predisposition syndrome characterized by germline mutations in the *NF1* gene encoding neurofibromin, a negative regulator of RAS. NF1 is associated with an increased risk of gliomas, with low-grade gliomas more common in children and high-grade gliomas more prevalent in adults. To assess the genetic and epigenetic landscape of NF1 gliomas and compare this molecular profile to that of sporadic gliomas, D'Angelo, Ceccarelli, and colleagues performed whole-exome sequencing, RNA sequencing, and DNA methylation analysis of a cohort of NF1 glioma samples consisting of both low- and high-grade gliomas. Pediatric low-grade NF1 gliomas exhibited few recurrent somatic mutations, which occurred primarily in genes involved in MAPK signaling. However, a subset of low-grade tumors was characterized by increased infiltration of cytolytic effector CD8⁺ T cells, expression of mutation-derived neoantigens with enhanced HLA binding, and activation of immune-related signatures as a result of decreased DNA methylation of immune genes. In contrast, high-grade NF1 gliomas in adults exhibited a significantly higher mutation



burden, including genetic alterations in genes involved in transcription and chromatin regulation and the PI3K pathway. In particular, high-grade gliomas frequently harbored copy-number loss of *CDKN2A/B* together with inactivating mutations in *TP53* and the chromatin remodeling gene *ATRX*. Consistent with this finding, high-grade NF1 gliomas displayed loss of *ATRX* protein expression and induction of an alternative lengthening of telomeres phenotype. Integrative analyses of DNA methylation profiles revealed that NF1 gliomas recapitulate molecular features of the LGM6 *IDH*-wild-type subgroup of sporadic gliomas defined by The Cancer Genome Atlas, which are characterized by frequent somatic mutations in *NF1*, *TP53*, and *ATRX*. Taken together, these data identify genetic and epigenetic alterations that distinguish low- and high-grade NF1 gliomas and provide further insights into the classification of sporadic gliomas. ■

D'Angelo F, Ceccarelli M, Tala, Garofano L, Zhang J, Frattini V, et al. The molecular landscape of glioma in patients with neurofibromatosis 1. *Nat Med* 2019;25:176–87.

Targeted Therapy

Major finding: Combined CDK4/6 and MEK inhibition blocks *Kras*-mutant cell growth and induces NK cell surveillance.

Mechanism: RB-dependent activation of the senescence-associated secretory phenotype induces NK-cell activity.

Impact: Evasion of senescence and immune surveillance in tumors can be reversed by some targeted therapies.

NON-CELL AUTONOMOUS NK CELL EFFECTS UNDERLIE COMBINATION THERAPY EFFICACY

Targeted anticancer therapies block tumor cell-autonomous signaling pathways, but these agents may also have tumor-extrinsic effects on host cells that could contribute to antitumor efficacy. Following previous observations that the combination of CDK4/6 and MEK inhibitors could block the proliferation of *KRAS*-mutant cancer cells and have immunomodulatory effects on T cells, Ruscetti, Leibold, Bott, and colleagues evaluated the non-tumor cell-autonomous effects of combined treatment with palbociclib (a CDK4/6 inhibitor) and trametinib (a MEK inhibitor) on the immune system in a syngeneic orthotopic model of *Kras*-mutant;*Trp53*-null lung cancer. No changes in macrophage infiltration or T-cell activation were observed in the lungs of treated mice, but natural killer (NK) cell accumulation was significantly increased in mice receiving combination therapy compared with single-agent treatment. Depletion of NK cells reduced the efficacy of combination but not single-agent treatment, suggesting that the efficacy of combined CDK4/6 and MEK inhibition in this model was dependent on tumor-extrinsic effects of NK cells. Palbociclib and trametinib are known to coop-

erate to prevent phosphorylation and inactivation of RB, which plays a key role in both cell-cycle arrest and cellular senescence. Only combination-treated tumor cells showed an increase in senescence markers and upregulation of a program of microenvironment-modulating proteins known as the senescence-associated secretory phenotype (SASP). SASP factors include secreted cytokines like TNF α that promote NK cell proliferation and activation as well as cell-surface NK adhesion modules like ICAM1, both of which were required for the antitumor efficacy of palbociclib plus trametinib in orthotopic as well as autochthonous *Kras*-mutant;*Trp53*-null lung cancer models. These findings illustrate that, in addition to their cell-autonomous effects on tumors, some targeted therapy combinations can also exert antitumor activity through restoration of senescence and NK cell-dependent immune surveillance. ■

Ruscetti M, Leibold J, Bott MJ, Fennell M, Kulick A, Salgado NR, et al. NK cell-mediated cytotoxicity contributes to tumor control by a cytostatic drug combination. *Science* 2018;362:1416–22.

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CANCER DISCOVERY

Non–Cell Autonomous NK Cell Effects Underlie Combination Therapy Efficacy

Cancer Discov 2019;9:165. Published OnlineFirst January 4, 2019.

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