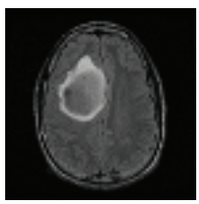
Glioma

Major finding: Recurrent gliomas genetically diverge from the initial tumor following surgical resection.

Clinical relevance: Temozolomide may promote high-grade glioma recurrence by inducing oncogenic mutations.

Impact: Mutational analysis of gliomas at diagnosis may not predict therapeutic targets in recurrent tumors.

CHEMOTHERAPY AMPLIFIES GENETIC DIVERGENCE OF RECURRENT GLIOMAS



A large proportion of low-grade gliomas recur following surgical resection, and some progress to a more malignant state. To better understand the malignant progression of recurrent low-grade gliomas after surgery and determine the role of chemotherapy in tumor recurrence, Johnson and colleagues compared the mutational profiles of grade II gliomas at diagnosis and recurrence and the effects of adjuvant chemotherapy with temozolomide (TMZ) on the genetic landscape of residual disease. Exome sequencing of 23 grade II astrocytic gliomas and their recurrences revealed that only an average of 54% of somatic coding mutations in the initial tumors were detected in the recurrent tumors. Genetic variation between initial and recurrent tumors suggests that seeding of recurrent tumors can occur throughout the evolution of the initial tumor. Although sequencing of multiple geographic regions revealed intratumoral heterogeneity within initial and recurrent tumors, many mutations were shared, suggesting that intratumoral heterogeneity could not completely explain the genetic divergence between initial and recurrent tumors. To understand whether mutagenic chemotherapies can promote genetic variance in recurrent disease, the authors sequenced initial and recurrent tumors from patients treated with the alkylating agent TMZ. A hypermutated phenotype not present in the initial samples was observed in the recurrent gliomas of 6 out of 10 patients treated with TMZ. Moreover, hypermutated recurrent tumors progressed to malignant glioblastoma and were found to harbor TMZ-associated oncogenic mutations in driver genes previously linked with high-grade gliomas in the RB and AKT–mTOR signaling pathways. Together, these findings suggest that recurrent gliomas diverge from the initial tumor early in their evolution and that adjuvant chemotherapy can dramatically amplify the genetic diversity, which can, in some but not all cases, accelerate malignant progression. ■

Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science 2014;343:189–93.

Myeloproliferative Disease

Major finding: *CALR* is mutated in approximately 70% of myeloproliferative neoplasms without *JAK2* or *MPL* mutations.

Concept: All *CALR* mutations result in a 1-bp frameshift that generates a protein with a novel C-terminus.

Impact: *CALR* mutations may facilitate the diagnosis of essential thrombocythemia and myelofibrosis.

CALRETICULIN MUTATIONS ARE COMMON IN MYELOPROLIFERATIVE NEOPLASMS

The identification of activating mutations in *JAK2* in almost all patients with polycythemia vera and *JAK2* or *MPL* mutations in 55% to 70% of patients with essential thrombocythemia and myelofibrosis has simplified the diagnosis of these myeloproliferative neoplasms, but diagnosis remains difficult in the remaining 30% to 45% of patients who lack *JAK2* or *MPL* mutations. Through a combination of exomic and targeted sequencing, Nangalia and colleagues identified somatic calreticulin (*CALR*) mutations in 70% of patients with essential thrombocythemia or myelofibrosis that lacked *JAK2* or *MPL* mutations, and Klampfl and colleagues found *CALR* mutations in 73% of essential thrombocythemia or myelofibrosis with nonmutated *JAK2* or *MPL*. *CALR* mutations were acquired early in the major clones of patient samples, providing support for a role in the initiation of myeloproliferative neoplasms. Every *CALR* mutation identified was a frameshift mutation within exon 9 that resulted in an expressed protein with a novel C-terminus that also lacked an endoplasmic reticulum-retention sequence, suggesting that the mutations affect CALR function and localization. Klampfl and colleagues also found that expression of the most common CALR mutant increased STAT5 phosphorylation and induced cytokine-independent growth that could be blocked by a JAK inhibitor, suggesting that *CALR* and *JAK2* mutations may have similar consequences, although the mechanism by which mutant CALR activates JAK–STAT signaling remains unclear. Both groups noted differences in hemoglobin levels and platelet counts between patients with *CALR* and *JAK2* mutations, and Klampfl and colleagues found that patients with *CALR* mutations had a significantly longer overall survival, suggesting that *CALR* mutations may also have clinical and prognostic significance. The identification of *CALR* as a frequently mutated gene in essential thrombocythemia and myelofibrosis addresses a gap in the molecular diagnosis of myeloproliferative neoplasms and may have implications for management of these cancers. ■

Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, Wedge DC, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. *N Engl J Med 2013;369:2391–405.*

Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 2013;369:2379–90.