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Pediatric Oncology

Major finding: Recurrent somatic H3.3 and H3.1 mutations occur specifically in pediatric GBMs.

Mechanism: Covalent histone modifications may be affected by Lys-27 and Gly-34 mutations.

Impact: Cancers driven by regulatory histone mutations may be candidates for epigenetic therapy.

HISTONE H3 MUTATIONS ARE FREQUENT IN PEDIATRIC GLIOBLASTOMAS

Although pediatric glioblastomas (GBM) are morphologically indistinguishable from adult glioblastomas and have similarly dismal outcomes, mounting evidence suggests that they are distinct molecular entities. Wu and colleagues performed whole-genome and targeted sequencing of pediatric brainstem GBMs, also known as diffuse intrinsic pontine gliomas (DIPG), and nonbrainstem pediatric GBMs. These authors identified mutations in either *H3F3A* (encoding histone H3.3) or in *HIST1H3B* (encoding histone H3.1) resulting in an amino acid substitution at Lys-27 or Gly-34 in 78% of DIPGs and 36% of nonbrainstem GBMs. Schwartzentruber and colleagues sequenced the exomes of 48 nonbrainstem pediatric GBMs and identified *H3F3A* mutations affecting the same residues in 31% of the samples, as well as recurrent loss-of-function mutations in *ATRX* and *DAXX*, which encode proteins required for H3.3 recruitment to pericentric heterochromatin and telomeres. The consequences of the H3 mutations remain unclear, though the nonrandom recurrence of the same mutation and the lack of truncating mutations suggest that the alterations affecting Lys-27 and Gly-34 are gain-of-function mutations. Because Lys-27 and Lys-36 are critical sites for posttranslational histone modifications, it is possible that mutations that mimic or disrupt methylation or acetylation at these residues may alter epigenetic regulation of gene expression or global chromatin structure. Consistent with this possibility, Schwartzentruber and colleagues observed distinct expression patterns and aberrant telomere elongation in histone H3 Lys-27– and Gly-34–mutant tumors. Histone H3 mutations seem to occur exclusively in GBM and are far more prevalent in the high-grade pediatric gliomas, suggesting that an altered chromatin landscape may specifically confer a selective growth advantage in the developing brain and that epigenetic therapies may be particularly effective in the pediatric setting. ■

Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfort J, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 2012 Jan 29. [Epub ahead of print].

Schwartzentruber J, Korshunov A, Liu XY, Jones DT, Pfaff E, Jacob K, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 2012;482:226–31.

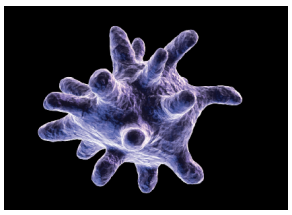
Tumor Microenvironment

Major finding: The TSC2–mTOR pathway regulates the differentiation of monocytes into TAMs.

Concept: Inhibition of mTOR causes a reduction in TAM-induced tumor angiogenesis.

Impact: mTOR pathway inhibitors may prevent tumor growth via immune system modulation.

mTOR PLAYS A CRITICAL ROLE IN TAM-MEDIATED ANGIOGENESIS



Macrophages are phagocytic immune cells that play important roles in tumor growth. Classic M1 macrophages display antitumor effects, and M2 macrophages, known as tumor-associated macrophages (TAM), have been shown to support tumor invasion via the promotion of angiogenesis. Although the behavior of macrophages is determined by their differentiation into one of these two polarized phenotypes, the molecular mechanisms that regulate this development remain unclear. In a recent article, Chen and colleagues demonstrate that the mTOR pathway, which is involved in the regulation of cell growth, plays a critical role in the differentiation of monocytes into TAMs and is required for TAM-mediated angiogenesis. The authors found that when peripheral monocytes were stimulated in the presence of the mTOR inhibitor rapamycin, they developed into M1 macrophages that did not promote angiogenesis. However, peripheral monocytes that overexpressed mTOR, secondary to knockdown of the upstream negative regulator tuberous sclerosis complex 2 (TSC2), differentiated into proangiogenic TAMs. These findings were confirmed *in vivo* when monocytes expressing differing levels of TSC2 were reintroduced into tumor-bearing mice. Tumor growth and angiogenesis were reduced in the presence of rapamycin or when TSC2 was overexpressed but were increased in the absence of TSC2. In addition, the transcription factor STAT3 was identified as the downstream target of mTOR that mediates TAM-dependent tumor angiogenesis *in vivo*. These studies establish an essential role for the TSC2–mTOR pathway in the differentiation of proangiogenic TAMs. Inhibition of mTOR in monocytes therefore may represent an antitumor therapeutic strategy. ■

Chen W, Ma T, Shen X, Xia X, Xu G, Bai X, et al. Macrophage-induced tumor angiogenesis is regulated by the TSC2-mTOR pathway. Cancer Res 2012 Jan 27. [Epub ahead of print].

AACR American Association for Cancer Research

CANCER DISCOVERY

Histone H3 Mutations are Frequent in Pediatric Glioblastomas

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