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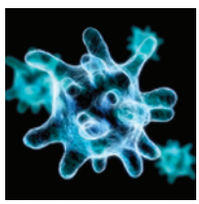
Glioma

Major finding: CSF1R blockade inhibits glioma growth via reeducation of tumor-associated macrophages (TAM).

Mechanism: Inhibition of CSF1R reduces protumor M2 TAM marker expression without affecting TAM survival.

Impact: The gene signature associated with CSF1R blockade is prognostic in patients with proneural GBM.

TAMs ARE A POTENTIAL THERAPEUTIC TARGET IN GLIOMA



The presence of tumor-associated macrophages (TAM) has been linked to increased tumor grade and poor clinical outcome in glioblastoma multiforme (GBM), suggesting that depletion or inhibition of these cells may suppress tumor growth. Colony-stimulating factor 1 receptor (CSF1R) is required for macrophage differentiation and survival, prompting Pyonteck and colleagues to investigate the therapeutic potential of CSF1R blockade in preclinical models of GBM. Treatment with BLZ945, a brain-penetrant, selective CSF1R inhibitor, specifically reduced macrophage proliferation and survival *in vitro* without affecting glioma cell viability. Furthermore, in a transgenic mouse model of proneural GBM driven by expression of the platelet-derived growth factor B (*PDGFB*) oncogene, CSF1R blockade reduced the malignant progression of GBMs and induced tumor regression in mice bearing established high-grade gliomas, resulting in prolonged survival. In addition, CSF1R inhibition impaired the intracranial growth of xenografts derived from human proneural GBM cell lines or primary patient samples. This antitumor effect was mediated by decreased tumor cell proliferation and vascularity and increased apoptosis following BLZ945 treatment. However, BLZ945 did not promote depletion of TAMs, which were protected from CSF1R inhibition by glioma-secreted factors, including granulocyte-macrophage colony-stimulating factor (GM-CSF, also known as CSF2) and IFN-γ, that promoted TAM survival. In contrast, BLZ945 triggered downregulation of protumorigenic, alternatively activated M2 macrophage markers and enhanced the phagocytic function of glioma-derived TAMs, suggesting that CSF1R blockade–induced depolarization inhibits the tumor-promoting activity of TAMs. Indeed, BLZ945 suppressed glioma cell–TAM heterotypic signaling, resulting in decreased glioma cell proliferation. Moreover, gene signatures associated with BLZ945 treatment were predictive of increased overall survival in patients with proneural GBM, independent of macrophage numbers. These findings suggest that reeducation, rather than depletion, of macrophages in the tumor microenvironment may provide therapeutic benefit in the proneural subtype of GBM. ■

Pyonteck SM, Akkari L, Schuhmacher AJ, Bowman RL, Sevenich L, Quail DF, et al. CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nat Med 2013;19:1264–72.

Prostate Cancer

Major finding: The lncRNA *SChLAP1* is overexpressed in some prostate cancers and is predictive of poor outcome.

Mechanism: *SChLAP1* antagonizes gene regulation by the SWI/SNF complex by attenuating its genomic binding.

Impact: Cancer-associated lncRNAs can antagonize chromatin remodeling complex activity.

SChLAP1 ANTAGONIZES THE SWI/SNF COMPLEX IN AGGRESSIVE PROSTATE CANCER

The molecular characteristics that distinguish high-risk, aggressive prostate cancers from indolent tumors are not well understood. Prensner and colleagues identified a long noncoding RNA (lncRNA), second chromosome locus associated with prostate-1 (*SChLAP1*), that was overexpressed in approximately 25% of prostate cancer samples, particularly in metastatic cancers. *SChLAP1* expression was strongly correlated with higher Gleason scores and was a robust single-gene predictor of biochemical recurrence, clinical progression, and prostate cancer–specific mortality in patients initially diagnosed with localized prostate cancer. *SChLAP1* knockdown significantly reduced prostate cancer cell proliferation and invasion *in vitro* and led to a marked reduction in invasion, intravasation, and metastatic seeding *in vivo*, providing support for a role of this lncRNA in prostate cancer aggressiveness. Genes deregulated upon *SChLAP1* knockdown were enriched for those regulated by the SWI/SNF nucleosome remodeling complex, but knockdown of *SChLAP1* had the opposite effect on these genes as knockdown of the essential SWI/SNF subunit SNF5, suggesting an antagonistic relationship that would be consistent with an oncogenic role of *SChLAP1* and the known tumor-suppressive role of SWI/SNF complex subunits. *SChLAP1* did not affect SNF5 expression, but RNA immunoprecipitation assays showed that endogenous *SChLAP1* selectively interacted with SNF5, raising the possibility that *SChLAP1* directly interferes with SWI/SNF activity. Indeed, *SChLAP1* overexpression strongly reduced SNF5 genomic binding and led to deregulation of a subset of genes normally occupied by SNF5 near their transcription start sites. Unlike other lncRNAs, which have been found to facilitate the binding and activity of epigenetic regulators, these findings suggest that *SChLAP1* may promote prostate cancer aggressiveness by antagonizing genomic binding and gene regulation by the SWI/SNF complex. ■

Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, Patel L, et al. The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. Nat Genet 2013 Sept 29 [Epub ahead of print].

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AACR American Association for Cancer Research

CANCER DISCOVERY

SChLAP1 Antagonizes the SWI/SNF Complex in Aggressive Prostate Cancer

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