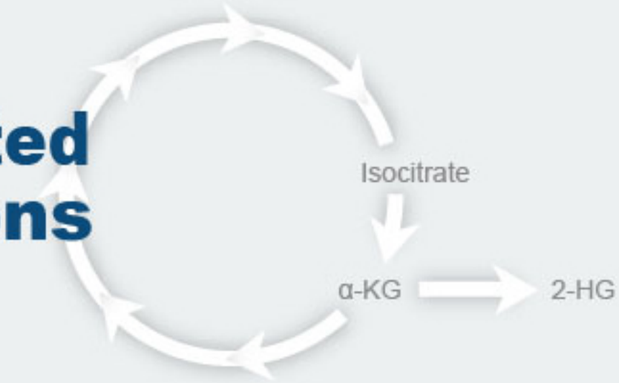
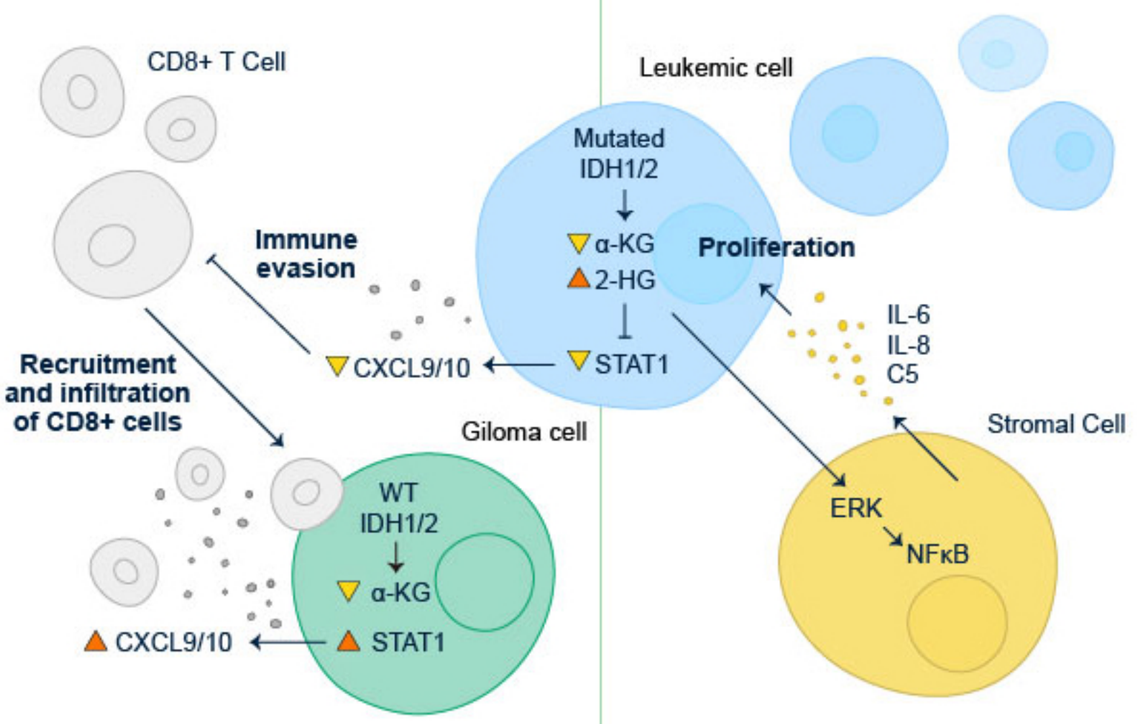
Cancer-Associated IDH1/2 Mutations



Mechanisms of IDH Mutations Associated to Tumorigenesis

Isocitrate dehydrogenases 1 (IDH1) and IDH2 mutations have been identified in >80% of low-grade gliomas and secondary glioblastomas (GBM), ~60% of chondrosarcomas, ~20% of intrahepatic cholangiocarcinomas (ICC), and as well as in ~10% of acute myeloid leukemia (AML) cases. IDH1/2 mutations exhibiting a significant alteration in cellular metabolism, epigenetic regulation, redox states, and DNA repair are involved in the development and progression of early events in tumorigenesis.



Gliomas Infiltration

In the presence of WT IDH1/2, intact STAT1 expression drives the production of chemokines CXCL9 and CXCL10 that attract CD8+ T cells infiltrate to the tumor. 2HG generated by tumors harboring IDH1/2 mutations represses STAT1, leading to immune evasion.

Lucca and Hafler, 2017

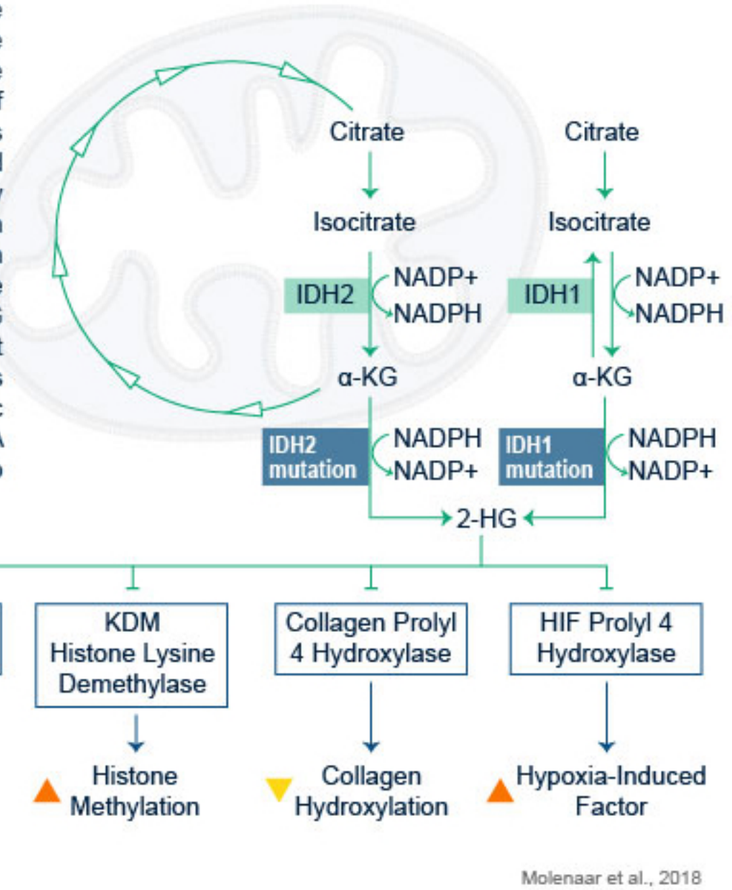
Leukemogenesis

Secretion of 2-HG by tumors harboring IDH1/2 mutations activates ERK dependent signaling and causes NF-κB stabilization in stromal cells inducing production of IL-6, IL-8 and C5 which stimulate the proliferation of leukemic cells.

Montalban-Bravo and DiNardo, 2018

IDH1/2 Mutations

IDH1 in the cytoplasm and IDH2 in the mitochondria catalyze the reversible oxidative decarboxylation of isocitrate to α-KG with concomitant reduction of NADP+ to NADPH. The heterozygous somatic mutations at R132 (IDH1) and at R172 (IDH2) in the catalytically active sites confer a gain-of-function neomorphic enzymatic activity, which can both produce the oncometabolite 2-HG.The resulting elevated 2-HG competitively inhibits α-KG-dependent enzymes, causing cellular alterations in cellular metabolism, epigenetic regulation, redox states, and DNA repair, all of which may contribute to tumorigenesis.



Molenaar et al., 2018

FDA Approval of First-In-Class Inhibitors for the Treatment of IDH1/2-Mutated Cancers

Idhifa (enasidenib), Celgene Corporation
FDA approved August 1st, 2017

For the treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation.

Tibsovo (ivosidenib), Agios Pharmaceuticals
FDA approved July 20th, 2018

For the treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH1 mutation.

FDA Drug Approvals and Databases, USA

- mutaFISH™; IDH1 R132H R132wt IDH2 R172K R172wt RNA Probes
- IDH2 Pre-design Chimera RNAi
- IDH1 monoclonal antibody, clone IDH1/1152
- IDH2 monoclonal antibody (M01), clone 5F11
- IDH1 purified MaxPab rabbit polyclonal antibody (D01P)
- IDH2 MaxPab rabbit polyclonal antibody (D01)
- IDH1 (Human) Recombinant Protein (P01)
- IDH2 (Human) IP-WB Antibody Pair