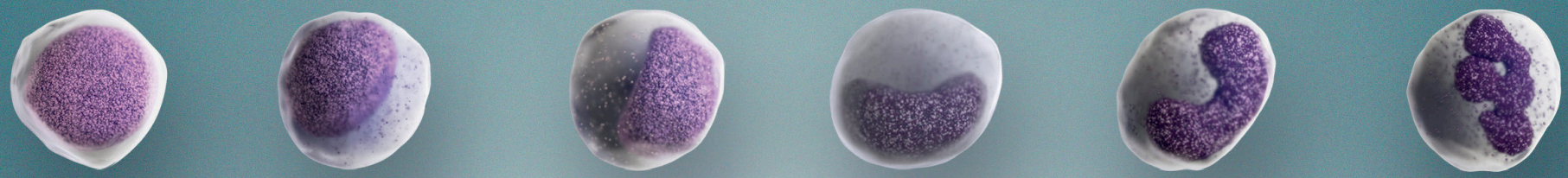


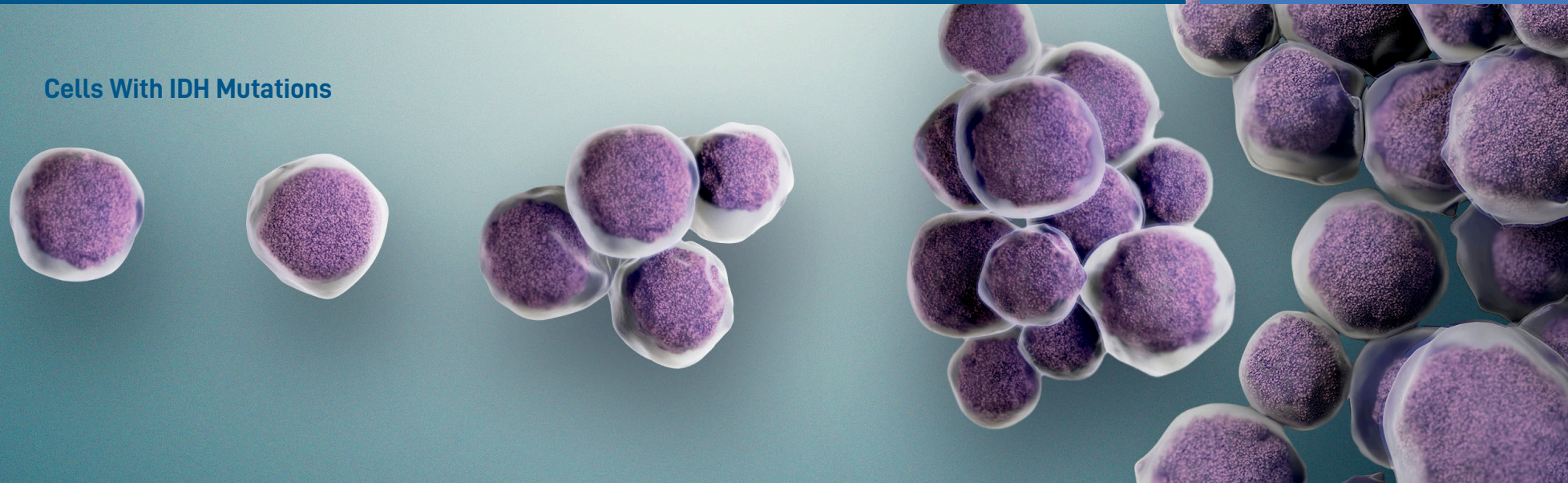
Normal Cellular Differentiation

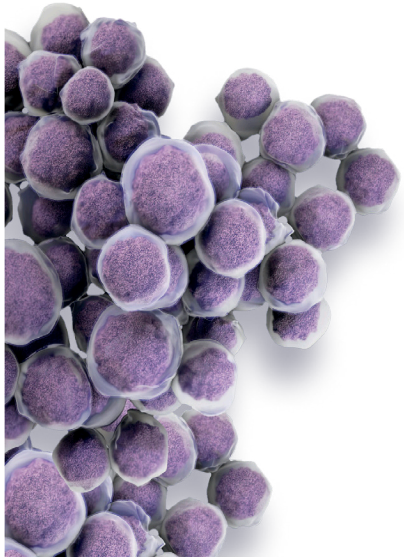
Understanding Mutations in mIDH

Isocitrate dehydrogenase mutations (mIDH) and their role in mIDH-positive cancers

agios

Cells With IDH Mutations





An Overview of IDH

Cellular metabolism is essential for all cells to carry out their normal functions. Abnormal cellular metabolism is one of the key hallmarks of cancer because of its ability to promote and drive tumor growth.[1]

Isocitrate dehydrogenase (IDH) is a metabolic enzyme that helps generate energy from glucose and other metabolites, catalyzing the conversion of isocitrate to α-ketoglutarate.[1]

IDH enzymes are mutated in several hematologic and solid malignancies, which produce high levels of the oncometabolite 2-HG (2-hydroxyglutarate) and disrupt normal cellular differentiation.[1-5]

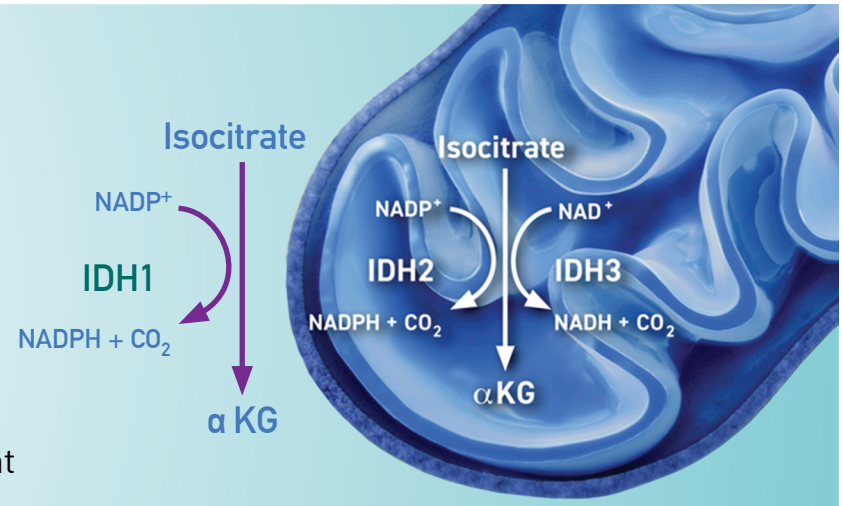
Preclinical studies suggest that **mutant IDH (mIDH) inhibition** prevents the excess production of 2-HG and may restore cellular differentiation.[6-8]

The Normal Role of IDH in Cellular Metabolism

There are three isoforms of IDH[1,3]:

- IDH1 is primarily found in the cytoplasm and in peroxisomes[1]
- IDH2 and IDH3 are found in the mitochondria and are part of the Krebs cycle[1]

IDH enzymes convert isocitrate to the metabolite α-ketoglutarate, which is required to properly regulate DNA/histone methylation and gene expression (turning genes on and off), including those important for cellular differentiation.[1,9,10]



IDH1 and IDH2 are metabolic enzymes that catalyze conversion of isocitrate to α-ketoglutarate

While normal cells undergo a process of maturation, mIDH blocks cellular differentiation, which may lead to an accumulation of immature cells and tumor formation/progression

Mutations in IDH1 and IDH2 Are Found in Both Hematologic and Solid Malignancies[1,2]

mIDH has a gain-of-function activity that results in excess 2-HG levels.[3,11] 2-HG is normally present in cells at low levels, but becomes significantly elevated in mIDH-positive cancers.[12]

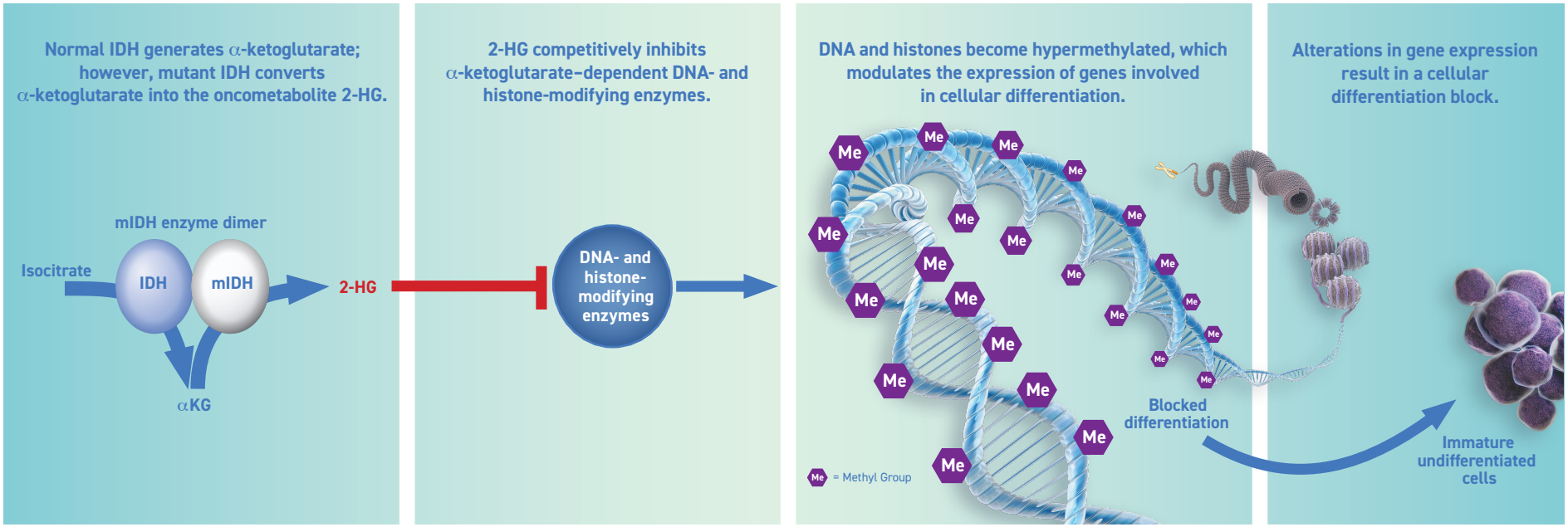
It also functions as a competitive inhibitor of DNA- and histone-modifying enzymes that require α-ketoglutarate.[12]

- 2-HG induces global changes in DNA and histone methylation, which alter gene expression[4,5,12]
- Alterations in DNA/histone methylation and gene expression lead to a cellular differentiation block, which may further lead to accumulation of immature cells that persist or progress to a tumor[5,12,13]

Cancers Shown to Have Mutations in IDH Include[1,14-19]:

- Acute myeloid leukemia (~20% of patients)
- Low-grade glioma and secondary glioblastoma (~80% of patients)
- Chondrosarcoma (~50-60% of patients)
- Intrahepatic cholangiocarcinoma (~20% of patients)
- Angioimmunoblastic T-cell lymphoma (~30% of patients)
- Myelodysplastic syndromes/myeloproliferative neoplasms (~6-9% of patients)

mIDH Generates Abnormally High Levels of the Oncometabolite 2-HG



Testing for IDH Mutations in AML, Other Hematologic Malignancies, and Solid Tumors

Explore IDH

Molecular profiling for isocitrate dehydrogenase (IDH) mutations can help identify patients with AML or other hematologic malignancies or solid tumors who are eligible for approved targeted therapies and participation in clinical trials

Why you should test for IDH mutations in certain cancers

Mutations in IDH1 and IDH2 have been identified in AML, other hematologic malignancies, and solid tumors.

Acute myeloid leukemia
IDH1 or IDH2 mutations are present in ~20% of patients with AML.[26,27]

Cholangiocarcinoma
Mutations in IDH1 or IDH2 may be present in ~20% of patients with cholangiocarcinoma.[21,22]

Glioma
Mutations in IDH1 and IDH2 are very common in grade II and grade III glioma.[20] They are important molecular markers and are associated with a more favorable prognosis.[23,24] They also have diagnostic utility in differentiating a primary glioblastoma from a secondary glioblastoma that has transformed from a lower-grade glioma and may not be as aggressive.[16,25]

Test your patients with IDH mutations and learn more at exploreIDH.com

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