Understanding Mutations in IDH
Isocitrate dehydrogenase mutations (IDHm) and their role in IDHm-positive cancers
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.1 IDH enzymes catalyze the conversion of isocitrate to alpha-ketoglutarate.1

IDH enzymes are mutated in several hematologic and solid malignancies.1,2 In cancers with IDH mutations, the mutant IDH enzyme (IDHm) produces high levels of an oncometabolite, 2-hydroxyglutarate (2-HG), that disrupts cellular function by preventing the normal process of differentiation.3-5 The accumulation of immature IDHm-positive cells can often result in tumor formation and progression.3-5

Preclinical studies suggest that IDHm inhibition prevents the excess production of 2-HG and may restore cellular differentiation.6-8

While normal cells undergo a process of maturation, IDHm blocks cellular differentiation, which may lead to an accumulation of immature cells and tumor formation/progression.
The Normal Function of IDH

Metabolism is required for all cells in the body to carry out their normal functions.¹ IDH enzymes facilitate the cell’s energy production from glucose and other metabolites.¹ They do this by generating a metabolite called alpha-ketoglutarate.¹ There are three isoforms of IDH, which are located in different cellular compartments.¹,³

- IDH1 is primarily found in the cytoplasm, as well as in peroxisomes¹
- IDH2 and IDH3 are found in the mitochondria and are a part of the Krebs cycle¹

The Normal Role of IDH in Cellular Metabolism

IDH enzymes catalyze the conversion of isocitrate to alpha-ketoglutarate.¹ Alpha-ketoglutarate is required by DNA- and histone-modifying enzymes to properly regulate DNA and histone methylation.⁹,¹⁰ DNA and histone methylation helps regulate gene expression—by turning genes on and off—including those important for cellular differentiation.¹,⁹,¹⁰

IDH1 and 2 are metabolic enzymes that catalyze the conversion of isocitrate to alpha-ketoglutarate
Mutations in IDH1 and IDH2 are found in both hematologic and solid malignancies\textsuperscript{1,2}

IDHm has a gain of function activity that results in excess production of the oncometabolite 2-HG.\textsuperscript{3,11} 2-HG is normally present in cells at low levels, but becomes significantly elevated in IDHm-positive cancers.\textsuperscript{12} It also functions as a competitive inhibitor of DNA- and histone-modifying enzymes that require alpha-ketoglutarate.\textsuperscript{12}

- 2-HG induces global changes in DNA and histone methylation, which alter gene expression\textsuperscript{4,5,12}
- Alterations in DNA/histone methylation and gene expression lead to a cellular differentiation block\textsuperscript{5,12}
- These events may lead to an accumulation of immature cells that persist or progress to a tumor\textsuperscript{5,12,13}
Mutations in IDH1 and IDH2 are found in both hematologic and solid malignancies.  
IDHm generates abnormally high levels of the oncometabolite 2-HG.

Immature undifferentiated cells
Blocked differentiation

DNA and histones become hypermethylated, which modulates the expression of genes involved in cellular differentiation.

Alterations in gene expression result in a cellular differentiation block.

2-HG competitively inhibits alpha-ketoglutarate-dependent DNA- and histone-modifying enzymes.

Excess production of the oncometabolite 2-HG induces global changes in DNA and histone methylation that block cellular differentiation.

Cancers shown to have mutations in IDH include:\(^1,14-18:\)

- Acute myeloid leukemia (~20% of patients)
- Low-grade glioma and secondary glioblastoma (~70% 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)
To learn more about the role of IDHm in cancer please visit www.ExploreIDH.com
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