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Review

# The role of mutation of metabolism-related genes in genomic hypermethylation

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ABSTRACT

Genetic mutations, metabolic dysfunction, and epigenetic misregulation are commonly considered to play distinct roles in tumor development and maintenance. However, intimate relationships between these mechanisms are now emerging. In particular, mutations in genes for the core metabolic enzymes IDH, SDH, and FH are significant drivers of diverse tumor types. In each case, the resultant accumulation of particular metabolites inhibits TET enzymes responsible for oxidizing 5-methylcytosine, leading to pervasive DNA hypermethylation.



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## 1. Introduction

Pioneering work in the first half of the twentieth century established many of the core steps in human metabolism including the tricarboxcylic (TCA) or Krebs cycle through which sugars, amino acids, and fatty acids are broken down to produce chemical energy and molecular building blocks [1]. In the 1950s Otto Warburg discovered that cancer cells have a characteristic type of metabolism, with a high rate of glycolysis despite elevated oxygen levels, and argued that this metabolic shift (the "Warburg effect") is in fact the central cause of cancer [2]. While the relative contributions to tumorigenesis of metabolism, genetic mutation, and epigenetic misregulation have sometimes been debated, new findings in multiple tumor types have shown the three to be intimately related. Certain malignancies arising in hematopoietic, mesenchymal, neural, as well as epithelial tissues share the common quality that mutations in genes coding for core metabolic proteins drive the

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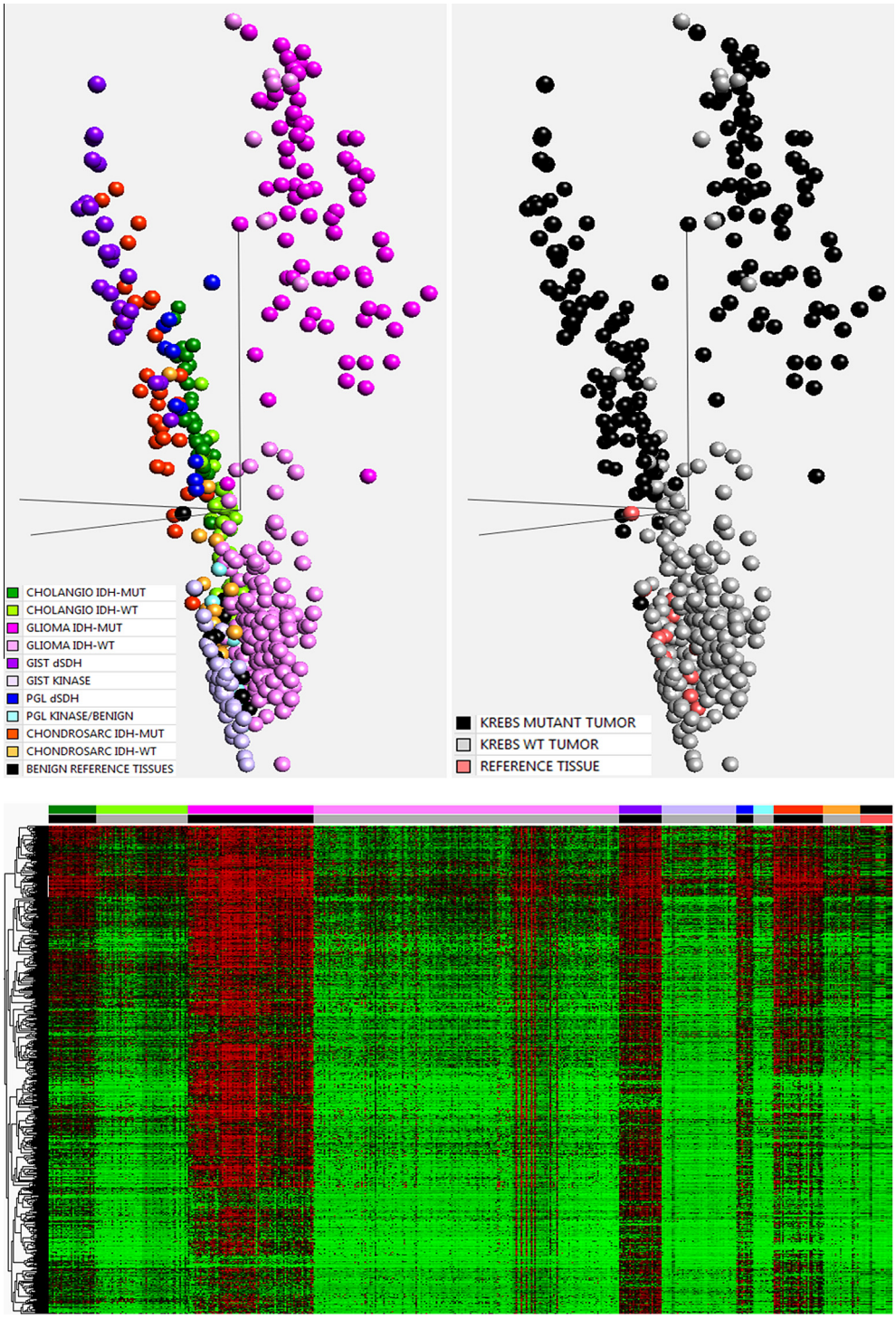


**Fig. 1.** Epigenomic relatedness of *IDH*/*SDH*/*FH* mutant- versus non-mutant- tumors, as shown by PCA plots and heatmap of DNA methylation profiles. Samples included here are: (1) *IDH*-mutant versus -wildtype cholangiocarcinoma (GSE49656, $n = 32$; GSE32286, $n = 50$), *IDH*-mutant versus -wildtype glioma (GSE36278, $n = 136$; GSE48461, $n = 56$; GSE32286, $n = 62$) and *IDH*-mutant versus -wildtype chondrosarcoma (GSE40853, $n = 51$); (2) *SDHx*- versus kinase-mutant GIST (GSE34387, $n = 69$) and *SDHx*- versus kinase-mutant paraganglioma/pheochromocytoma (GSE43293, $n = 22$); and (3) multiple normal associated tissue lineages ($n = 19$). (Sample color legends shown in PCA plots also correspond to heatmap colorbars.) Variables included here are the CpG methylation β-values, as measured by Infinium 450 K array, of the top 10 K differentially-methylated CpG targets between *IDH*/*SDH*/*FH* mutant- and non-mutant tumor groups (statistical calculations and graphics performed with Qlucore Omics Explorer software). In general, *IDH*/*SDH*/*FH* mutant tumors of diverse histological types and embryonic lineages show significantly greater global DNA hypermethylation than non-mutant counterparts.

accumulation of DNA hypermethylation (Fig. 1). While much remains to be learned about these phenomena, the recurrent reconciliation of these distinct pathways across such diverse tumor types provides new insights into oncogenic mechanisms and tumor biology.

## 2. Discovery of IDH mutations

One of the most unanticipated discoveries of the early genome wide cancer mutation profiling efforts was the report of recurrent somatic mutations in the *IDH1* gene. In 2008 and 2009 recurrent