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KMT2D deficiency confers a therapeutic vulnerability to glycolytic and *IGFR* inhibitors in melanoma

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ABSTRACT

We reported that histone H3 lysine (K) 4 methyltransferase, *KMT2D*, serves as a potent tumor-suppressor in melanoma, which was identified via *in vivo* epigenome-focused RNA interference (RNAi) screen. *KMT2D*-deficient tumors show substantial reprogramming of key metabolic pathways including glycolysis via reduction of H3K4me1 (Histone H3K4 mono-methylation)-marked active enhancers, conferring sensitivity to inhibitors of glycolysis and IGFR (Insulin Growth Factor Receptor) pathway.

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Metastatic melanoma is an aggressive skin cancer with a 5-year survival of less than 25%, and in the past decade, the number of people affected by this disease has increased alarmingly.[1] Melanoma is also notorious for its resistance mechanisms to current therapies and is characterized by genetic and epigenetic alterations.[2,3]

Melanoma pathogenesis, commonly known as melanomagenesis, involves the acquisition of sequential alterations in specific genes and molecular pathways that control vital cellular processes. The epigenome is an important player in cancer progression;[4] however, we have a limited understanding of how specific epigenetic modifiers aberration impact melanomagenesis. In this context, our main aim is to further learn about the disease onset. Thus, systematic functional approaches are needed to elucidate how aberrations in epigenetic regulators impact tumorigenesis through reprogramming of chromatin states and downstream gene expression changes.

Although the landscape of current treatment options for metastatic melanoma has expanded, it remains insufficient due to poor treatment outcomes which continue to cause several thousand patients deaths annually.[1] A detailed mechanistic understanding of role of epigenetic regulators in melanomagenesis will pave the path for new therapeutic strategies, which will guide patients to receiving appropriate treatments.

To identify epigenetic regulators that function as a tumor suppressor in melanoma, we isolated *KMT2D* (Lysine methyltransferase 2D) in an *in vivo* RNAi (RNA interference) screen, a cell-based system for discovering tumor-promoting events. Utilizing the unbiased epigenome-focused RNAi screen *in vivo*, we identified and validated eight epigenetic modifiers (Lysine Methyltransferase – *KMT2D* and *KMT2F*, Lysine Demethylase – *KDM1A* and *KDM5B*, Lysine Acetyltransferase – *KAT4*, Histone Deacetylase – *HDAC6*, histone methyltransferase – SET domain-containing protein 4 (*SETD4*) and cytidine deaminase – Apolipoprotein B mRNA Editing enzyme Complex 2 (*APOBEC2*)) whose loss can significantly accelerate tumor growth.[5] As, the strongest phenotypes were seen for *KMT2D*, we focused on this gene for deep mechanistic studies.

To investigate the molecular phenotypes conferred by *KMT2D* loss, RNA sequencing-based transcriptome profiling was performed in the wild-type (WT) and mutant murine melanoma lines. We found that genes overexpressed in the *KMT2D* mutant cells were associated with immune response, cell adhesion, and several metabolic pathways (including glycolysis as the top pathway). This observation was also made across multiple different cancer types where *KMT2D* mutations occur in more than 5% abundance. Inhibition of the glycolysis pathway using three different inhibitors – 2-Deoxy-D-glucose (2-DG, a glucose competitor), pomhex (an Enolase 1 inhibitor[6]), and lonidamine (Hexokinase inhibitor) particularly reduced the proliferation of *KMT2D* mutant melanoma cells compared with that of *KMT2D* WT melanoma cells in both murine as well as human systems. *In vivo* treatment with 2-DG also showed specific sensitivity in *KMT2D* mutant mouse models,[5] suggesting upregulated glycolysis to be a vital contributor to enhanced tumorigenesis in *KMT2D* mutant melanomas. Importantly, such a sensitivity to glycolysis inhibitors was also observed in accompanying paper from Alam et al.,[7] suggesting that this could be a potential treatment strategy in this specific genetic context.

Unbiased epigenome profiling of *KMT2D*-deficient versus WT cells showed specific chromatin switches in H3K4me1 (Histone H3 lysine K4 mono-methylation)-enriched active enhancer states. To understand how enhancer deregulation can lead to metabolic reprogramming, we integrated gene expression and active enhancer differences between *KMT2D* WT and mutant-murine tumor lines. This suggested a significant association between the loss of expression and loss of H3K4me1 patterns in nearby loci; the genes were involved in various cell signaling processes and are tumor suppressors.[5] With a focus on IGF (Insulin Growth Factor) signaling

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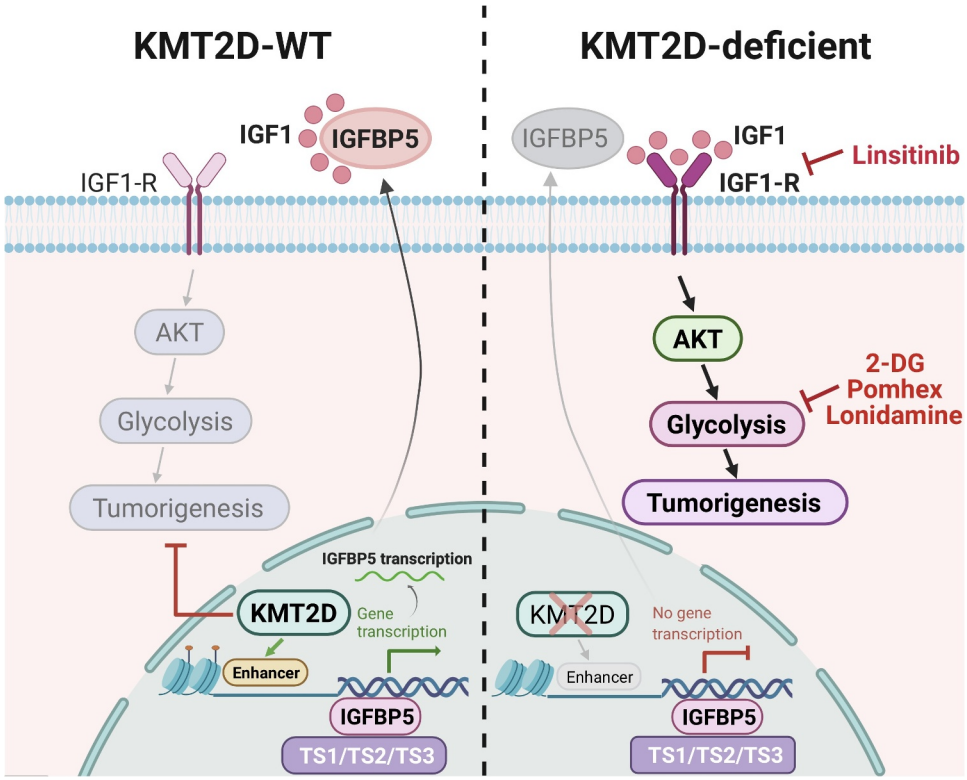

Figure 1. Impact of *KMT2D* function in melanoma. Our data suggest that *KMT2D* (Lysine methyltransferase 2D) loss leads to enhancer reprogramming on tumor suppressor genes including *IGFBP5* (Insulin Like Growth Factor Binding Protein 5) which control various pathways such as *IGF1R* (Insulin Growth Factor Receptor 1) signaling that leads to activation of *AKT* and rewires metabolic pathways. Glycolytic and *IGFR* inhibitors serve as a novel therapeutic strategy in the patients with melanoma harboring *KMT2D* mutations. 2DG (2-Deoxy-D-glucose); TS1/TS2/TS3 (Tumor suppressor 1/2/3).

pathway, we noted higher levels of phosphorylated-Serine-*AKT* (*pAKT*) and phosphorylated-Insulin Growth Factor Receptor 1 (*pIGF1R*) in *KMT2D* mutant murine and human lines, which suggests aberrant activation of the *IGF-AKT*-glycolysis pathway (Figure 1).[8]

To gain a direct mechanistic link between *KMT2D* and *IGF1R* pathway deregulation, we searched for presumed regulators of *IGF* signaling and subsequent metabolic reprogramming that lose active enhancers and gene expression in *KMT2D* mutants. *IGFBP5* (Insulin Like Growth Factor Binding Protein 5) expression was consistently lost in *KMT2D* mutant murine and human cell lines and *IGFBP5* expression was markedly reduced in *KMT2D* mutant human and murine melanoma tumors.[5] Follow-up mechanistic data suggested that *KMT2D* plays the role of a tumor suppressor through eliciting enhancer reprogramming on tumor suppressor genes, like *IGFBP5*,[9] that regulate key pathways such as *IGF1R* signaling which ultimately leads to metabolic rewiring (Figure 1).

Over 6% of all cancers harbor loss-of-function mutations in *KMT2D*, but there is little information about why these mutations are selective over the duration of tumor evolution.[10] Enhancer reprogramming via *KMT2D* loss can rewire metabolic pathways for increased energy needs of cancer cells as suggested by drastic deregulation of several metabolic pathways in *KMT2D* mutant melanomas and lung cancers.[5,7] *KMT2D* mutant cancers are dependent on glycolysis as this pathway is a central node for catering to needs of proliferating cells by contributing to several different biomass needs.

Further research may be needed to better stratify the functional driver mutations in *KMT2D* because it is likely to harbor high mutations due to its excessive length and some of the observed mutations may be passenger events, particularly in cancers such as melanoma and lung cancers, which possess a high mutation burden. Additionally, while we show importance in focusing on the role of glycolysis, many other metabolic pathways are highly upregulated in *KMT2D* mutant cancers which require further exploration. In fact, metabolic reprogramming functions of *KMT2D* is only one of a multitude of factors contributing to the growth of *KMT2D*-deficient cells. Future studies will bring attention to other key aspects of *KMT2D* biology such as investigating the tumor microenvironment.

Overall, our study serves as evidence for the dependency of *KMT2D* mutant melanomas on the glycolysis pathway and the *IGF* pathway through enhancer reprogramming. These results implicate glycolysis inhibition as a potential therapeutic strategy in patients with melanoma and other cancers harboring mutations in this epigenetic regulator, thus providing a novel biomarker-driven precision oncology approach that can be tested in clinic.

Disclosure statement

No potential conflicts of interest were disclosed.

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