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METABOLISM

IDH2 drives cancer *in vivo*

Two recent studies show that mutations in the metabolic gene isocitrate dehydrogenase 2 (*IDH2*) can drive the development of leukaemia and sarcoma *in vivo*. Monoallelic point mutations in *IDH1* or *IDH2* have been associated with various cancer types, which suggests that these mutations may be drivers of tumorigenesis; however, the study of IDHs has been hindered by a lack of *in vivo* models.

IDH enzymes normally convert isocitrate to α-ketoglutarate (αKG). However, cancer-associated IDH mutations result in an enzyme that converts αKG to 2-hydroxyglutarate (2HG). 2HG can competitively inhibit the targets of αKG, which have DNA and histone demethylase activity. Thus, 2HG production leads to changes in gene expression that have previously been reported to result in impaired differentiation.

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Lu and colleagues investigated *IDH2* mutations in sarcomas, which are mesenchymal tumours that show poor differentiation and that frequently contain mutated *IDH2*. The authors used non-transformed multipotent 10T mouse cells that expressed the mutant form of *IDH2*, and they observed that the cells failed to differentiate into mesenchymal lineages and that this failure was associated with high levels of 2HG. Moreover, the treatment of cells expressing IDH2-mutant proteins with a DNA methyltransferase inhibitor restored the ability of the cells to functionally differentiate into mature cell types. Subcutaneous injection of 10T cells that expressed mutant *IDH2* into mice resulted in a striking increase of sarcoma growth, whereas no sarcomas developed in mice that were injected with cells expressing wild-type *IDH2* or vector alone. Furthermore, the tumours were poorly differentiated with no detectable expression of mature cell markers, which mimics the immunohistochemical profile of human sarcomas. The sarcomas also had increased levels of 2HG, as seen in cell culture studies.


IMAGE 100

In another study, Chen and colleagues described a novel mouse model of mutant *IDH2*-driven acute myeloid leukaemia (AML), and they used this model to test possible treatments. The authors investigated whether *IDH2* mutations would cooperate with mutations in two other known AML-associated genes: *Flt3* and *Nras*. Mice that carry *Flt3* mutations develop chronic myelomonocytic leukaemia, which is a milder form of leukaemia that does not progress to AML, whereas mice that carry *Nras* mutations develop a myeloproliferative disorder. Haematopoietic stem and progenitor cells (HSPCs) were isolated from *Flt3*- or *Nras*-mutant mice and transduced with vectors that contained human mutant IDH2 or control vectors. Mice that were transplanted with HSPCs that contained mutant IDH2 and *Nras*, or mutant IDH2 and *Flt3*, developed aggressive AML. These mice had increased proliferation of leukaemic cells and these leukaemic cells expressed only progenitor markers, which suggests that these cells had failed to differentiate, mimicking AML in humans. Similar to the result observed in the Lu study, these cells exhibited high levels of 2HG and altered DNA methylation. In addition, when leukaemic cells that were derived from mice with *IDH2*-driven AML were treated with a small-molecule inhibitor for a specific IDH2 mutation (AGI-6780), *in vitro*, AML cells ceased proliferating and differentiated. This demonstrates that mutant *IDH2* is required for continued tumour maintenance. The authors also showed that mice with *IDH2*-driven AML responded to treatment with a bromodomain-containing protein 4 (BRD4) inhibitor *in vivo*, which is another AML-associated therapeutic target, providing a potential new avenue to target leukaemias that have *IDH2* mutations.

Together, these studies confirm that, *in vivo*, *IDH2* mutations cause inhibition of differentiation, altered DNA methylation and hyperproliferation in different tumour contexts. In addition, they confirm speculation that *IDH2* is required for tumour maintenance rather than simply for tumour initiation, and they provide models to investigate possible therapeutics for *IDH2*-driven tumours

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ORIGINAL RESEARCH PAPERS Lu, C. *et al.* Induction of sarcomas by mutant IDH2. *Genes Dev.* **27**, 1986–1998 (2013) | Chen, C. *et al.* Cancer-associated IDH2 mutants drive an acute myeloid leukemia that is susceptible to Brd4 inhibition. *Genes Dev.* **27**, 1974–1985 (2013)