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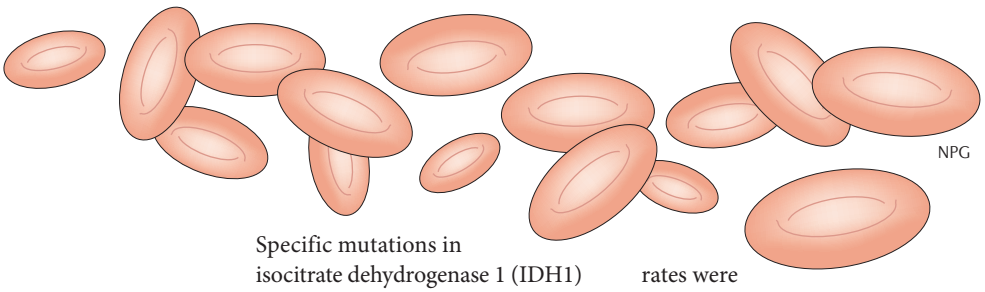
THERAPEUTICS

Targeting an oncometabolite



NPG

Specific mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 result in the generation of a particular metabolite — the (*R*)-enantiomer of 2-hydroxyglutarate ((*R*)-2HG). The production of high concentrations of (*R*)-2HG is associated with biological outcomes that promote tumour progression. Thus, there has been considerable interest in developing drugs that target mutant IDH1 and IDH2.

Janeta Popovici-Muller and colleagues have developed a selective inhibitor (AGI-5198) of R132H-IDH1, which is the most common mutant of IDH1 in glioma. Along with colleagues from the laboratories of Katharine Yen, Thomas Graeber and Ingo Mellinghoff, they tested the activity of this drug in a patient-derived glioma cell line that has an endogenous R132H-IDH1 mutation. AGI-5198 inhibited, in a dose-dependent manner, the production of (*R*)-2HG and also limited colony formation in soft agar by up to 60%. By contrast, it had no effect on two patient-derived glioma cell lines with wild-type IDH1. In mice, orally administered AGI-5198 limited the growth of human R132H-IDH1 glioma xenografts by 50–60%. Proliferation rates were reduced in these xenografts, but apoptosis rates were unaffected. Gene expression studies on mRNA isolated from treated xenografts indicated that the transcription of genes involved in the differentiation of oligodendrocytes and astrocytes was increased. This and other analyses indicated that R132H-IDH1 restricts glial differentiation and that this is restored when R132H-IDH1 is inhibited.

> “orally administered AGI-5198 limited the growth of human R132H-IDH1 glioma xenografts by 50–60%”

Mutant IDH1 has been associated with specific epigenetic changes, such as DNA and histone methylation, owing to the inhibitory effects of (*R*)-2HG on α-ketoglutarate (αKG)-dependent dioxygenases, including TET methyl cytosine hydroxylases and Jumonji-C domain histone demethylases. The authors used two different concentrations of AGI-5198 that either partially reduced or almost fully reduced the concentration of (*R*)-2HG to physiological levels. Inhibition of xenograft growth occurred as a result of partial (*R*)-2HG blockade, and further experiments showed that this was uncoupled from effects on histone and DNA methylation. Thus, the authors conclude that the roles of additional αKG-dependent dioxygenases in the maintenance of IDH1-mutant glioma need to be better understood.

Jeremy Travins and colleagues have also developed a drug, AGI-6780, that targets R140Q-IDH2, a mutation that is present in approximately 9% of patients with acute myeloid leukaemia (AML). Expression of R140Q-IDH2 in the human erythroleukaemia cell line, TF-1, which is dependent on granulocyte–macrophage colony-stimulating factor (GM-CSF) for survival and proliferation, resulted in the production of high concentrations of (*R*)-2HG, GM-CSF-independent growth and the attainment of a stem cell and/or progenitor cell phenotype. Moreover, erythropoietin failed to induce the differentiation of TF-1 cells that expressed R140Q-IDH2, but this was restored in the presence of AGI-6780 at concentrations that reduced the expression of (*R*)-2HG to near physiological concentrations. Additional *ex vivo* experiments that used patient-derived AML samples showed that AGI-6780 induces the differentiation of leukaemic blasts specifically in patient samples that have the R140Q-IDH2 mutation. Whether this translates to clinical efficacy has not yet been determined.

Both papers indicate that (*R*)-2HG is associated with a block in differentiation in glioma and AML cells, as several studies have previously indicated, and that this can be reversed by specific inhibitors that reduce the production of (*R*)-2HG by mutant IDH.

Nicola McCarthy

ORIGINAL RESEARCH PAPERS Rohle, D. *et al.* An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. *Science* 4 Apr 2013 (doi:10.1126/science.1236062) | Wang, F. *et al.* Targeted inhibition of mutant IDH2 in leukemia cells induces cellular differentiation. *Science* 4 Apr 2013 (doi:10.1126/science.1234769)