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First Author: Cornelis Van Noorden
Cancer Center Amsterdam at the Academic Medical Center
Medical Biology Meibergdreef 15 Amsterdam
Netherlands
Phone:
c.j.vannoorden@amc.uva.nl

First Author is a: Investigator
First Author is a member of: American Society for Investigative Pathology
First Author Degree: PhD, DSc, or equivalent

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Sponsor: Cornelis Van Noorden
Sponsor Phone: 31638639561
c.j.vannoorden@amc.uva.nl
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MECHANISMS OF THE IDH1/2 MUTATIONS AND ITS ASSOCIATION WITH CONTRADICTORY SURVIVAL OF GLIOBLASTOMA PATIENTS VERSUS AML PATIENTS

Cornelis Van Noorden. Medical Biology, Cancer Center Amsterdam at the Academic Medical Center, Amsterdam, Netherlands

Cornelis J.F. van Noorden, Mohammed Khurshed, Vashendriya V.V. Hira and Remco J. Molenaar

Cancer Center Amsterdam, Department of Medical Biology, Academic Medical Center, Amsterdam, The Netherlands

Isocitrate dehydrogenase 1 and 2 (IDH1/2) is mutated (IDH1/2mt) in various types of human cancer such as glioma and acute myeloid leukemia (AML), a structural alteration that leads to catalysis of α-ketoglutarate to the oncometabolite D-2-hydroxyglutarate (D2HG). Heterozygous IDH1/2mt cancer cells produce less IDH1/2-mediated NADPH, such that after exposure to ionizing radiation (IR) there were higher levels of reactive oxygen species, DNA double-strand breaks and cell death compared to IDH1 wild-type (IDH1wt) cells. These effects were reversed by the IDH1mt inhibitor AGI-5198. Exposure of IDH1wt cells to D2HG was sufficient to reduce IDH-mediated NADPH production and increase IR sensitivity. Mechanistic investigations revealed that the radiosensitivity of heterozygous cells was independent of the well-described DNA hypermethylation phenotype in IDH1mt cancers. Thus, our results argue that altered oxidative stress responses are a plausible mechanism to understand the radiosensitivity of IDH1mt glioma. Further, they offer an explanation for the relatively longer survival of patients with IDH1mt glioma, and they imply that administration of IDH1mt inhibitors in these patients may limit irradiation efficacy in this setting.

Whether this also holds true for IDH1/2mt AML was investigated using primary human IDH1mt, IDH2mt and IDH1/2wt AML cells. It was investigated whether IDH1/2 mutations cause increased DNA damage and sensitization to daunorubicin, irradiation, and the PARP inhibitors olaparib and talazoparib. IDH1/2mt inhibitors protected against these treatments. Combined treatment with a PARP inhibitor and daunorubicin had an additive effect on killing of IDH1/2mt AML cells. We provide evidence that the therapy sensitivity of IDH1/2mt cells was caused by D2HG-mediated downregulation of expression of the DNA damage response gene ATM and not by altered redox responses due to metabolic alterations in IDH1/2mt AML cells. Thus, IDH1/2mt AML cells are sensitive to PARP inhibitors as monotherapy but especially when combined with a DNA-damaging agent such as daunorubicin, whereas concomitant administration of IDH1/2-mutant inhibitors during cytotoxic therapy decreases the efficacy of both agents in IDH1/2mt AML cells.

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