Clinical Cancer Research

Shedding Light on *IDH1* Mutation in Gliomas

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IDH mutation is of central importance in the diagnosis and treatment of gliomas. Fourier-transform infrared spectroscopy, in combination with a supervised machine-learning approach, can be used to detect metabolic alterations induced by *IDH1* mutations in a fraction of the time of conventional techniques. *Clin Cancer Res; 24(11); 2467–9. ©2018 AACR.*

See related article by Uckermann et al., p. 2530

In this issue of *Clinical Cancer Research*, Uckermann and colleagues report on the detection of isocitrate dehydrogenase-1 (*IDH1*) mutational status in glioma using an optical technique called Fourier-transform infrared spectroscopy (FT-IR; ref. 1). *IDH* mutations are essential for glioma diagnosis and hold major prognostic significance for patients with glioma. On a cellular level, *IDH* mutations result in a cascade of metabolic alterations. Employing an FT-IR spectrometer, Uckermann and colleagues compared the biochemical properties of *IDH1*-mutant glioma cell lines, human cryosections, and fresh brain tumor specimens with their *IDH1* wild-type counterparts. To evaluate subtle spectral differences, the authors employ quadratic discriminate analysis, a supervised machine-learning method, to achieve an *IDH* classification accuracy of 92.2% in glioma cells lines, 88% in human cryosections, and 86% in fresh brain tumor specimens.

On a biochemical level, one of the most significant metabolic aberrations induced by IDH mutation is the production of the oncometabolite 2-hydroxyglutarate (2-HG), resulting from gain-of-function mutation, typically at the 132nd amino acid residue of IDH. The presence of 2-HG results in multiple, presumably oncogenic, alterations to cellular metabolism, altering levels of amino acids, glutathione metabolites, choline derivatives, and phospholipids (Fig. 1; ref. 2). Interestingly, although detectable with FT-IR in *IDH*-mutant cell lines, spectral evidence of 2-HG accumulation was not obvious in *IDH*-mutant glioma tissue, in part due to the variability of 2-HG levels among *IDH*-mutant tumors. In contrast, other FT-IR spectral differences between *IDH*-mutant and wild-type tumors were detected, including C-O stretching vibrations characteristic of carbohydrates, CH2 bending characteristics of lipids, and amide bond–specific vibrations seen in proteins. Uckermann and colleagues conclude that these findings are consistent with expected downstream metabolic effects of *IDH* mutation in glioma induced by 2-HG (1). Indeed, the observed spectral evidence suggesting alterations in protein and lipid levels induced by *IDH* mutation is harmonious with detailed metabolomic analysis performed on *IDH*-mutant human oligodenroglial cells utilizing multiple mass spectrometry platforms (2). Further mechanistic studies, possibly in conjunction with mass spectrometry, which provides unparalleled chemical resolution, would be helpful in understanding the specific chemical species that underlie the FT-IR differences between *IDH*-mutant and wild-type cell lines and tumors.

Regardless of the specific biochemical alterations detected, FT-IR holds promise for intraoperative detection of *IDH* mutation, as spectra can be rapidly acquired (~1 minute). In contrast, current methods for determining *IDH* status require intensive laboratory testing (DNA sequencing, PCR, and/or IHC), precluding access to *IDH* genotyping during surgery. Although several methods have been developed to establish preoperative or intraoperative molecular diagnosis, including magnetic resonance spectroscopy, rapid glioma genotyping assay (3), and desorption electrospray ionization mass spectrometry (4), they are limited by issues related to specimen preparation and highly specialized intraoperative instrumentation. Notably, Uckermann and colleagues utilize a commercially available FT-IR instrument that has promise for further validation in a manner that would create the possibility of wide clinical use.

Beyond its diagnostic value in detecting *IDH* mutation, FT-IR could conceivably be used as a tool by surgeons to ensure optimal surgical results: maximal tumor removal with minimal damage to adjacent healthy brain. Consequently, the value of FT-IR as a surgical tool is highly dependent on its ability to detect tumor infiltration by *IDH*-mutant glioma cells, especially at the periphery of a resection cavity where the margins may be indistinct. In its current implementation, FT-IR is prone to classification errors between *IDH*-mutant and wild-type tissues. The majority of the classification errors observed in fresh brain tumor specimens studied by Uckermann and colleagues (1) occurred in tissue with infiltrating or recurrent tumor. This indicates that the classification accuracy may be sensitive to the degree of tumor infiltration, presumably working best where tumor cells are most concentrated. Understanding the degree of tumor infiltration required for detection of IDH mutation by FT-IR will be essential in determining the clinical value of this technique for surgical guidance.

Although further clinical studies are required to establish a consensus on the role of *IDH* mutation in surgical planning and intraoperative decision-making, several studies highlight

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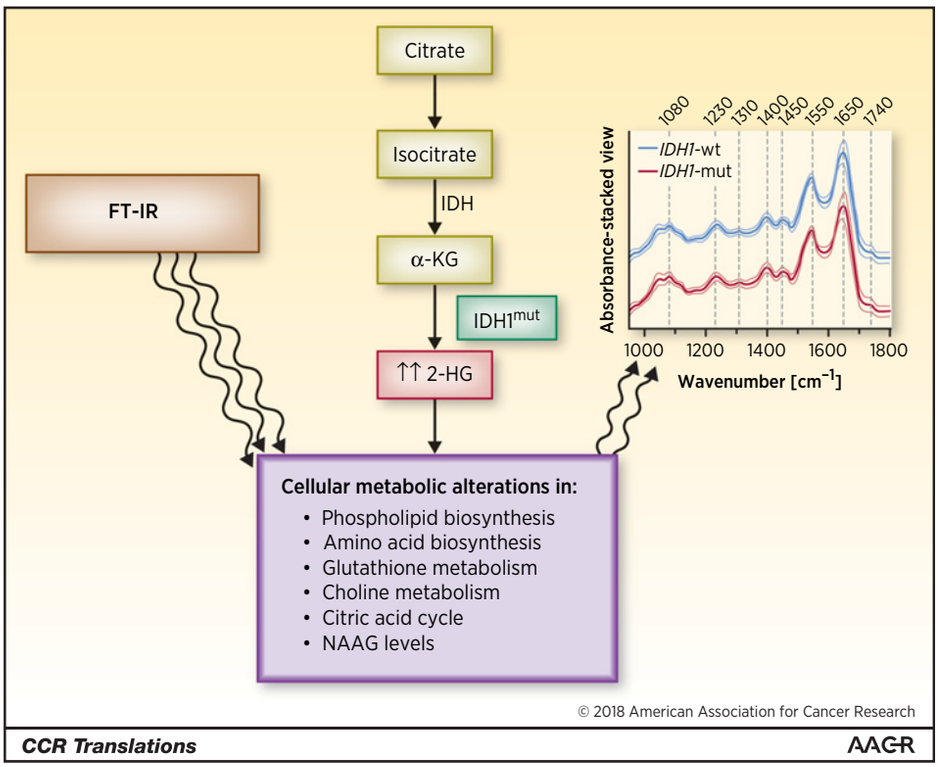

Figure 1.
Molecular and metabolomics aberrations in *IDH*-mutant cell lines and human tissue detected by FT-IR. *IDH1* mutations lead to increased levels of 2-HG. Multiple downstream metabolic changes provide the substrate for machine learning–based classification of *IDH* mutational status using spectral data from FT-IR. mut, mutation; NAAG, N-acetylaspartylglutamate; wt, wild type.

the translational potential of intraoperative detection of *IDH* mutation. Recent evidence demonstrates that patients with *IDH1*-mutant malignant gliomas [World Health Organization (WHO) grades 3 and 4] display better overall survival from maximal resection of both enhancing and nonenhancing tumor (median survival 9.75 years for >5 cc residual vs. not reached for <5 cc; ref. 5). This effect was not seen in patients with *IDH1* wild-type malignant gliomas, where only resection of enhancing tumor provided a survival benefit. In a subsequent study investigating low-grade gliomas (WHO grade 2), *IDH* wild-type tumors demonstrated prolonged time to malignant transformation and overall survival with greater volumetric extent of resection; however, these findings were not reproduced in the *IDH*-mutant group (6). We anticipate larger and more comprehensive clinical studies to evaluate the role of *IDH* status on intraoperative decision-making and how this impacts clinical outcome.

In summary, rapid detection of key cancer driver mutations like *IDH* creates the possibility of improving the accuracy of preliminary diagnosis and the quality of surgical intervention for patients with glioma. Although Uckermann and colleagues (1) focus on detection of *IDH* mutation, FT-IR and related optical techniques may ultimately be applied to the detection of other essential cancer-specific genetic abnormalities that alter cellular metabolism. As our understanding of the genetic basis of cancer deepens, so will the potential for a molecularly tailored approach to surgical intervention. In the future, rapid molecular diagnostic techniques may serve to link our growing understanding of cancer genetics with the safest, most accurate surgical treatment of patients with cancer.

Disclosure of Potential Conflicts of Interest

D.A. Orringer holds ownership interest (including patents) in and is a consultant/advisory board member for Invenio Imaging, Inc. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: T.C. Hollon, D.A. Orringer
Development of methodology: T.C. Hollon, D.A. Orringer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T.C. Hollon, D.A. Orringer
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.C. Hollon, D.A. Orringer
Writing, review, and/or revision of the manuscript: T.C. Hollon, D.A. Orringer
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