

CT scans could account for up to 2% of all cancers. Plainly, the balance of risk and benefit must be keenly examined.

The second article, by Smith-Bindman et al., looked retrospectively at the radiation dose attributable to 11 types of diagnostic CT scans performed in 1119 consecutive adult patients in 2008. The median effective dose varied widely by type of scan, ranging from 2 millisieverts (mSv) for a plain head CT up to 31 mSv for a multiphase abdomen and pelvis CT scan. Interestingly, the variation in effective dose between different CT scanners for the same study varied as much as 13-fold. This begs the question as to what the minimum necessary dose for each type of CT scan is. Like the study above, they projected estimates of future cancer using estimates. They conclude that the risk of a routine head CT in a woman at age 40 is 1 in 8100, whereas the risk from a coronary CT angiogram is a shocking 1 in 270.

Both studies project the risks rather than demonstrate them in a comparative fashion and produce different numbers. Nonetheless, the concerns they raise require serious consideration. However, despite this and despite significant socioeconomic pressures to reduce cost by driving down physician use of diagnostic tests, the risk of far future cancer is unlikely to result in fewer brain scans. Rather, it is likely to shift utilization to the even more costly modality of mag-

netic resonance imaging (MRI). The neurosurgeon will most likely be caught again in the classic double-bind. No legislative force currently will protect the physician who misses an important intracranial finding because he or she decided to forego a scan because of the cancer risk. Yet as our understanding of the risk of CT scans looms larger, so rises the specter that physicians could be sued by cancer patients for “unnecessary” scans done many years before. If our response is going to be to shift more scans to MRI, there must be a commensurate increase in their availability, and allowance must be made in the health care system for the additional cost. This puts even more pressure on the developing world, where access to a CT scanner may be achievable but MRI remains often out of reach.

For now, it behooves us to study more closely how much radiation a scan exposes the patient to, what the true future impact is, and how this risk may be reduced. The implications are wide-ranging for neurosurgery, particularly for specialty areas reliant on fluoroscopy, such as endovascular therapy and instrumented spine surgery.

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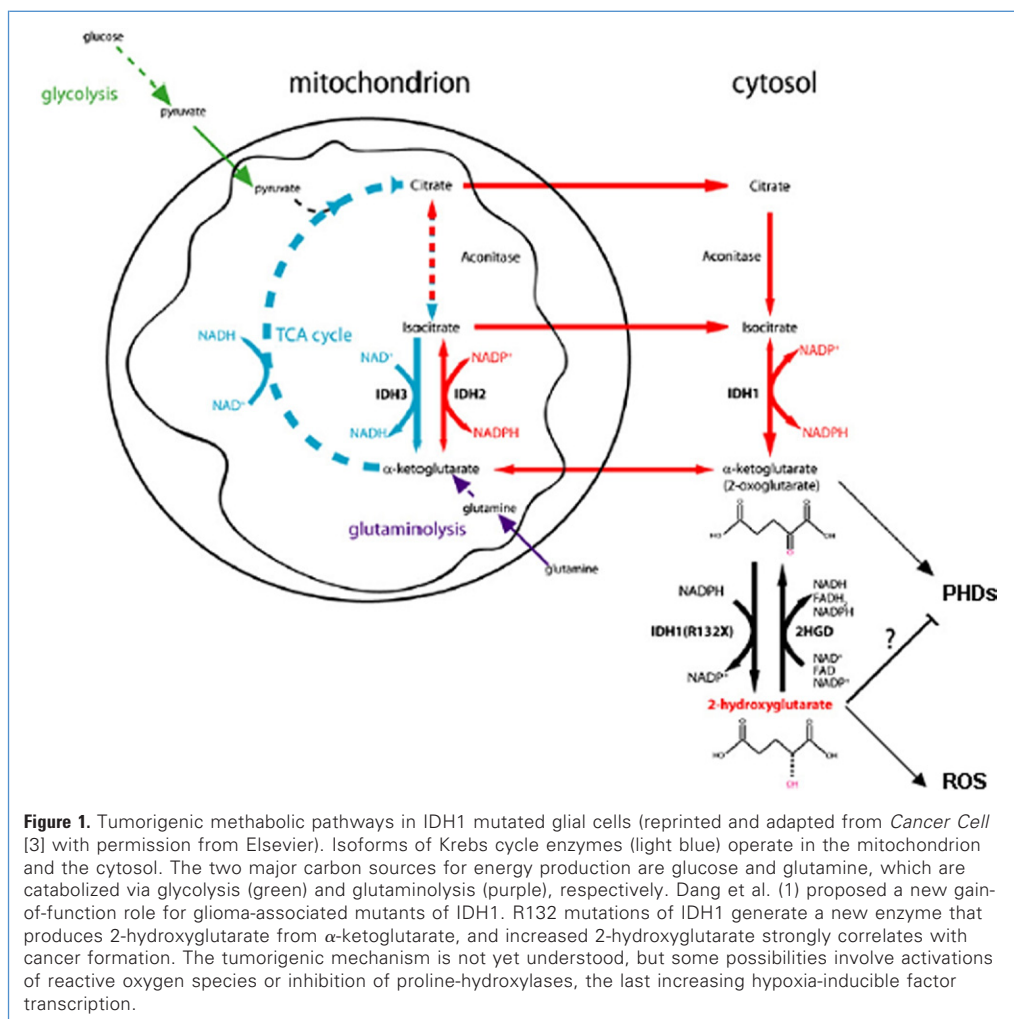
## From Standard Treatment to Personalized Medicine: Role of IDH1 Mutations in Low-Grade Glioma Evolution and Treatment

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For glioma patients today, therapy is chosen and implemented essentially on histopathological bases. Currently, an individual patient's biologic data is rarely used in a systematic way to guide and predict the best course of therapy (2). The advent of low-cost, individual genomic and proteomic analysis provides hope that we are entering a new era of personalized, patient-specific care. As far as glioma evolution and therapy are concerned, a new study by Dang et al. published in *Nature* in December 2009 (1) focused on the role of mutated NADP<sup>+</sup>-dependent isocitrate dehydrogenase enzyme (IDH) genes as possible oncogenes (Figure 1). The possibility that tumor cells may develop typical metabolic profiles contributing to tumorigenesis is not a new concept (6). IDH in astrocytes is involved in the conversion of isocitrate to  $\alpha$ -ketoglutarate both in the mitochondria as part of the Krebs cycle (IDH2, IDH3) and in the cytoplasm (IDH1), resulting in production of NADPH as a source of energy for cell metabolism. Mutations of IDH1 had been demonstrated in approximately 80% of Grade II and III gliomas and secondary glioblastomas (GBMs) (7, 8). In GBMs and anaplastic astrocytomas, the presence of the mutated phenotype was associated with a better prognosis (8). The mutations that had been studied occurred at a single amino acid residue of IDH1, arginine 132, which was most commonly mutated to histidine (R132H) (7, 8). When considering other possible mutations that had been implicated in the tumorigenesis of brain tumors, it seemed that IDH1 was often the first one to occur (7). Therefore, it had been postulated that IDH1 mutations were selected for

early tumorigenesis. More recently, data had been provided showing a reduced conversion of isocitrate to  $\alpha$ -ketoglutarate by the mutated IDH1 isoform as compared to wild type. How this reduced activity could lead to early damages and tumorigenesis was still unclear. One of the hypotheses implicated that in IDH mutated cells, because of the low levels of  $\alpha$ -ketoglutarate that acts as a cofactor together with oxygen, the activity of proline hydroxylases was reduced. This enzyme is involved in the catabolism of hypoxia-inducible factor 1 (HIF1), involved in tumor angiogenesis. The loss of inhibition ensured by proline hydroxylases could increase HIF1 levels and related angiogenesis, as already demonstrated in nonglial cancer (4). The fact that only the single codon of arginine 132 had to be mutated in glial cells to promote malignant transformation was suggestive of a mechanism different from simple enzyme inactivation and decreased  $\alpha$ -ketoglutarate production.

Dang et al. (1) explored the hypotheses that IDH1 mutations may influence the enzyme's ability to act on  $\alpha$ -ketoglutarate. First of all, they analyzed the metabolic profiles of U87 and LN-18 glioblastoma cells transfected with R132H mutated IDH1: No differences between mutated and wild type cells were found in the amount of metabolites involved in Krebs cycle, including  $\alpha$ -ketoglutarate; on the contrary, an increase in 2-hydroxyglutarate (2-HG) was found in cell extracts and in the medium of glioma cells bearing the IDH1 mutation. The authors elegantly demonstrated that, in addition to impaired oxidative decarboxylation of isocitrate, all different forms of IDH1 mutations found in



**Figure 1.** Tumorigenic metabolic pathways in IDH1 mutated glial cells (reprinted and adapted from *Cancer Cell* [3] with permission from Elsevier). Isoforms of Krebs cycle enzymes (light blue) operate in the mitochondrion and the cytosol. The two major carbon sources for energy production are glucose and glutamine, which are catabolized via glycolysis (green) and glutaminolysis (purple), respectively. Dang et al. (1) proposed a new gain-of-function role for glioma-associated mutants of IDH1. R132 mutations of IDH1 generate a new enzyme that produces 2-hydroxyglutarate from  $\alpha$ -ketoglutarate, and increased 2-hydroxyglutarate strongly correlates with cancer formation. The tumorigenic mechanism is not yet understood, but some possibilities involve activations of reactive oxygen species or inhibition of proline-hydroxylases, the last increasing hypoxia-inducible factor transcription.

human glioma cells provide the ability to catalyze direct NADPH-dependent reduction of  $\alpha$ -ketoglutarate to 2-HG. A similar significant increase in 2-HG levels was then measured directly on human IDH1 mutated glioma samples, thus further confirming *in vitro* findings. Finally, X-ray analyses of the mutated enzyme revealed that mutation at arginine 132 caused a different conformation of the active site, which could change affinity for the substrate.

These data open a new perspective on the oncogenic mechanism of IDH1 mutation in gliomas. The authors give different explanations. Regardless of the mechanisms, it seems likely that the gain-of-function ability of cells to produce 2HG as a result of R132 mutations in IDH1 contributes to tumorigenesis. We have previously proposed that patients suffering with 2-hydroxyglutaric aciduria, a condition associated with the presence of high levels of 2-HG in brain and other organs, are at a high risk of developing brain tumors

(5). In addition, elevated brain levels of 2HG could result in increased ROS levels that, associated with alterations in NADPH metabolism, could contribute to an increased risk of cancer. 2HG may also be toxic to cells by competitively inhibiting enzymes involved in glial cell metabolism, such as transaminases, which allow use of glutamate nitrogen for amino and nucleic acid biosynthesis, and  $\alpha$ -ketoglutarate-dependent proline-hydroxylases, such as those that regulate Hif1 $\alpha$  levels. The apparent codominance of the activity of mutant and wild-type IDH1 is consistent with the possibility that wild-type IDH1 could directly provide NADPH and  $\alpha$ -ketoglutarate to the mutant enzyme. These findings may have relevant clinical implications. First, the mutation of IDH1 and possibly detection of increased levels of 2-HG could be used to identify patients with glioblastoma with a better prognosis. In addition, patients with lower-grade gliomas may potentially benefit by the therapeutic inhibition of 2HG production, in terms of slowing or halting conversion of lower-grade glioma into lethal secondary glioblastoma, changing the course of the disease. However, a number of questions remain unanswered. From a clinical point of view, low-grade gliomas are mostly diagnosed when they are already symptomatic and with a sizable tumor mass. This implies that a number of different intracellular pathways have been activated after the initial mutation. Even if the hypothesis that IDH1 mutation is the first hit in glioma tumorigenesis, leading to 2-HG overproduction, will be confirmed in future studies, we cannot infer that pharmacological inhibition of 2-HG would be sufficient to inhibit glioma evolution to glioblastoma. Despite these limitations, this important study invites neurosurgeons to switch their minds from standardized protocols and surgeries toward customized and biomolecular-guided treatments.

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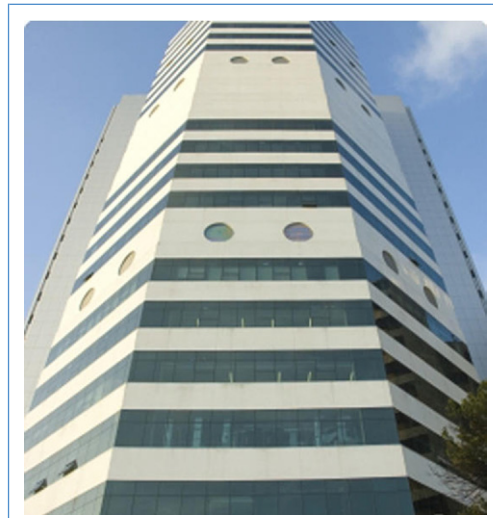
## Cancer, Cerebrovascular Diseases, and Neurosurgery at the University of São Paulo

**Eberval G. Figueiredo**

Economical development, technological advances, and industrial progress are well-known factors that traduce what is a developed country. Proportionally, however, chronic diseases such as malignant tumors and cerebrovascular disorders increasingly become prevalent health problems as economical development takes place. Even though Brazilian economical figures have progressively increased in the past decades, the relative prevalence of these diseases has slightly changed since the 1940s, although the absolute number has largely augmented. Currently, cardiovascular diseases and cancer represent major health care issues worldwide, being the first and second causes of deaths, respectively, in Brazil. Unlike other groups of disorders, these are very expensive to manage, demanding considerable public investments. Treatment is only one of the multiple facets involved in patient care, and multimodal strategies are usually required to properly treat these disorders.

Recently, an entirely *cancer-devoted* hospital was established in São Paulo, Brazil: the Instituto do Câncer de São Paulo (ICESP) Octávio Frias de Oliveira (**Figure 1**). Linked to the University of São Paulo School of Medicine (**Figure 2**), it was projected to be the largest oncologic center in Latin America. It is perhaps the world's largest "vertical" hospital. Within its 28 floors, 6000 patients have been cared for monthly. Several diagnostic procedures, surgeries, radiotherapy, chemo- and immunotherapy, rehabilitation, teaching, and basic research activities are performed routinely in ICESP's facilities. Operative center counts with 22 operating rooms equipped with state-of-the-art resources and an intensive care unit with 84 beds provide support for postoperative management. Private practice is not allowed, providing access for patients who cannot afford the high costs of contemporary cancer treatment.

At this scenario, the Division of Neurological Surgery of the University of São Paulo has played a major role. Malignant tumors of the central and peripheral nervous system and spine, including gliomas and metastasis, are nowadays integrally treated at the ICESP. In addition, complications of malignant



**Figure 1.** Instituto do Câncer de São Paulo

tumors, including intractable pain, are also managed by neurosurgeons. The ICESP will significantly impact cancer treatment in Brazil, either in patient care, teaching, or basic research. Neurosurgery certainly will greatly contribute to this important task.

In addition, a new facility dedicated exclusively to cerebrovascular diseases will soon be established at the Division of Neurological Surgery and Department of Neurology at the University of São Paulo (**Figure 3**). Patients with intracranial aneurysms, arteriovenous malformations, and cavernous malformations will be treated. Twenty-two neurologic intensive care beds will be available for the pre- and postoperative care of these patients. A multidisciplinary team constituted by cerebrovascular surgeons, neurologists, interventional therapists, radiologists, radiosurgeons, neurosonologists, physical therapists, and psychologists and a complete structure for rehabilitation will assist the Cere-