Cell Research (2010) 20:1279-1281.

www.nature.com/cr

RESEARCH HIGHLIGHT

# IDH1 mutant structures reveal a mechanism of dominant inhibition

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*Cell Research* (2010) **20**:1279-1281. doi:10.1038/cr.2010.160; published online 16 November 2010

Pioneered by a major cancer genome sequencing project [1] and followed by numerous cancer genomic sequencing studies [2-4], the cytosolic isocitrate dehydrogenase (*IDH1*) gene and mitochondria isocitrate dehydrogenase (*IDH2*) gene are found to be frequently mutated in low grade gliomas and secondary glioblastoma multiforme (GBM), acute myeloid leukemia (AML), and to a much lower frequency in other types of tumors. The significance of these findings was immediately appreciated by the cancer research community partially because both glioma and AML are among the most malignant tumors that have worst prognoses but probably more importantly, these findings demonstrate that IDH1 and IDH2, together with a few other metabolic genes such as succinate dehydrogenase (*SDH*) and fumarate hydratase (*FH*), provide compelling evidence for metabolic alteration in human cancer development.

Accumulating evidence showed that dysregulated metabolism could be cancerous. However, the mechanism from altered metabolism to tumorigenicity is not completely elucidated. Studies on consequence of IDH1 and IDH2 mutations have shed lights on this problem. Unique features of IDH1 and IDH2 mutations include that no truncation or frameshift mutants have been identified so far and all mutations are heterozygous. Both features indicate a gain of function mutations in a genetic sense. However, a biochemical study carried out by Zhao *et al*. revealed that $IDH1^{R132H}$ mutant is a catalytically inactive missense mutation which has a much reduced activity to convert isocitrate (ICT) and $NADP^+$ to α-ketoglutarate (αKG) and NADPH [5]. Moreover, the R132H mutant, when co-expressed with wild type IDH1 in cells, exerts dominant negative inhibition to the wild type enzyme by forming a catalytically inactive herterodimer. It is also proposed that the R132H mutant IDH1 decreased cellular concentration of αKG [5], which is a substrate essential for hydroxylation and degradation of hypoxia inducible factor (HIF). Therefore, the IDH1 mutant functions as a tumor suppressor by decreasing αKG and increasing HIF. Although this tumor suppressor model well explains clinical observations, some researchers accept it with reluctance. The reason is that dominant inhibition by the mutant IDH1, the core mechanism of this model, is proposed primarily based on the results of enzymatic analysis and lack of additional supports. The doubt about the above model was raised when Dang *et al*. [6] reported and Ward *et al*. [3] confirmed that glioma- and AML-derived IDH1 and IDH2 mutations actually gained a new catalytic activity that reduces αKG to D-hydroxyglutarate (D-2HG) in a NADPH dependent manner. These studies suggest that the accumulation of D-2HG contributes to tumorigenesis although direct evidence for oncogenic activity of D-2HG has not been established.

In the paper published in Nov issue of Cell Research, Ding and coworkers have solved crystal structures of the $IDH1^{R132H}$ homo-dimer ($IDH1^{H/H}$) and its herterodimer with wild type $IDH1^{R/H}$ [7]. This new study provides critical structural bases for the proposed dominant inhibition mechanism and also explains the new activity of the $IDH1^{H/H}$. Since IDH1 mutation is always heterozygotic and IDH1 functions as a dimer, theoretically there will be 25% each wild type and mutant homo-dimers and 50% hetero-dimers present in the tumor cells. The authors thus compared structures for all three possible forms of IDH1. Among a series of interesting findings, they uncovered a previously undefined initial isocitrate (ICT) binding state and demonstrated that a conformational change to a closed pre-transition state is essential for IDH1 catalytic activity. Restructuring of two key segments, designated as seg1 and seg2, respectively, are responsible for this open to close conformational

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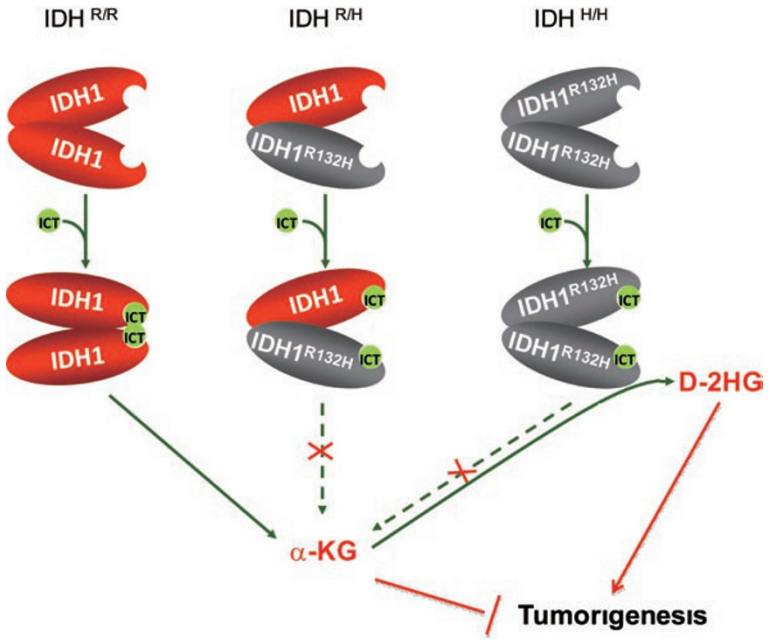


**Figure 1** Conformational switch of IDH1 dimers. Structural study predicted conformational switch of IDH1 wild type homo-dimer, IDH1$^{R132H}$ mutant homo-dimer and hetero-dimer upon ICT binding are shown.

change. For wild type IDH1 homo-dimer (IDH1$^{R/R}$), an asymmetric open conformation for one subunit and a quasi-open conformation state for another subunit are required to initiate substrate ICT binding. Binding of ICT to IDH1$^{R/R}$ induces a catalytically required close conformation, primarily by conformational changes of seg1 and seg2, to activate the enzyme. The recycling of the open-close cycles ensures IDH1 to carry out its catalytic activity continuously. However, for IDH1$^{R132H}$ mutant homo-dimer (IDH1$^{H/H}$), although two subunits form similar conformation as that of IDH1$^{R/R}$ when ICT is not bound, the binding of ICT to IDH1$^{H/H}$ is not capable of inducing a close conformation due to lack of functional seg1 and seg2 in the mutant structure. Therefore, the mutant IDH1$^{H/H}$ is enzymatically inactive. Additionally, they found that in IDH1$^{H/H}$, tyrosine139 is re-positioned in a way that it can help transferring a hydride anion from NADPH to the C2 of αKG, thus explaining the newly gained reductive activity of IDH1$^{H/H}$. The most striking findings they had were from the analysis of IDH1 hetero-dimer (IDH1$^{R/H}$). IDH1$^{R/H}$ assumes similar conformation as wild type enzyme when ICT is not bound, however, when ICT is bound to IDH1$^{R/H}$, IDH1$^{R/H}$ structure resembles the corresponding structure of IDH1$^{H/H}$ rather than IDH1$^{R/R}$, the change from an open to an close conformation is thus hindered, suggesting that IDH1$^{R/H}$ dimer would be unable to convert ICT to αKG in a way similar to wild type IDH1$^{H/H}$. These elegant observations not only provide structural basis for the dominant inhibition model but also explain the gain of function of the mutant IDH1 (Figure 1).

Although only structures for IDH1 and its mutant forms are solved, one can expect IDH2 mutations to function similarly as IDH1 mutation, owing to high degree of amino acid sequence homology (> 85%) between IDH1 and IDH2. The elucidation of the structural mechanism and thus confirming dominant inhibition of IDH1 mutation are of significant importance to understand the tumorigenic mechanism of IDH1 and IDH2 mutations. Although Dang *et al*. [6] and Ward *et al*. [3] reported significant amount of D-2HG accumulation but no significant decrease of αKG in primary gliomas and AML samples bearing IDH1 and IDH2 mutations, leaning to a conclusion that the accumulation of D-2HG is the major factor contributes to tumorigenicity of IDH1 and IDH2 mutations, the hypothesis is vulnerable due to lack of tumor cases in D-2HG aciduria patients that also accumulate high amount of D-2HG caused by D-2HG dehydrogenase defect [8]. Oncogenic activity of 2HG has not been formally demonstrated. Furthermore, the hypothesis can also be challenged by that the detected αKG levels may not reflect the actual αKG concentrations in living tumor cells given the fact that αKG is dynamically synthesized and turned over in cells. With the dominant inhibition mechanism confirmed by structural studies, a more plausible model is that both the decrease of αKG and increase of 2HG associated with mutation of IDH1 or IDH2 synergistically contribute to tumorigenesis. They may affect multiple cellular dioxygenases, such as PHD, to facilitate oncogenic transformation.

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