Pathomechanisms of Cancer-Associated Point Mutations in Isocitrate Dehydrogenase

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In Short

- IDH wildtype catalyzes the oxidative decarboxylation of ICT to α-KG
- Mutations in IDH1/2 can lead to AML and glioblastoma
- Molecular Dynamics simulations are used to study the effect of mutations on IDH1/2 dynamics
- Analysing the binding and/or releas of substrates, cofactors and products in IDH1/2

Cancer incidence in human populations is rising due to changing environmental conditions and extended life expectancy. Acute myeloid leukemia (AML) and glioblastoma, both affecting the central nervous system, contribute significantly to the annual mortality rate. Genome studies have provided insights into the impact of specific base substitutions within the genetic code, producing erroneous amino acids in isocitrate dehydrogenase proteins[1].

Isocitrate dehydrogenase (IDH) is an enzyme family responsible for the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG), utilising either nicotinamide adenine dinucleotide phosphate ($NADP^+$) or nicotinamide adenine dinucleotide (NAD^+) as cofactors. The three isoforms of IDH are classified as IDH1, IDH2, and IDH3. IDH1 is predominantly located in the cytosol, while IDH2 and IDH3 are primarily found in the mitochondria. The conversion of isocitrate (ICT) to α-ketoglutarate (α-KG) occurs in IDH1 and IDH2, employing $NADP^+$ as the cofactor, whereas IDH3 utilizes NAD^+. During this reaction, the cofactors are reduced. (Figure 1)

α-ketoglutarate (α-KG) is an intermediate in the citric acid cycle and functions as an essential cofactor for various other enzymes. However, due to the incorporation of incorrect amino acids in IDH1 or IDH2, the conversion of isocitrate to α-ketoglutarate is significantly impeded, resulting in a loss of function. Interestingly, a gain of function emerges, converting α-ketoglutarate into an oncometabolite known as R-2-hydroxyglutarate (2HG) [2 **??**].

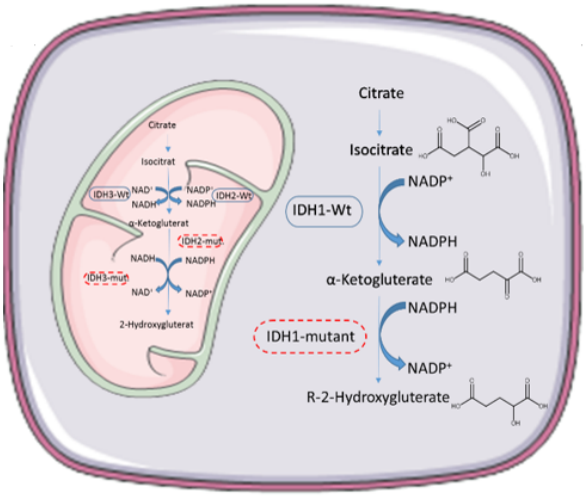

***Figure 1:** Within the cellular environment, isocitrate dehydrogenase 1 (IDH1) is predominantly located in the cytosol, whereas IDH2 and IDH3 are primarily present within the mitochondria. As integral components of the citric acid cycle, the wildtype form of IDH (IDH-Wt) catalyzes the conversion of isocitrate (ICT) to α-ketoglutarate (α-KG) in a process reliant on $NADP^+$. However, in the presence of mutations, known as mutated IDH (IDH-mut), the enzymatic activity of IDH is significantly diminished. IDH-mut gains a neomorphic function, enabling it to initiate a novel reaction that produces the oncometabolite 2-hydroxyglutarate (2HG) from α-ketoglutarate (α-KG).*

These mutations may also be believed to interfere with required conformational changes for initiating enzyme catalysis. The proposed project aims to use enhanced sampling molecular dynamics (MD) simulations to investigate conformational changes in IDH1 and IDH2 and to provide a thermodynamic description of the effects of mutations on the structure and dynamics of IDH1 on substrate or cofactor binding and product release from the enzymes. We want to study an initial substrate binding site in IDH1, and how are binding and/or releasing substrates, cofactors and products associated with conformational changes in IDH? Do the mutations lead to unresolved conformational substates?

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More Information

[1] Fantin, V. R., Dang, L., White, D. W., Gross, S., Bittinger, M. A., Driggers, E. M., Jang, H. G., Jin, S., Keenan, M. C., Marks, K. M., Yen, K. E., Ward, P. S., Prins, R. M., Liau, L. M., Bennett, B. D., Rabinowitz, J. D., Cantley, L. C., Thompson, C. B., Heiden, M. V., Su, S. M.,

Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *American Association for Cancer Research*, **70** 33–33 (2010). doi: doi.org/10.1158/1538-7445.AM10-33

[2] Figueroa, M. E., Abdel-Wahab, O., Lu, C., Ward, P. S., Patel, J., Shih, A., Li, Y., Bhagwat, N., Vasanthakumar, A., Fernandez H. F., Tallman, M. S., Sun, Z., Wolniak, K., Peeters, J. K., Liu, W., Choe, S. E., Fantin, V. R., Paietta, E., Löwenberg, B., Licht, J. D., Godley, L. A., Delwel, R., Valk, P. M. J., Thompson, C. B., Levine, R. L., Melnick, A., Leukemic IDH1 and IDH2 Mutations Result in a Hypermethylation Phenotype, Disrupt TET2 Function, and Impair Hematopoietic Differentiation. *Cancer Cell*, **18** 553-567 (2010). doi:doi.org/10.1016/j.ccr.2010.11.015

[3] Yang, B., Zhong, C., Peng, Y., Lai, Z., Ding, J., Molecular mechanisms of "'off-on switch"' of activities of human IDH1 by tumor-associated mutation R132H. *Cell Research*, **20** 1188–1200 (2010). doi:doi.org/10.1038/cr.2010.145

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