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COMMENTARY

Oncometabolite modification of Keap1 links GSTZ1 deficiency with cancer

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Abstract Metabolic abnormalities are emerging as an active driver to the development, progression and metastasis of various tumors. In the recent issue of the *EMBO Journal*, Yang and colleagues identified that succinylacetone (SA) could act as an oncometabolite and that accumulation of SA activates the NRF2/IGF1R axis in hepatocellular carcinoma (HCC) development. These discoveries not only yield great insights in the understanding of tumor biology, but also hold significant clinical ramifications, as these findings may pave a new way for the early diagnosis and treatment of HCC.

Metabolic reprogramming to support and enable cancer cells' rapid proliferation, continuous growth, survival in harsh conditions, invasion, metastasis, and resistance to cancer treatments was enumerated in 2011 by Hanahan and Weinberg as one of the ten cancer hallmarks.[1] Metabolic abnormalities have long been viewed as a mere epiphenomenon of cancer rather than an active contributor to tumorigenesis and cancer development. The discovery that germline mutations in fumarate hydratase (FH) and succinate dehydrogenase (SDH), two enzymes involved in the Krebs cycle, are associated with an increased risk of tumorigenesis established the concept of "oncometabolites" and paved the way for the study of metabolites as oncogenic factors.[2] Technological advances such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) imaging, and application of next-generation sequencing (NGS) technologies in the cancer genomics have substantially increased our knowledge of the interplay between the oncometabolites and tumor initiation/progression; however, these linkages require further exploration to better understand the cancer biology.

In the recent issue of the *EMBO Journal*, Yang and colleagues indicated that succinylacetone (SA) could act as an oncometabolite and that accumulation of SA activates the NRF2/IGF1R axis in hepatocellular carcinoma (HCC)[3]. The authors initially analyzed GEO and TCGA public datasets and found that glutathione S-transferase zeta 1 (GSTZ1) mRNA expression was significantly decreased in human liver

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cancer tissues compared with normal liver tissues. GSTZ1, also known as maleylacetoacetate isomerase (MAAI), is a member of the glutathione S-transferase (GSTs) superfamily. It catalyzes the conversion of maleylacetoacetate (MAA) to fumarylacetoacetate (FAA), which is one of the steps in the phenylalanine/tyrosine degradation pathway.[4] Gstz1 knockout mice accumulate MAA and SA, suffer from constitutive oxidative stress and have an active nuclear factor erythroid 2-related factor 2 (NRF2) antioxidant response pathway.[5] Although recent research shows that GSTZ1 is downregulated in HCC and upregulated in breast cancer,[6] which indicates that dysregulation of GSTZ1 may be involved in the tumorigenesis in humans, the underlying mechanism remain(s) elusive. The authors further showed that GSTZ1 exerts its role as a tumor suppressor *in vitro* and *in vivo*, and confirmed SA accumulation and NRF2 activation in GSTZ1 knockout mice.

Adam et al[7] and Mills et al[8] demonstrated that fumarate or itaconate could activate NRF2 by alkylating its negative regulator, KEAP1, on cysteine residues. This finding begs the question, could SA interact with KEAP1 in a similarly way? To address this question, Yang and colleagues directly analyzed KEAP1 modification by MS/MS. They identified KEAP1 SA modification at residues Cys23, Cys319, Cys406, and Cys513. They further performed site-directed mutagenesis experiments, which indicated that Cys406 of KEAP1 plays a critical role in sensing SA.

In an analysis of transcriptome profiling of GSTZ1-overexpressing cells, Yang and colleagues found that IGF1R is significantly induced by NRF2 and activates an anti-apoptotic pathway. The authors went on to show that phenylalanine overloading and exogenous SA promote the binding of SP1 to the IGF1R promoter and increase IGF1R transcription. They further demonstrated that treatment with picropodophyllin, a specific kinase inhibitor of IGF1R, or brusatol, an inhibitor of NRF2, could reverse the tumor promoting effect of Gstz1 depletion in the mouse model.

The discoveries of Yang and colleagues have significant implications, as they reveal a novel oncometabolite that accumulates to activate NRF2, induce IGF1R expression, and subsequently promote the progression of HCC. The findings that an IGF1R or NRF2 inhibitor could mitigate the adverse effect of GSTZ1 deficiency are also of clinical significance, as they provide potential targets for personalized therapy in HCC. Recently, Viraj et al reported that loss of NRF2 glycation activates the NRF2 pathway and triggers HCC development, which emphasizes the importance of the NRF2 pathway and its connection with metabolites from a different angle.[9] Additional experiments are warranted to explore the diverse mechanisms that regulate this pathway. In a broader context, this study expands our knowledge of how an aberrant cancer transcriptome disrupts metabolism and contributes to tumorigenesis and cancer development. Undoubtedly, identification of new oncometabolites and a better understanding of the interaction between metabolism and cancer is nonetheless a substantial and ongoing challenge.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646—674.
2. Yang M, Soga T, Pollard PJ. Oncometabolites: linking altered metabolism with cancer. *J Clin Investig*. 2013;123:3652—3658.
3. Yang F, Li J, Deng H, et al. GSTZ1-1 Deficiency Activates NRF2/IGF1R Axis in HCC via Accumulation of Oncometabolite Succinylacetone. *EMBO J*. 2019;38(15). https://doi.org/10.15252/embj.2019101964.
4. Fernandez-Canon JM, Penalva MA. Characterization of a fungal maleylacetoacetate isomerase gene and identification of its human homologue. *J Biol Chem*. 1998;273:329—337.
5. Blackburn AC, Matthaei KI, Lim C, et al. Deficiency of glutathione transferase zeta causes oxidative stress and activation of antioxidant response pathways. *Mol Pharmacol*. 2006;69:650—657.
6. Jahn SC, Solayman MH, Lorenzo RJ, Langaee T, Stacpoole PW, James MO. GSTZ1 expression and chloride concentrations modulate sensitivity of cancer cells to dichloroacetate. *Biochim Biophys Acta*. 2016;1860:1202—1210.
7. Adam J, Hatipoglu E, O'Flaherty L, et al. Renal cyst formation in Fh1-deficient mice is independent of the Hif/Phd pathway: roles for fumarate in KEAP1 succination and Nrf2 signaling. *Cancer Cell*. 2011;20:524—537.
8. Mills EL, Ryan DG, Prag HA, et al. Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1. *Nature*. 2018;556:113—117.
9. Sanghvi VR, Leibold J, Mina M, et al. The oncogenic action of NRF2 depends on de-glycation by fructosamine-3-kinase. *Cell*. 2019;178:807—819 e821.