Editorial Commentary

Vitamin C's essential role in DNA and histone demethylation and a preclinical rationale for its therapeutic high-dose potential in renal cell carcinoma

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Renal cell carcinoma (RCC) accounts for 2–3% of all malignancies in adults and 85% of all cases of adult kidney cancer (1). With an insidious disease course, nearly 25–30% of patients will present with metastatic RCC (2). Otherwise, 30% of patients undergoing nephrectomy progress to distant metastasis or local recurrence during follow-up (3). It is important to be able to predict the risk of early RCC recurrence (4,5). The last two decades have witnessed the development of a number of targeted therapies including tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors, but these advancements have largely ignored first-line and subsequent therapies for patients with metastatic RCC (6). It is clear that there is a need for new therapy strategies in advanced RCC.

In the last issue of the *Journal of Clinical Investigation* (7), the authors, via Shenoy *et al.*, analyzed 576 cases of primary clear cell RCC (ccRCC), the most common cell type in RCC. They also noted that samples with the loss of 5-hydroxymethylcytosine (5hmC) were strongly associated with fulminant clinico-pathologic features and independent adverse prognostic factor. Loss of 5hmC could also predict the reduced progression-free survival of non-metastatic disease after resection. The study also provides a preclinical rationale for exploring the therapeutic potential of ascorbic acid (AA), especially in high doses, for ccRCC (7). In another study (8), the authors reported that ccRCC with widespread aberrant cytosine methylation and loss of 5hmC was associated with recurrence. It is well-known that DNA methylation at cytosine bases in the genome is tightly linked to gene expression and modified cytosines, resulting in a G/T mismatch, and has long been recognized as a hotspot for mutations (9).

Shelar *et al.* noted that the reduced expression of L-2-hydroxyglutarate (L-2-HG) dehydrogenase (L2HGDH) in RCC cause the elevation of L-2-HG (10). The authors simultaneously identified that elevations of L-2-HG in RCC may mediate DNA and histone demethylation in their study (10). In L2HGDH knockdown model (6), the oncometabolite of L-2-HG accumulated in the immortalized renal epithelial cells. Also, transfection of wild type L2HGDH into L2HGDH deficient cancer cells demonstrated a reduced migratory phenotype and growth rate of the cancer cells (6). Otherwise, high L-2-HG tumors demonstrated lower DNA levels of 5hmC (11), and this finding is consistent with L-2-HG-mediated inhibition of ten eleven translocation (TET) enzymes to convert 5-methylcytosine (5mC) to 5hmC (12). L2HGDH reconstitution in RCC cells may decrease L-2-HG level and promote 5hmC accumulation (12). The TET enzymes enhance oxidization of 5mCs and promote locus-specific

reversal of DNA methylation. *TET* genes, especially *TET2*, are frequently mutated in various cancers (11). As is known, lower 5hmC is related to a loss of TET activity and a markedly lower level of 5hmC is also noted in a variety of human cancers (13-16). The loss of TET activity may be as a result of down-regulation of *TET* gene expression, inactivating mutations, or an insufficient supply of TET co-factors, such as vitamin C. Appropriate vitamin C might be important to the maintenance of normal 5hmC levels. More recent studies revealed that vitamin C addition inspired DNA demethylation through enhanced TET activity (17,18).

Vitamin C has various biologic effects in almost all tissues of the body and enhances the activity of numerous enzymes (19). Vitamin C deficiency has been suspected to play a central role in carcinogenesis for more than fifty years. In addition to this, several recent studies have suggested that vitamin C in combination with chemotherapy can enhance the effects of chemotherapy and reduce the side effects (20), without affecting the anti-cancer actions of the chemotherapy (21). These studies also suggest an increased need for vitamin C in cancer patients or individuals with epigenetic regulator mutations (20). Interestingly, the reprograming cell enriched with vitamin C presented diminished levels of DNA cytosine methylation (18-21). Emerging functional studies have made the prospective mechanisms of vitamin C in varying cancer cells clear. The novel potential action of vitamin C in cancer treatment is derived from the activation of TET and Jumonji dioxygenases which remove the methyl groups from DNA and histones (21-24), this process is known as demethylation. Both pre-clinical and clinical studies indicate that higher doses (>50 g/d) of intravenous vitamin C, prescribed with more frequent dosing and with the longer duration of over years rather than a few weeks or months, exhibit enhanced efficacy and anti-cancer activity (21,22); even lower doses (10 g/d) of intravenous vitamin C can be sufficient for reducing symptoms of chemotherapy side-effects and improving quality of life. In a study on pre-leukemic clonal hematopoiesis, the investigators also emphasized that adequate nutritional ascorbate might compensate TET activity insufficiency (25).

Aberrant epigenetic regulation is a common finding in all cancers and new drugs have been developed to improve the catalytic activity of histone demethylases. We suppose that the basic biologic functions of vitamin C, via the recovery of methylation of DNA and histones, may have effects far beyond treatment in ccRCC.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Purdue MP, Moore LE, Merino MJ, et al. An investigation of risk factors for renal cell carcinoma by histologic subtype in two case-control studies. Int J Cancer 2013;132:2640-7.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2018; 68:7-30.
3. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii49-56.
4. Sun M, Shariat SF, Cheng C, et al. Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. Eur Urol 2011;60:644-61.
5. Eichelberg C, Junker K, Ljungberg B, et al. Diagnostic and prognostic molecular markers for renal cell carcinoma: a critical appraisal of the current state of research and clinical applicability. Eur Urol 2009;55:851-63.
6. Hart S, Gupta G. Editorial on "Biochemical and Epigenetic Insights into L-2-Hydroxyglutarate, a Potential Therapeutic Target in Renal Cancer". Ann Transl Med 2018;6 Suppl 2:S105.
7. Shenoy N, Bhagat TD, Cheville J, et al. Ascorbic acid-induced TET activation mitigates adverse hydroxymethylcytosine loss in renal cell carcinoma. J Clin Invest 2019;130:1612-25.
8. Mendoza-Pérez J, Gu J, Herrera LA, et al. Prognostic significance of promoter CpG island methylation of obesity-related genes in patients with nonmetastatic renal cell carcinoma. Cancer 2017;123:3617-27.
9. Rasmussen KD, Helin K. Role of TET enzymes in DNA methylation, development, and cancer. Genes Dev 2016;30:733-50.
10. Shelar S, Shim EH, Brinkley GJ, et al. Biochemical and Epigenetic Insights into L-2-Hydroxyglutarate, a Potential Therapeutic Target in Renal Cancer. Clin Cancer Res 2018;24:6433-46.
11. Rasmussen KD, Helin K. Role of TET enzymes in

DNA methylation, development, and cancer. Genes Dev 2016;30:733-50.
12. Shim EH, Livi CB, Rakheja D, et al. L-2-Hydroxyglutarate: an epigenetic modifier and putative oncometabolite in renal cancer. Cancer Discov 2014;4:1290-8.
13. Haffner MC, Chaux A, Meeker AK, et al. Global 5-hydroxymethylcytosine content is significantly reduced in tissue stem/progenitor cell compartments and in human cancers. Oncotarget 2011;2:627-37.
14. Jin SG, Jiang Y, Qiu R, et al. 5-hydroxymethylcytosine is strongly depleted in human cancers but its levels do not correlate with IDH1 mutations. Cancer Res 2011;71:7360-5.
15. Kraus TF, Globisch D, Wagner M, et al. Low values of 5-hydroxymethylcytosine (5hmC), the 'sixth base,' are associated with anaplasia in human brain tumors. Int J Cancer 2012;131:1577-90.
16. Kudo Y, Tateishi K, Yamamoto K, et al. Loss of 5-hydroxymethylcytosine is accompanied with malignant cellular transformation. Cancer Sci 2012;103:670-6.
17. Blaschke K, Ebata KT, Karimi MM, et al. Vitamin C induces Tet-dependent DNA demethylation and a blastocyst-like state in ES cells. Nature 2013;500:222-6.
18. Hore TA, von Meyenn F, Ravichandran M, et al. Retinol and ascorbate drive erasure of epigenetic memory and enhance reprogramming to naïve pluripotency by complementary mechanisms. Proc Natl Acad Sci U S A 2016;113:12202-7.
19. Gillberg L, Ørskov AD, Liu M, et al. Vitamin C - A new player in regulation of the cancer epigenome. Semin Cancer Biol 2018;51:59-67.
20. Jacobs C, Hutton B, Ng T, et al. Is there a role for oral or intravenous ascorbate (Vitamin C) in treating patients with cancer? A systematic review. Oncologist 2015;20:210-23.
21. Carr AC, Cook J. Intravenous Vitamin C for Cancer Therapy - Identifying the Current Gaps in Our Knowledge. Front Physiol 2018;9:1182.
22. Lee SJ, Jeong JH, Lee IH, et al. Effect of High-dose Vitamin C Combined with Anti-cancer Treatment on Breast Cancer Cells. Anticancer Res 2019;39:751-8.
23. Tahiliani M, Koh KP, Shen Y, et al. Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. Science 2009;324:930-5.
24. Tsukada Y, Fang J, Erdjument-Bromage H, et al. Histone demethylation by a family of JmjC domain-containing proteins. Nature 2006;439:811-6.
25. Agathocleous M, Meacham CE, Burgess RJ, et al. Ascorbate regulates haematopoietic stem cell function and leukaemogenesis. Nature 2017;549:476-81.

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