RESEARCH HIGHLIGHT

R-2-HG assists IDH1-mutant solid tumors by promoting angiogenesis

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Mutations in isocitrate dehydrogenase lead to the elevated production of the oncometabolite R-2-hydroxyglutarate (R-2-HG), which, albeit insufficient for malignant transformation, exerts intrinsic and paracrine effects that promote tumor propagation and progression. In a recent paper of *Cell Research*, Wang and colleagues describe a novel extrinsic proangiogenic function of tumor-secreted R-2-HG that, upon uptake by the sodium-dependent glutamate transporter SLC1A1 in tumor endothelial cells, promotes mitochondrial respiration and ATP production leading to enhanced tip cell activity and endothelial cell migration.

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are homodimeric enzymes that convert isocitrate to α-ketoglutarate (α-KG) (Fig. 1a), which besides being a constituent of the tricarboxylic acid (TCA) cycle, is also a cofactor of several histone-modifying enzymes to promote cell differentiation processes. However, a single somatic arginine amino acid substitution in IDH1 or IDH2 changes the catalytic activity and enables mutated IDH1/2 (IDH^{mut}) to convert α-KG to R-2-hydroxyglutarate (R-2-HG) (Fig. 1a). R-2-HG shares oncometabolic characteristics because it inhibits α-KG-dependent dioxygenases necessary for DNA and histone methylation, triggering genetic instability and epigenetic alterations that impair differentiation efficiency and hypoxic responsiveness.[1,2] Nonetheless, IDH^{mut} itself is insufficient to drive malignant transformation in cells raising the question of whether additional non-tumor cell-autonomous effects of the oncometabolite R-2-HG contribute to tumor initiation and progression. Indeed, R-2-HG levels not only can be detected in tumor cells but also in the extracellular tumor space and body fluids, where they are substantially higher than in tumor cells.[3] This was first considered as a mere adaptation mechanism of the tumor cells to maintain a metabolic equilibrium and cellular fitness when intracellular R-2-HG became too high. Recent evidence, however, demonstrated that the poorly cell-penetrative R-2-HG could be transported into intratumoral immune cells via specific proteins of the solute carrier (SLC) family, where it triggers immunosuppressive rewiring. In myeloid cells, R-2-HG alters the amino acid metabolism and leads to degradation of tryptophan and subsequent activation of the aryl hydrocarbon receptor (AHR) driving macrophage reprogramming and immunosuppression.[4] In T cells, R-2-HG induces suppression of anti-tumor T-cell immunity by restricting nuclear factor of activated T cells (NFAT) activity and polyamine biosynthesis.[5] Thus, one can envision that other resident cell constituents within the tumor microenvironment are also capable of taking up extracellular R-2-HG, which could instigate additional tumor-promoting effects. In a recent paper of *Cell Research*, Wang and colleagues asked whether R-2-HG can affect tumor endothelial cells (ECs) because the vascular compartment undergoes continuous remodeling and expansion, in part to satisfy the tumor's demands of nutrients and oxygen.[6]

Using PDX tumor models for cholangiocarcinoma and glioblastoma, the authors observed increased tumor vascularization and enhanced tumor growth in IDH^{mut} compared to wild-type tumors. Direct co-cultures of HUVECs and primary human retinal ECs with either IDH^{mut} tumor cells or R-2-HG enhanced their ability to migrate, sprout and form vascular tubes. Vascular sprouting is a dynamic process by which an endothelial tip cell with its extending filopodia and lamellipodia moves at the front of a sprouting vessel towards a gradient of proangiogenic factors that are commonly induced by low oxygen tension. Tip cells are followed by proliferating stalk cells that elongate the sprout until vessels coalesce. These complex angiogenic processes are not only regulated by growth factor signals but also by metabolic programs since they are energy-demanding. Recently, ECs have been shown to favor glycolysis during angiogenesis because glycolytic enzymes, including PFKFB3, compartmentalize with actin filaments in filopodia and lamellipodia providing localized rapid ATP production and enabling cytoskeleton remodeling necessary for tip cell migration.[7] Wang and colleagues elegantly demonstrated that R-2-HG was transferred into the endothelium by the endothelial-specific glutamate transporter SLC1A1 and further translocated by SLC1A1 to mitochondria, where it increased mitochondrial respiration and ATP production. Subsequent cytoskeletal rearrangement in tip cells accounted for heightened vessel sprouting without affecting EC proliferation (Fig. 1b). In vivo experiments confirmed that blood vessels of $IDH1^{mut}$ tumors were more abnormal with less pericyte coverage, although tumors appeared surprisingly less hypoxic likely owing to the increased vessel density. Importantly, these IDH^{mut} vascular effects were abrogated in SLC1A1-deficient mice confirming that R-2-HG function in ECs is SLC1A1-dependent. The effects of R-2-HG are remarkably specific because its mirrored configuration has been shown to have opposing effects (Fig. 1a). While R-2-HG promotes EC migration, the chiral S-2-HG, which is intrinsically induced by the transcription factor FOXO1, keeps ECs in a

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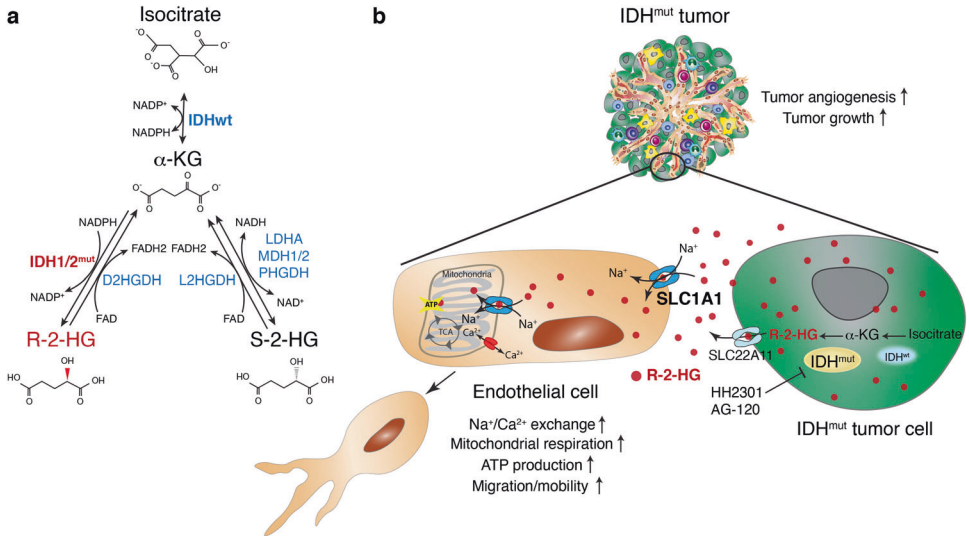

Fig. 1 R-2-HG rewires angiogenesis in IDH-mutant tumors. a Generation of R-2-HG and L-2-HG from isocitrate. **b** IDH mutation leads to accumulation of R-2-HG in tumor cells and in the tumor microenvironment. The EC-specific SLC1A1 transporter imports R-2-HG into ECs, which produce ATP by mitochondrial respiration. Local ATP supply supports EC cytoskeleton rearrangement, EC migration and tumor angiogenesis. Inhibition of R-2-HG production by IDH^{mut} inhibitors, HH2301 or AG-120, blocks R-2-HG-dependent tumor angiogenesis.

quiescent state by restricting EC proliferation and vascular expansion.[8] Another layer of complexity relates to the cell type-specific effects of R-2-HG. R-2-HG in ECs promotes ATP production, whereas it has opposing effects in T-cells because it inhibits ATP synthase, thereby reducing ATP levels and T cell proliferation.[5] Moreover, R-2-HG uptake is regulated by cell type-specific SLC transporters, which enables R-2-HG to display heterogeneous effects in a cell type-specific manner. While SLC1A1 shuttles R-2-HG into ECs, SLC13A3 transports R-2-HG in T-cells, and SLC13A3, SLC22A6, and SLC22A11 in renal cells and astrocytes, respectively.

Finally, the authors explored the therapeutic relevance of their mechanistic findings and provided encouraging translational data by comparing the approved $IDH1^{mut}$ inhibitor AG-120 to the new and more selective inhibitor HH2301 (Haihe Biopharma Co.) in three PDX IDH^{mut} cholangiocarcinoma models.[9] HH2301 more efficiently reduced tumor and blood vessel growth and enhanced vessel normalization and pericyte coverage in PDX models in a SLC1A1-dependent manner (Fig. 1b). These observations suggest that IDH^{mut} inhibitors affect tumor growth retardation not by tumor cell-intrinsic mechanism but by affecting the tumor vasculature. However, it is unknown whether IDH^{mut} inhibitors may also act by impairing the effects of R-2-HG in innate and adaptive immune cells. Further, it will be very interesting to see whether R-2-HG can be taken up by other tumor microenvironment constituents like pericytes and cancer-associated fibroblasts, or even normal resident epithelial cells, and affect their functions.

Overall, Wang and colleagues have provided new and exciting insight into the extrinsic function of R-2-HG by enhancing tumor angiogenesis in IDH^{mut} tumors, identified SLC1A1 as an endothelial-specific gatekeeper of R-2-HG and demonstrated superior therapeutic benefits of a new and more potent IDH1 inhibitor which could potentially become more efficacious than AG-120 for patients with IDH^{mut} cholangiocarcinomas, and potentially other IDH^{mut} tumors.

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ADDITIONAL INFORMATION

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