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EDITORIAL

Potent immunosuppressive effects of the oncometabolite *R*-2-hydroxyglutarate

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ABSTRACT

Somatic gain-of-function mutations in isocitrate dehydrogenase (NADP(+)) 1, cytosolic (*IDH1*) or isocitrate dehydrogenase (NADP(+)) 2, mitochondrial (*IDH2*) are *bona fide* oncogenic drivers of acute myeloid leukemia and glioma because the neomorphic enzymes catalyze the synthesis of R-2-hydroxylutarate (*R*-2-HG), an oncometabolite with robust epigenetic effects. Recent data indicate that *R*-2-HG released by malignant cells can accumulate in the extracellular space and be taken up by T lymphocytes, ultimately compromising their capacity to mediate anticancer immune responses. Thus, *R*-2-HG drives oncogenesis and tumor progression not only as a cancer cell-autonomous epigenetic modifier, but also as an immunosuppressive metabolite. Chemical inhibitors of mutant IDH1 and IDH2, which currently are under clinical evaluation, may therefore mediate dual anticancer effects by targeting cancer cells and, at the same time, relieving *R*-2-HG-mediated immunosuppression.

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R-2-hydroxyglutarate (*R*-2-HG) is a *bona fide* 'oncometabolite' because it accumulates in (pre-) malignant cells as a consequence of a somatic gain-of-function mutations and is causally involved in malignant transformation and tumor progression.[1] In particular, gain-of-function mutations in isocitrate dehydrogenase (NADP(+)) 1, cytosolic (*IDH1*) or isocitrate dehydrogenase (NADP(+)) 2, mitochondrial (*IDH2*), which are particularly prevalent among acute myeloid leukemia (AML) and glioma patients,[2,3] result in the acquisition of a neomorphic enzymatic function that catalyzes the direct conversion of alpha-ketoglutarate (α-KG, a key intermediate of the Krebs cycle) into *R*-2-HG.[4–6] Intracellular *R*-2-HG accumulation coupled to α-KG depletion has oncogenic effects because it inhibits histone lysine demethylases (KDMs) and the TET family of DNA hydroxylases,[7,8] resulting in histone hypermethylation, epigenetic programming and disruption of normal stem cell differentiation coupled to the acquisition of additional mutations.[9] Until recently, *R*-2-HG has received considerable attention also because it can be detected in body fluids (including the plasma and cerebrospinal fluid) and organs (by nuclear magnetic resonance), hence constituting a biomarker that can be monitored non-invasively for diagnostic purposes as well as for measuring the therapeutic effects of clinically relevant IDH1 or IDH2 inhibitors.[10,11] Recent clinical data from a Phase I trial demonstrate indeed that ivosidenib, a chemical inhibitor of mutant IDH1 can be safely administered to AML patients and is associated with an objective response rate of 40%.[12] These findings constituted the ground for the approval of ivosidenib (commercialized under the name of Tbsovo®) by the US Food and Drug Administration for the treatment of relapsed or refractory AML.[13]

Although cancer has long been considered as a cellular disease driven by (epi-)genetic alterations, it has recently become clear that malignant cells emerge, progress and respond to therapy in the context of a complex and bidirectional crosstalk with the host immune system.[14] In particular, tumors become clinically manifest only when immunosurveillance fails, which can occur for different reasons that include, but are not limited to: (i) primary immune defects rendering the host immune system unable to recognize (pre-)malignant cells, (ii) active secretion by (pre-)malignant cells of inhibitory factors that interfere with immune functions locally or systemically; or (iii) evolution of (pre-)malignant cells towards a state of reduced antigenicity of adjuvanticity.[15–18] In this context, it appeared logical that *R*-2-HG would mediate some immunosubversive effects.

Recent data confirm that *R*-2-HG may mediate both direct and indirect immunosuppressive effects (Figure 1). First, *R*-2-HG limits the ability of cancer cells to secrete C-X-C motif chemokine ligand 10 (CXCL10), thus reducing the recruitment of T cells to the tumor bed.[19,20] Second, *R*-2-HG can be taken up by non-malignant cells of the tumor microenvironment, including cancer-associated fibroblasts and myeloid cells, which respond to *R*-2-HG with increased proliferation rates and activation of the pro-inflammatory transcription factor NF-κB, respectively,[21,22] ultimately generating a microenvironment that favors tumor progression.[23] Third, *R*-2-HG and its enantiomer (*S*-2-HG) can be incorporated by immune effectors and mediate immunosuppressive effects. Reportedly, *S*-2-HG enters

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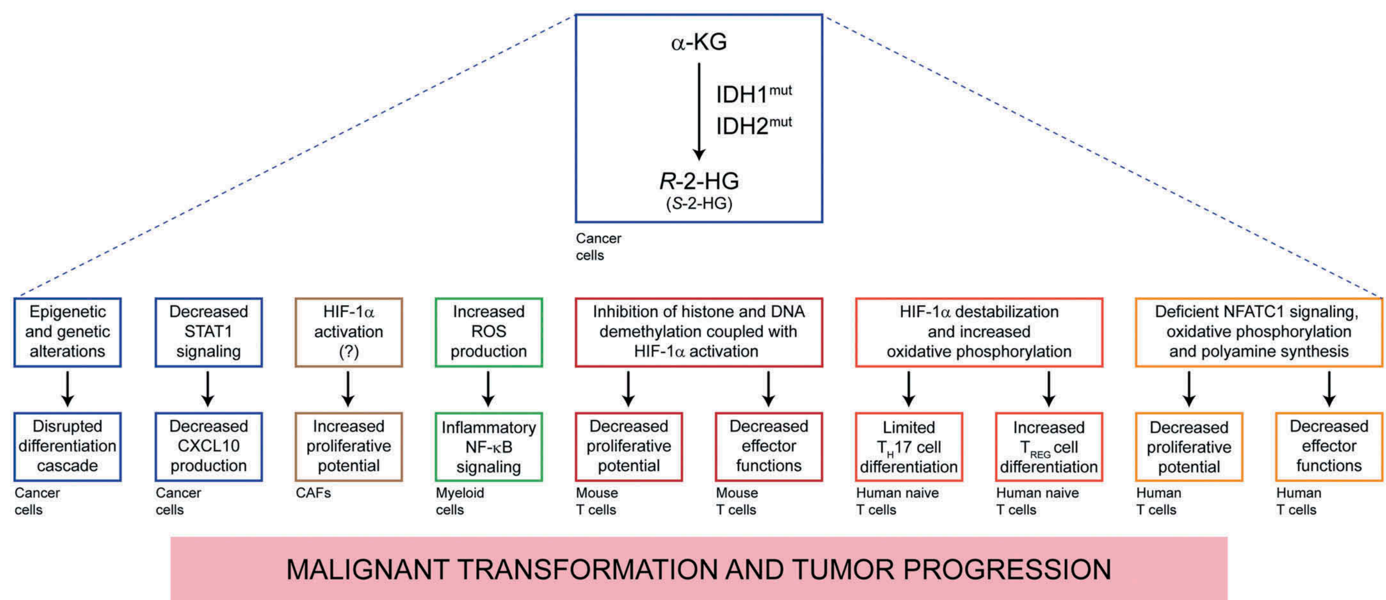

Figure 1. Dual action of *R*-2-HG in the pathogenesis of cancers with *IDH1* or *IDH2* mutations. Gain-of-function mutations in isocitrate dehydrogenase (NADP(+)) 1, cytosolic (*IDH1*) or isocitrate dehydrogenase (NADP(+)) 2, mitochondrial (*IDH2*) drive the synthesis of *R*-2-hydroxylutarate (*R*-2-HG). The accumulation of *R*-2-HG (and to some extent its enantiomer *S*-2-HG) supports oncogenesis and tumor progression not only by causing the epigenetic reprogramming of (pre-)malignant cells, but also by favoring the establishment of an immunosuppressive microenvironment. The therapeutic activity of IDH1 inhibitors may therefore involve a robust immunological component. α-KG, alpha-ketoglutarate; CXCL10, C-X-C motif chemokine ligand 10; HIF-1α (official name, HIF1A), hypoxia inducible factor 1 subunit alpha; NFATC1, nuclear factor of activated T cells 1; ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1; T_{REG}, regulatory T.

activated mouse $CD8^+$ T cells to inhibit histone and DNA demethylation and activate hypoxia inducible factor 1 subunit alpha (HIF1A, best known as HIF-1α), resulting in suppressed T cell proliferation and effector functions.[24] Conversely, *R*-2-HG has been suggested to destabilize HIF-1α in human naïve T cells to boost oxidative phosphorylation, culminating with increased differentiation towards $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells at the expenses of T_H17 helper cells.[25] Yet another recent paper indicates that *R*-2-HG can be taken up by human T cells through the plasma membrane transporter solute carrier family 13 member 3 (SLC13A3) irrespective of their activation status, hence interfering with nuclear factor of activated T cells 1 (NFATC1) signaling and limiting proliferative potential and effector functions.[26]

Intriguingly, these effects are at least partially mediated by some degree of ATP shortage resulting from inhibition of oxidative phosphorylation,[27] because they can be reverted by supplementation of *R*-2-HG-treated T lymphocytes with a cell-permeable variant of ATP.[26] Moreover, they are tied to a pathway in which *R*-2-HG inhibits the activity of ornithine decarboxylase (ODC), the rate-limiting enzyme for polyamine biosynthesis, either directly or indirectly upon ODC phosphorylation by 5′-AMP-activated protein kinase (AMPK). Thus, the polyamine putrescine can interfere with the ability of *R*-2-HG to suppress T cell proliferation *in vitro*.[26] Unfortunately, it has not been determined whether polyamines would negate the immunosuppressive effects of *IDH1* or *IDH2* mutations *in vivo*. This stands out as a feasible strategy because spermidine has potent immunostimulatory effects that can be harnessed for boosting natural and therapy-driven anticancer immunosurveillance.[28,29]

Based on these observations, it is tempting to speculate (pending mechanistic validation) that the clinically efficacy of IDH1 (and presumably also IDH2) inhibitors may be ascribed to a dual effect, namely (i) a cancer cell-autonomous action that interferes with *R*-2-HG-dependent epigenetic reprogramming, and (ii) the reinstatement of anticancer immunosurveillance. Thus, IDH1 inhibitors do not seem to escape the general rule that anticancer agents can only be successful if they favor anticancer immune responses.[30,31] Future will tell whether IDH1 inhibitors can be combined with other immunotherapeutic agents to improve the clinical management of patients with AML or glioma.

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