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Review

Antagonistic functional duality of cancer genes

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ABSTRACT

Cancer evolution is a stochastic process both at the genome and gene levels. Most of tumors contain multiple genetic subclones, evolving in either succession or in parallel, either in a linear or branching manner, with heterogeneous genome and gene alterations, extensively rewired signaling networks, and addicted to multiple oncogenes easily switching with each other during cancer progression and medical intervention. Hundreds of discovered cancer genes are classified according to whether they function in a dominant (oncogenes) or recessive (tumor suppressor genes) manner in a cancer cell. However, there are many cancer "gene-chameleons", which behave distinctly in opposite way in the different experimental settings showing antagonistic duality. In contrast to the widely accepted view that mutant $NADP^+$-dependent isocitrate dehydrogenases 1/2 (*IDH1/2*) and associated metabolite 2-hydroxyglutarate (R)-enantiomer are intrinsically "the drivers" of tumourigenesis, mutant IDH1/2 inhibited, promoted or had no effect on cell proliferation, growth and tumorigenicity in diverse experiments. Similar behavior was evidenced for dozens of cancer genes. Gene function is dependent on genetic network, which is defined by the genome context. The overall changes in karyotype can result in alterations of the role and function of the same genes and pathways. The diverse cell lines and tumor samples have been used in experiments for proving gene tumor promoting/suppressive activity. They all display heterogeneous individual karyotypes and disturbed signaling networks. Consequently, the effect and function of gene under investigation can be opposite and versatile in cells with different genomes that may explain antagonistic duality of cancer genes and the cell type- or the cellular genetic/context-dependent response to the same protein. Antagonistic duality of cancer genes might contribute to failure of chemotherapy. Instructive examples of unexpected activity of cancer genes and "paradoxical" effects of different anticancer drugs depending on the cellular genetic context/signaling network are discussed.

Contents

Abbreviations: BCR-ABL, breakpoint cluster region-Abelson tyrosine-protein kinase; CD95/FAS, cluster of differentiation 95/cell surface death receptor; DDR1, discoidin domain receptor tyrosine kinase 1; EGFR, epidermal growth factor receptor tyrosine kinase; EF1A2, eukaryotic translation elongation factor 1 alpha; ESPL1, extra spindle pole bodies homolog 1; FGF18, fibroblast growth factor 18; HYAL1/2, hyaluronoglucosaminidase 1/2; IDH1/2, isocitrate dehydrogenases 1/2; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, tyrosine kinase receptor; LCK, lymphocyte-specific protein tyrosine kinase; LTF, lactotransferrin; L1MD1, L1M domain containing gene 1; MAPK, mitogen-activated protein kinase; MTOR, mechanistic target of rapamycin serine/threonine kinase; NQO2, NAD(P)H dehydrogenase, quinone 2; PDGFRβ, pletelet derived growth factor receptor beta; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RNASET2, ribonuclease T2; STAT1, signal transducer and activator of transcription 1; TGFB3, transforming growth factor, beta 3; VHL, von Hippel-Lindau tumor suppressor, E3 ubiquitin protein ligase; WNT1, wingless-type MMTV integration site family, member 1.

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1. Introduction

The Network of Cancer Genes (NCG 3.0, http://bio.ifom-ieo-campus.it/ncg) collects information on hundreds of cancer genes that have been found mutated in different cancer types. These genes were collected from the Cancer Gene Census (www.sanger.ac.uk/genetics/CGP/Census) as well as from genome and whole exome screenings of cancer samples (D'Antonio et al., 2012). Tumor-promoting effect of cancer genes as well as mutagenic or non-mutagenic carcinogens is directly linked to chromosome instability. Chromosome instability significantly correlates with tumorigenic potential of cells, tumor progression, patient survival, treatment sensitivity, and the risk of acquired therapy resistance (reviewed in Stepanenko and Kavsan, 2012a,b, 2013). Cancer genes are often classified according to whether they function in a dominant or recessive manner in a tumor cell. Dominant cancer genes (also known as oncogenes) are usually constitutively activated by the gain-of-function mutations, which stimulate cell growth, division, and survival. Loss-of-function mutations in recessive cancer genes (also known as tumor suppressor genes) usually result in inactivation of the encoded protein that normally helps to prevent unrestrained cellular growth and promotes DNA repair and cell cycle checkpoint activation (Lee and Muller, 2010). However, there are many gene-"chameleons", which can be attributed to both oncogenes and tumor suppressors, they behave distinctly in the different experimental settings demonstrating antagonistic functional duality.

2. Gene-"chameleons"

One of the supportive examples of gene-"chameleons" with opposite effects in tumor cells is $NADP^+$-dependent isocitrate dehydrogenases 1 and 2 (IDH1/2). Recurrent mutations in *IDH1/2* genes are found in several (e.g., glioma and acute myeloid leukemia) but not in most solid tumor types (reviewed in Oermann et al., 2012; Reitman and Yan, 2010). A shared feature of the mutant IDH1/2 is the simultaneous loss of activity in the production of α-ketoglutarate (α-KG) and gain of activity in the production of 2-hydroxyglutarate (2HG) (Ward et al., 2010). 2HG is a competitive inhibitor of the multiple α-ketoglutarate-dependent enzymes in vitro including the collagen prolyl 4-hydroxylases (P4HA), ten-eleven-translocation 1 and 2 (TET1/2) 5-methylcytosine (5mC) hydroxylases, hypoxia-inducible factor asparaginyl hydroxylase (HIF1AN), HIF prolyl 4-hydroxylases (EGLN1, EGLN2, and EGLN3), and JMJD2D/KDM4D histone demethylase (Koivunen et al., 2012; Xu et al., 2011). In glioma and acute myeloid leukemia *IDH1/2* mutations are associated with increased global DNA hypermethylation. In support, conditional knock-in heterozygous expression of the *IDH1* R132H allele or ectopic expression of tumor-derived *IDH1/2* mutants inhibited genome-wide histone demethylation and DNA 5-methylcytosine hydroxylation (Duncan et al., 2012; Figueroa et al., 2010; Lu et al., 2012; Turcan et al., 2012; Xu et al., 2011). Such global epigenetic changes resulted in increased stem/progenitor cell marker expression and impaired hematopoietic (Figueroa et al., 2010; Losman et al., 2013), astrocyte (Lu et al., 2012; Turcan et al., 2012), and adipocyte differentiation (Lu et al., 2012).

In contrast to the widely accepted view that mutant *IDH1/2* and associated metabolite 2HG (R)-enantiomer are "the drivers" of tumorigenesis, high-grade glioma patients with mutant *IDH1/2* usually have better outcomes than those with wild-type *IDH1/2* genes (Ahmadi et al., 2012; Ichimura, 2012; Oermann et al., 2012; Reitman and Yan, 2010; Sun et al., 2013; Zhu et al., 2011). Similarly, *IDH* mutations confer improved overall survival in patients with acute myeloid leukemia (AML), although their prognostic effect in cytogenetically normal AML is versatile, varies according to the specific mutation and depends on the genetic background of tumors (reviewed in Rakheja et al., 2012). Analysis of tumor velocity of diameter expansion (mm/year) during preoperative spontaneous growth period in patients with grade II gliomas (according to World Health Organization) demonstrated that *IDH1* mutations were not significantly involved in tumor growth rate (Gozé et al., 2012). Also, there are no differences in intratumoral 2HG/isocitrate ratios in patients with paired samples of low grade glioma and their consecutive secondary glioblastoma (Juratli et al., 2013) and no correlation between 2HG levels and size of glioma of the WHO grades II and III (Capper et al., 2012). Furthermore, a significant portion of glioma-associated microglial cells/macrophages also harbors the mutant *IDH1* (Zheng et al., 2012). Considering the slow growth and less invasiveness of *IDH*-mutant gliomas Oermann et al. (2012) have supposed that in addition to tumor-promoting effects mutant *IDH1/2* may also cause growth inhibition. Zhu et al. (2011) have hypothesized that IDH mutations are "protective" and affect the tumor cell metabolism through energy metabolism (via α-KG alterations) and synthesis or decomposition metabolism (via GAPDH changes). Profiling of more than 200 metabolites in human oligodendroglioma cells stably expressing mutant *IDH1* or *IDH2* showed that levels of amino acids, glutathione metabolites, choline derivatives, and tricarboxylic acid cycle intermediates were altered in these cells (Reitman et al., 2011). To explain increased survival of glioma patients with *IDH1/IDH2* mutation Baldewpersad Tewarie et al. (2013) have proposed the following mechanism. Radio- and chemotherapy promote oxidative stress. As NADPH production is reduced (up to 38%) in *IDH1/IDH2* mutant cells, then NADPH-dependent systems should less effectively scavenge oxygen radicals, which will result in increased sensitivity of the cancer cells to treatment and more pronounced cell damage. However, this hypothesis has to be experimentally tested. For example, reactive oxygen species levels were dramatically reduced in different types of brain cells derived from $IDH1^{R132H/WT}$ conditional knock-in mice and brain cells also demonstrated high catalase activity (Sasaki et al., 2012). Importantly, the *IDH1* mutation did not influence proliferation or differentiation of brain cells during embryogenesis. In most cases, *IDH1* mutation resulted in hemorrhage and perinatal lethality. Survived mice manifested significantly shorter life span than wild type mice but without observable glioma formation.

Expression of mutant *IDH1* in immortalized astrocytes enhanced their proliferation and colonies formation in soft agar (Koivunen et al., 2012). Also, mutant but not wild type *IDH1* promoted cytokine independent proliferation of the TF-1 human erythroleukemia cell line (Losman et al., 2013). However, tet-inducible D54 glioblastoma cells overexpressing mutant *IDH1* or wild type had no obvious growth differences with control D54 cells (Seltzer et al., 2010). Similarly, U373 glioblastoma cells overexpressing mutant *IDH1* or wild type had no obvious growth and migration differences with control U373 cells (Li et al., 2013). In contrast, U87 glioblastoma cells expressing mutant *IDH1* showed lower proliferation rates, decreased growth in soft agar, altered morphology and cellular migration pattern; mice injected with these cells had significantly better survival than the control group (Bralten et al., 2011; Li et al., 2013). Tumors formed by U87 cells overexpressing mutant *IDH1* were characterized by more extensive areas of necrosis (about 40%–50% of the entire tumor volume) compared with less than 20% necrosis observed in U87 tumors overexpressing wild type *IDH1* or *IDH1* non-transfected U87 tumors (Lazovic et al., 2012). Controversly, another research group observed the opposite effects: the overexpression of mutant *IDH1* fostered U87 cellular proliferation, growth, and migration in comparison to *IDH1* non-transfected U87 cells (Zhu et al., 2012). Growth analysis of G361 melanoma cell line clones ectopically expressing the wild or mutated *IDH1* gene revealed no significant difference among them in vitro (Shibata et al., 2011). However, mutant *IDH1*-expressing clones formed significantly more colonies in soft agar and produced more frequently and larger tumors than wild type *IDH1*-expressing clones. The same experiment was performed with GAK melanoma cell line clones, which showed neither significant difference in growth nor in colony-forming activities (Shibata et al., 2011). *IDH1* knockdown enhanced, whereas *IDH1* overexpression suppressed TPA-induced cell transformation in murine skin epidermal JB6 P+ cells (Robbins et al., 2012). Selective suppression of mutant *IDH1* inhibited cell proliferation and decreased clonogenic potential of fibrosarcoma cell line HT1080 with a heterozygous *IDH1* mutantion (Jin et al., 2012).

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