Ten-Eleven Translocation-2 gene mutations: A potential new molecular marker in malignant gliomas (Review)

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Abstract. Alterations of the Ten-Eleven Translocation-2 (*TET2*) gene in myeloid malignancies and isocitrate dehydrogenase (*IDH*) gene mutations in gliomas and myeloid malignancies have recently been identified using molecular, comparative genomic hybridization and single nucleotide polymorphism array techniques. The mutations of the *TET2* gene have been shown to be mutually exclusive with *IDH1/2* mutations in acute myeloid leukemia (AML) and evidence has been found to provide a biochemical basis for the mutual exclusivity of *IDH1/2* and *TET2* gene mutations. Based on mounting evidence, we aimed to investigate whether *TET2* mutations may be identified as novel mutations in malignant gliomas without *IDH1/2* mutations, and indicate their possible significance in gliomas.

Contents

1. Introduction

Malignant gliomas, the most common and lethal brain tumors, exhibit a great deal of diversity in their location, pathology, genetic status and response to therapy. Nevertheless, survival for patients with glioblastoma, the most aggressive glioma, although individually variable, has recently improved in the last 5 years from an average of 10 to 14 months after diagnosis due to improvements in the standard of care (1). A comprehensive understanding of the genetic basis and pathology of gliomas has provided new information regarding biologically based tumor classification and has identified molecular prognostic biomarkers to improve the management of patients with gliomas. Over the past decades the application of sequencing, comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) array techniques have revealed the molecular genetic background of neoplasms through the identification of novel oncogenes and tumor suppressor genes.

2. *IDH1/2* mutations in gliomas and myeloid malignancies

One recently identified class of genes mutated in cancer are those coding for isocitrate dehydrogenase (IDH), which catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) leading to NADPH production (2,3). The $NADP^+$-dependent IDH1 (located in the cytoplasm and peroxisomes) and its mitochondrial counterpart IDH2 are mutated in up to 75% of grade II-III gliomas and secondary glioblastoma multiforme (GBM) as well as myeloid malignancies including primary and secondary acute myeloid leukemia (AML, 15-30%) and preleukemic clonal malignancies, such as myelodysplasia and myeloproliferative neoplasms (2-9). *IDH1* mutation has rapidly emerged as a novel prognostic and diagnostic marker with which to identify low-grade gliomas and to distinguish secondary from primary GBM (4,10,11). *IDH1/2* mutations are heterozygous, with tumors retaining one wild-type copy of the relevant *IDH1* or *IDH2* allele and producing single amino acid substitutions at arginine 132 (R132) in IDH1 or corresponding arginine 172 (R172) in IDH2 in glioma and leukemia, or at arginine 140 (R140) in IDH2 in leukemia (8,12). Notably, the R132 mutation in IDH1 results not only in a marked decrease of normal catalytic activity, but also in a gain of novel function catalyzing the $NADPH^+$-dependent reduction of α-KG to R(-)-2-hydroxyglutarate (2-HG) (8,12). Decreased α-KG and α-KG-dependent prolyl hydroxylase (PHD) activity leads to an increase in hypoxia-inducible factor-1α (HIF-1α), since PHDs use α-KG as a substrate for a reaction that normally targets HIF-1α for degradation (13). α-KG reduction and D-2-HG accumulation cooperatively contribute to tumorigenesis (14), which may resolve the continuing controversy over whether mutant *IDH1* is a tumor suppressor gene or an oncogene (15,16).

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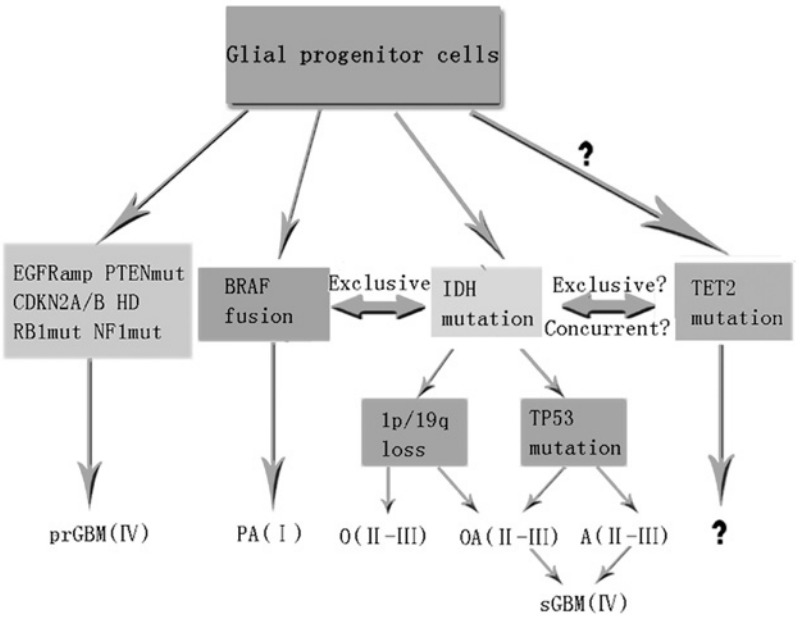

Figure 1. A model for tumorigenesis and progression of gliomas based on genetic alterations. *TET2* mutations are integrated into the model, but their role in gliomas is unknown. PAI, pilocytic astrocytomas; OII, oligodendrogliomas; OAII, oligoastrocytomas; AII, diffuse astrocytomas; OIII, anaplastic oligodendrogliomas; OAIII, anaplastic oligoastrocytomas; AIII, anaplastic astrocytomas; sGBMIV, secondary glioblastomas; prGBM IV, primary glioblastomas occurring *de novo*; EGFR, epidermal growth factor receptor; PTEN, phosphatase and tensin homolog; CDKN2A and 2B , cyclin-dependent kinase inhibitor 2A and 2B; HD, homozygous deletion; RB1, retinoblastoma 1; mut, mutation; NF1, neurofibromatosis type 1; BRAF fusion, v-raf murine sarcoma viral oncogene homolog B1; IDH, isocitrate dehydrogenase; TP53, tumor protein p53; 1p/19q loss, homozygous deletion of chromosome arms 1p and 19q; TET2, Ten-Eleven Translocation-2 gene.

3. *TET2* mutations in gliomas and myeloid malignancies

Other recently reported gene mutations are those of the Ten-Eleven Translocation-2 gene (*TET2*), which have been found in 20-26% of myelodysplastic syndromes or secondary AML (17,18), 14% of myeloproliferative neoplasms (17,19,20), and 12% of *de novo* AML (21). *TET2* is a putative tumor suppressor gene located at chromosome 4q24, encoding a dioxygenase that converts 5-methylcytosine to 5-hydroxymethylcytosine, leading to DNA demethylation at selective loci. It has also been indicated in the regulation of normal myelopoiesis (22-24), and the disruption of TET2 enzymatic activity favours myeloid tumorigenesis (24). Measurement of 5-hydroxymethylcytosine levels in myeloid malignancies may prove valuable as a diagnostic and prognostic tool to tailor therapies and assess responses to anticancer drugs (24). *TET2* abnormalities are highly heterogeneous and inactivating showing a relatively diverse pattern of frame shift, nonsense, and missense mutations scattered across several of its exons. Additionally, *TET2* may occur as hemizygous or heterozygous alterations, including loss of heterozygosity, due to hemizygous deletion or uniparental disomy (17,25). In contrast to the affirmatively prognostic value of *IDH1* mutation in gliomas (4,26), the prognostic value of *TET2* mutations in myeloid malignancies remains unclear (27). Similarly, survival in primary AML did not appear to be affected by the presence of *IDH* mutations (2,8,28).

4. Correlation between *TET2* and *IDH1/2* mutations

Mutations of *TET2* gene have been shown to coexist with other pathogenetically relevant mutations, including the retinoic acid receptor α gene, thrombopoietin receptor gene (myeloproliferative leukemia, MPL), janus kinase 2 gene (JAK2), KIT gene, FMS-like tyrosine kinase 3 gene (FLT3), renin-angiotensin system (RAS) gene, mixed lineage leukemia (MLL) gene, CCAAT enhancer binding protein α gene (CEBA+) or nucleophosmin 1 gene (NHMI) (18-21,29,30), but occur in a manner mutually exclusive with that of *IDH1* and *IDH2* genes in AML (30). Xu *et al* found that the expression of mutant IDH1/2 and D-2-HG inhibited the activity of TET2 in catalyzing the 5mC-to-5hmC conversion, which not only supported, but also provided a biochemical basis for the mutual exclusivity of *IDH1/2* and *TET2* gene mutations (14). The mechanisms of various gene mutations involved in disease initiation and/or progression are not isolated but associated, compatible or exclusive of each other. Considering the ubiquitous nature of mutant *TET2* in myeloid malignancies, mutant *IDH1/2* in gliomas and both mutations in myeloid malignancies, it may be possible that *TET2* mutation is also present in malignant gliomas, particularly those without *IDH1/2* mutation.

5. Discussion

Mounting evidence has indicated that *TET2* alterations are a common event in a spectrum of myeloid malignancies, that *IDH1/2* mutations are frequently present in gliomas, and that they both exhibit similar frequencies in myeloid malignancies. *IDH1/2* mutations were mutually exclusive with mutations in the α-KG-dependent enzyme TET2, and TET2 loss-of-function mutations were associated with similar epigenetic defects to those of IDH1/2 mutants in AML. Expression of mutant IDH1/2 or TET2 depletion impaired hematopoietic differentiation and increased stem/progenitor cell marker expression, indicating a shared proleukemogenic effect (30). Additionally,

the two mutations of *IDH1* and *TET2* have been reported to occur at a relatively early stage during glioma and leukemia development (17,18,31). These findings suggest that *TET2* mutations may be identified as novel mutations in malignant gliomas without *IDH1/2* mutations, since no reports are currently available regarding the association between *TET2* mutations and malignant gliomas.

IDH1/2 mutations are concurrent with *TP53* mutations in astrocytic tumors (9,31,32) and 1p19q codeletion in oligodendroglial tumors (9,32,33), but mutually exclusive with epidermal growth factor receptor (EGFR) amplification (34) and the BRAF fusion gene (10,35). *IDH1/2* mutations are inversely associated with numerous characteristic genetic changes of primary glioblastomas, including EGFR amplification, cyclin-dependent kinase inhibitor 2A or 2B deletion, and phosphatase and tensin homolog mutations (9,32). *IDH* mutations do not increase in frequency in the progression to higher-grade gliomas and occur prior to other genetic changes, indicating that these mutations arise at some point in the transition from glial progenitor cells to a clinically evident tumor (9,31,32,36,37). Common genetic changes associated with various glioma subtypes are shown in Fig. 1 in addition to the hypothesis that *TET2* mutations occur in gliomas. If the above-mentioned hypothesis holds true, several questions may be raised. The specific type of *TET2* mutation in malignant gliomas remains to be identified. It is also unknown whether *TET2* mutations are exclusive with *IDH1/2* mutations in gliomas, or perhaps even concurrent with them. In instances where mutant *TET2* coexists with *IDH1/2* mutations or other mutations, it is currently unclear as to whether it predates or postdates their emergence. Within the context of a specific disease, it is likely that the presence of mutant *TET2* affects phenotype, prognosis or treatment response. Finally, it is necessary to determine the pathogenetic contribution of mutant *TET2* in cancer, particularly in view of its occurrence across different molecular profiles.

Further clinical investigation from different centers is required to confirm our hypothesis. Additional laboratory studies are required to clarify the biological consequence of these mutations prior to any clinical applications.

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