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The role of *IDH1/2* mutations in the pathogenesis of secondary glioblastomas

O papel das mutações IDH1/2 *na patogênese dos glioblastomas secundários*

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ABSTRACT

Diffuse astrocytoma and glioblastoma (GBM) constitute a group of diffusely infiltrating astrocytic neoplasms, which more commonly arise in cerebral hemispheres of adults. The prevalence of malignant transformation of diffuse astrocytoma to anaplastic astrocytoma and GBM varies from 40% to 75% of cases in different series. Distinct genetic abnormalities are related to neoplastic progression, and the cells prone to glial neoplasm development include progenitor cells, stem cells, or differentiated cells. Primary GBM arises typically *de novo*, with no previous history of a lower-grade precursor lesion. Secondary GBM evolves from low-grade astrocytoma, is predominant in younger patients, and frequently exhibits isocitrate dehydrogenase (*IDH*) 1 and 2 mutations. *IDH1/2* mutated gliomas have been associated with a better prognosis when compared to *IDH*-wildtype gliomas. *IDH* mutations are rare in primary GBM and gliomas arising in children. Evidence suggests that *IDH* mutations lead to a hypermethylation phenotype and represent early events in tumoral transformation of the central nervous system (CNS) due to the production of the oncometabolite 2-hydroxyglutarate. *IDH1* mutations precede tumor protein p53 (*TP53*) mutations in around 63% of cases of diffuse astrocytomas, and result in loss in 10q and 19q chromosomes. Primary GBMs are also associated with alterations in cell proliferation [epidermal growth fator receptor (*EGFR*) amplification/mutation, platelet derived growth factor receptor alpha (*PDGFRA*) amplifications, neurofibromin 1 (*NF1*) mutations], abnormal apoptotic index [cyclin dependent kinase inhibitor 2A (*CDKN2A*) homozygous deletion and *TP53* mutation], and aberrant progression in G1/S phase of the cell cycle.

Key words: astrocytoma; glioblastoma; isocitrate dehydrogenase; pathology; prognosis; brain.

INTRODUCTION

Most primary central nervous system (CNS) neoplasms are neuroepithelial, and account for nearly 2% of all cancers. Clinical presentations of CNS neoplasms depend largely on their site and nature[1-4]. Factors associated with the etiology of these tumors include ionizing radiation and familial syndromes. In the latest decade, a marked improvement in the knowledge of the mechanisms of neoplastic transformation and the biology of CNS neoplasms has taken place[4-8].

Glial neoplasms are the most common CNS neoplasms. Embryologically, astrocytes and oligodendrocytes are derived from neuroectoderm and appear to arise from common progenitor cells[2-4, 9, 10]. Astrocytic tumors have a predilection for cerebral hemispheres in adults, and for the cerebellum and brain stem in children. Astrocytic tumors express glial fibrillary acidic protein (GFAP) and show a wide spectrum of clinical presentation, radiological characteristics, histological findings, genetic features, prognosis, and response to therapy[3-5, 11]. The 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System has grouped together all diffusely infiltrating gliomas (whether astrocytic or oligodendroglial)[3]. This dynamic classification is based on light microscopic features, immunohistochemical expression of lineage-associated proteins, and presence of different genetic alterations[3, 5]. Diffuse astrocytic tumors include astrocytoma, anaplastic astrocytoma, and glioblastoma (GBM). Localized or circumscribed astrocytic tumors include pilocytic astrocytoma, pilomyxoid astrocytoma, pleomorphic xantoastrocytoma, subependymal giant cell astrocytoma, and anaplastic pleomorphic xantoastrocytoma. In this new classification, diffuse gliomas include the WHO grade II and III astrocytic tumors, the grade II and III oligodendrogliomas, the grade IV GBM, as well as the diffuse gliomas of childhood[3, 5]. The WHO grade II diffuse astrocytomas and grade III anaplastic astrocytomas are divided into isocitrate dehydrogenase (*IDH*)-mutant, *IDH*-wildtype, and not otherwise specified. Diffuse astrocytoma *IDH*-wildtype, and anaplastic astrocytoma *IDH*-wildtype are uncommon

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diagnoses[3, 5]. Recent studies have established that the prognostic differences between *IDH*-mutant diffuse astrocytoma (WHO grade II) and *IDH*-mutant anaplastic astrocytoma (WHO grade III) are not highly significant in all cases[2, 3, 5, 11-13]. The 2016 WHO Classification of Tumors of the Central Nervous System has also divided GBM into GBM *IDH*-wildtype (about 90% of cases/primary GBMs), GBM *IDH*-mutant (about 10% of cases/secondary GBMs), and GBMs not otherwise specified[3, 5]. Current favorable prognostic indicators in diffuse astrocytic neoplasm are young age, high Karnofsky perfomance score, extent of gross surgical resection, low histological grade, presence of O(6)-methylguanine-DNA methyltransferase (*MGMT*) methylation, presence of proneural gene expression, and presence of *IDH1/IDH2* mutation[1, 2, 5, 11, 14, 15].

THE ROLE OF *IDH1/2* AND *ATRX* GENE ALTERATIONS AND CORRELATED MUTATIONS IN THE NEOPLASTIC TRANSFORMATION OF CNS PARENCHYMA, AND THE PROGRESSION OF LOW-GRADE DIFFUSE GLIOMA TO GLIOBLASTOMA IN ADULTS

The origin of astrocytic tumors may involve neural stem cells, differentiated glial cells, and progenitor cells. Neural stem cells are usually located in the dentate gyrus and subventricular zone[2, 4, 14, 16-18]. Stem cells can originate progenitor cells that exhibit limited self-renewal capacity and restricted ability to differentiate into other cell types[2, 4, 14, 16-18]. Different epigenetic and genetic changes can result in glioma formation and progression, and, currently, tumor protein p53 (*TP53*) gene mutations, methylation of the *MGMT* gene and *IDH* mutations are considered to be early events in tumor transformation and/or progression in CNS parenchyma[9, 16, 17, 19-21]. The **Figure** establishes the actual pathways

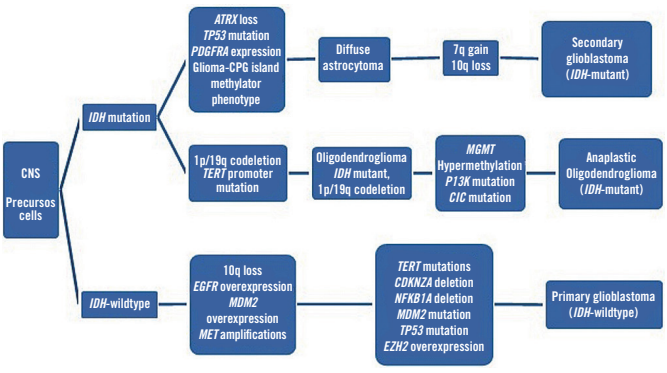

FIGURE – *A possible model to establish the development of diffuse gliomas and progression to glioblastoma*

CNS: central nervous system; IDH: isocitrate dehydrogenase.

related to *IDH* alterations and development of diffuse astrocytoma and glioblastoma.

The great majority of GBMs are primary rather than secondary, and epidermal growth fator receptor (*EGFR*) overexpression is a common finding[2, 3, 22-26]. Around 40%-75% of diffuse astrocytomas progress to anaplastic astrocytoma or GBM. *IDH*-wildtype GBM is a WHO grade IV primary glioma, which usually affects cerebral hemispheres in patients with a median age of 60 years. These cases account for about 90% of all GBMs and show extensive areas of necrosis. Conventional genetic alterations of *IDH*-wildtype glioblastoma include telomerase reverse transcriptase (*TERT*) promoter mutations (about 72%), *EGFR* amplification (about 40%), *TP53* mutations (about 27%), phosphatase and tensin homolog (*PTEN*) mutations (about 25%), homozygous deletion of cyclin dependent kinase inhibitor 2A and 2B (*CDKN2A/CDKN2B*) (about 60%), loss of chromosomes 10q (70%) and 10p (50%), and phosphatidylinositol-4,5-bisphosphate 3-kinase (*PI3K*) mutations (about 25%). The term *IDH*-wildtype GBM must be used to a GBM exhibiting negative immunoexpression for *IDH1* and presence of wildtype sequences at *IDH1* codon 132 and *IDH2* codon 172 on pyrosequencing[1, 2, 19, 27, 28]. *IDH*-mutant GBM is a secondary glioma occurring in patients with a median age of 44 years and prior history of diffuse or anaplastic astrocytoma. Secondary GBM more often affects women with a longer duration of symptoms, commonly arise in cerebral hemispheres, especially the frontal lobe, account for about 10% of GBM cases, and show limited areas of necrosis. Secondary GBMs are related to *TERT* promoter mutations (about 26%), *ATRX* mutations (about 71%), *TP53* mutations (about 81%), and rarely to *PTEN/EGFR* mutations[1, 3, 4, 19, 23, 27]. Presence of small neoplastic cells in GBM or the small cell variants of GBM are usually *IDH*-wildtype tumors. GBMs with a primitive neuronal component or gemistocytes are possibly *IDH*-mutant neoplasms[4, 5, 14, 26]. GBMs are among the most vascularized human tumors, and the presence and extension of necrosis is one of the strongest predictors of aggressive behavior. In general, GBM exhibits poor prognosis, with most patients dying within 12-17 months after diagnosis. The cases of GBM associated with longer survival show *IDH* mutation and/or *MGMT* promoter methylation. *IDH1/2* mutation is also common in diffuse astrocytoma (85% of all cases), oligodendrogliomas, and anaplastic astrocytoma. *IDH1* mutation has been associated with better prognosis, and is not predictive of response to radiotherapy or temozolomide[4, 11, 28-31].

GBM is most often located in the subcortical white matter and deeper gray matter of the temporal lobe (affected in 30% of cases) and parietal lobe (in 25%)[5, 7, 11, 13, 29]. GBM molecular classification includes proneural, classical, mesenchymal, and

neural subtypes. Proneural subtype is related to younger patients that developed secondary GBM due to platelet derived growth factor receptor alpha (*PDGFRA*) amplification/mutation and/or *IDH* mutation[1, 3, 7, 13, 27, 32]. Molecular abnormalities found in GBM also include deletions and mutations of p16; gain in chromosome 7; loss in chromosomes 9, 10 and 13; loss of heterozygosity of chromosome 17p; mutations in the neurofibromin 1 (*NF1*) gene (approximately 20%); amplification of *MDM2*; and alterations in the receptor tyrosine kinase signaling pathways (about 90% of cases). Glioma-CPG island methylator phenotype (*G-CIMP*) is associated with the proneural subtype, secondary GBM, and gliomas exhibiting *IDH1* mutation[2, 19, 30, 31, 33-36].

IDH enzymes have a normal function in cells. These several enzymes catalyze the oxidative carboxylation of isocitrate to alpha-ketoglutarate, which results in the antioxidant reduced nicotinamide adenine dinucleotide phosphate (RNADP)[2, 17, 34, 35, 37]. *IDH* mutation and *G-CIMP* are possibly associated with the maintenance of neoplastic cells in stem cell-like biological states, which promotes self-renewal and tumorigenesis. *IDH* mutation can be determined by the immunohistochemistry technique in paraffin-embedded sections, with the employment of a monoclonal antibody against *IDH1* R132H. The *IDH1* R132H mutation accounts for about 90% of all glioma-associated *IDH* mutations. In mutant tumors, the neoplastic cells show some degree of cytoplasmic (stronger) and nuclear (weaker) labeling. Normal glial cells show negative immunoexpression for *IDH1/2* antibodies, and *IDH1* mutation and *TP53* overexpression are useful molecular markers to distinguish glioma margin from reactive gliosis when positive[25, 35, 38, 39]. Adult *IDH*-wildtype diffuse gliomas with genotype showing 7q gain and 10q loss, regardless of their WHO grade, tend to show more aggressive biological behavior. *IDH* mutations are absent in pilocytic astrocytomas[17, 25, 27, 34, 35, 39].

IDH1 mutation is present in around 80% of cases of WHO grade II-III gliomas and secondary GBM. Mutations in *IDH2* have been found in fewer than 3% of all glial neoplasms. *IDH1* mutations are uncommon in primary GBM[2, 25, 34, 40, 41]. Actually, all mutations have been related to a single amino acid missense mutation in *IDH1* at arginine 132 (R132) or the analogous residue in *IDH2* (R172). *IDH* mutations can also be found in cartilaginous tumors, prostate cancer, acute lymphoblastic leukemia, acute myelogenous leukemia, and cholangiocarcinoma[2, 16, 22, 25, 42, 43]. The three human *IDH* catalytic isoenzymes (*IDH1*, *IDH2*, and *IDH3*) are encoded by five genes. *IDH1* and *IDH2* are found in the cytoplasm and mitochondria, and cells with low levels of *IDH* exposed to reactive oxygen species (ROS) and free radicals are more sensitive to oxidative damage[2, 5, 44]. The great majority of gliomas exhibiting *IDH1* mutations (over 85%) show a heterozygous missense mutation of arginine to histidine (R132H). This change is located in the active site of the enzyme, and the mutation of R132 inactivates *IDH* ability to bind isocitrate, and stops its normal catalytic activity[2, 9, 16, 28, 38]. *IDH* mutation can be associated with neoplastic transformation of CNS due to the synthesis of 2-hydroxyglutarate, a possible oncometabolite. This hypothesis suggests that mutant *IDH* is an oncogene that induces cell proliferation and inability to cell differentiation, and that *IDH* mutation is an early event in glioma transformation[2, 5, 44-46]. Reduced α-ketoglutarate and increased 2-hydroxyglutarate due to *IDH* mutation may predispose stem cells of CNS to neoplastic transformation via genomic epigenetic changes[2, 12, 16, 38, 45, 47]. Actually, the presence/formation of the oncometabolite 2-hydroxyglutarate can theoretically be evaluated by magnetic resonance spectroscopy[2, 3, 48]. Nearly all pediatric high-grade diffuse astrocytic tumors are primary lesions which involve genes coding for proteins related to transcription regulation, *pRb/TP53* pathways, or the receptor tyrosine kinase/*RAS*. *IDH* and *EGFR* mutations are rarely associated to high-grade diffuse gliomas affecting children[3, 5, 12, 18, 49].

The diagnosis of WHO grade II and III oligodendroglioma requires the evaluation of *IDH* mutation and presence of 1p/19q codeletion. Virtually all oligodendrogliomas with 1p/19q codeletion exhibit *IDH* mutations, and these cases rarely demonstrate *TP53* mutation. Combined loss of 1p and 19q is highly associated with *IDH* mutation, which suggests that 1p/19q codeletion in *IDH*-wild type lesions can be related to incomplete/partial deletions found in some cases of *IDH*-wildtype glioblastomas[11, 25, 32, 40, 50]. Oligodendroglial neoplasms, usually *IDH*-mutant and 1p/19q-codeleted tumors, exhibit frequent mutations in the *CIC* gene, the human homolog of *Drosophila capicua* gene (*CIC*). *IDH*-mutation, 1p/19q-codeletion, and *TERT* promoter mutation look to be the early genetic changes in oligodendroglioma development. Different genes on 1p and 19q have been implicated in the pathogenesis of oligodendrogliomas, *IDH*-mutant and 1p/19q-codeleted, and they are implicated in establishing aberrant promoter methylation and/or reduced expression of *IDH*. Epigenetic alterations in SLC9A1 can be associated with attenuation of acid load recovery and lower pH in oligodendroglial neoplastic cells[11, 25, 32, 40, 50]. It is important to establish that some cases of gliomas with *IDH*-mutation often occur with a *TP53* mutation, and these cases infrequently reveal loss in chromosomes 1p and 19q. *IDH* mutations precede *TP53* mutations in about 65% of diffuse astrocytomas, and 80% of anaplastic astrocytomas, and GBM with *IDH* mutations also have mutant *TP53*[5, 25, 28, 38, 50]. The less common R132C substitution of *IDH*-mutation is found in astrocytomas observed in patients with Li-Fraumeni syndrome, which can be related to a different cell lineage[2, 38]. A possible effect of *IDH*-mutation is also the decrease of oxidation of divalent ferrous iron by ROS, which can promote cellular accumulation of hypoxia-inducible factor 1α (HIF-1α). The accumulation of HIF-1α can induce angiogenesis, metabolism,

growth, apoptosis, and cell differentiation of mutant *IDH* glial cells, thus promoting neoplastic transformation and progression[2, 5, 46, 51, 52].

Diffuse astrocytomas can also exhibit *ATRX* mutations. *ATRX* encodes an essential chromatin-binding protein, and its deficiency is related to telomere dysfunction and epigenomic dysregulation. *ATRX* typically demonstrates strong nuclear expression in normal CNS tissue[3-5, 21, 28, 53]. *ATRX* expression is invariably lost in the setting of *ATRX* mutation, which can induce *TP53*-dependent cell death in some cases. Alternative lengthening of telomeres and *ATRX* mutations are mutually exclusive with activating mutations in the *TERT* gene, which encodes the catalytic component of telomerase. *TERT* mutations are found in most *IDH*-wildtype GBMs (present in approximately 80% of cases), and this alteration is inversely correlated with *TP53* mutations[5, 12, 18, 21, 23, 27, 28, 53].

Patients with *IDH* mutated gliomas carry the rs55705857 single nucleotide polymorphism on chromosome 8q24. Pyrosequencing remains the gold standard for *IDH*-mutation testing. *IDH* sequencing is recommended following negative *IDH1* immunohistochemistry in WHO grade II and III diffuse gliomas. The near absence of *IDH1/2* mutations in GBM from patients over about 55 years of age suggests that molecular studies/sequencing may not be necessary in the cases showing negative immunoexpression for *IDH1*[2, 5, 28, 37, 39, 54, 55].

IDH1/2 IS A POSSIBLE THERAPEUTIC TARGET AND PREDICTIVE FACTOR IN DIFFUSE GLIOMAS

Different target therapies have been suggested to clinical management of *IDH* mutant gliomas, including suppression of the possible oncometabolite 2-hydroxyglutarate or the employment of hypomethylating agents related to *GCIMP*[5, 11, 16, 32, 45]. Expression of mutant *IDH1* increases levels of *H3K9me2*, *H3K27me3* and *H3K36me3*; directly generates the methylation patterns present in *GCIMP*; and estimulates the expression of markers of self-renewal and stem cell identity[5, 11, 13, 16, 24, 32, 45]. Ebrahimi *et al.* (2016) determined that *ATRX* loss was strongly associated with *H3F3A* and *IDH1/2* mutations ($p = 0.0001$) in gliomas, and *ATRX* retention in *IDH1/2* mutant tumors was associated to 1p/19q codeletion[49]. The EORTC 22033-26033 study showed that *IDH* mutant/non-1p19q codeleted low-grade gliomas treated with radiotherapy had a longer progression-free survival than those treated with temozolomide ($p = 0.0043$)[32]. Millward *et al.* (2016) described that overall survival was related to *MGMT* methylation ($p < 0.0001$) and *IDH1* mutation ($p = 0.018$) in patients compromised by GBM and previously treated with chemoradiotherapy[24]. Kawaguchi *et al.* (2016) described that gross total resection is important to improve the prognosis in patients with mutant *IDH1/2* non-codeleted 1p19q WHO grade III gliomas[55]. Paldor *et al.* (2016) suggested that GBM arising in the frontal lobe are more prone to exhibit *IDH*-mutation ($p = 0.006$) and *MGMT* methylation ($p = 0.005$) than GBM arising in other lobes[15]. *MGMT* promoter methylation is predictive for chemotherapeutic response in GBM of the elderly and *IDH1/2*-wildtype anaplastic gliomas[13, 24, 47, 56, 57].

Zeng *et al.* (2015) established that patients with *IDH1/2* mutation survived significantly longer than patients with *IDH1/2*-wildtype gliomas ($p < 0.0001$)[58]. Zhang *et al.* (2015) analyzed 295 patients afflicted by WHO grade II and III gliomas treated with or without adjuvant therapies. *TERT* promoter mutations were found in 112 patients (38%), and were related to different responses to adjuvant therapies when compared *IDH*-wildtype WHO grade II and III diffuse gliomas. In that study, *IDH* mutated WHO grade II and III gliomas had a better overall survival than *IDH*-wildtype tumors when genotoxic therapies were administered after surgery[59]. Tanaka *et al.* (2015) described that combined *IDH1* mutation and *MGMT* methylation status ($p = 0.012$), tumor histology (oligodendroglioma versus astrocytoma/$p = 0.011$), and tumor size ($p = 0.008$) are important predictors for prolonged overall survival in low-grade gliomas[56]. Xia *et al.* (2015) conducted a meta-analysis of 55 observational studies, and found that *IDH1/2* mutation had significant advantages in progression-free survival ($p < 0.001$) and overall survival ($p < 0.001$) in diffuse gliomas[60]. De Quintana-Schmidt *et al.* (2015) evaluated 61 distinct cases of GBM and determined that median survival in patients with *IDH1* mutation was 23.6 months compared with 11.9 months in the cases exhibiting the phenotype *IDH1*-wildtype. In that study, *IDH1* mutation was found in 14 patients (23%)[61]. Yang *et al.* (2015) determined that *IDH*-wildtype GBM patients submitted to temozolomide and radiation combined therapy had improved overall survival in comparison to patients treated only with radiotherapy[57]. Sabha *et al.* (2014) analyzed 108 cases of WHO grade II and III diffuse gliomas and established that *IDH* mutations, 1p/19q codeletion, and *PTEN* deletion were predictive of overall survival ($p = 0.003$, $p = 0.005$ and $p = 0.02$, respectively)[30].

CONCLUSION

IDH mutation is a common finding in WHO grade II and III diffuse gliomas, but it is rare in most GBM cases. Mutant *TP53*, *NF1* and *ATRX* genes, *PDGFRA* overexpression, methylation of the *MGMT*

gene, and *IDH* mutations are possibly a set of correlated genetic changes that can result in glioma formation and progression. Around 40%-75% of diffuse astrocytomas progress to anaplastic astrocytoma or GBMs, and presence of reduced α-ketoglutarate due to *IDH*-mutation may predispose stem cells of CNS to neoplastic transformation via genomic epigenetic changes, which promotes self renew and tumorigenesis. *IDH*-mutant gliomas are associated with a better prognosis, WHO grade II tumors, younger patients, secondary GBMs, frontal lobe location, *GCIMP* phenotype, presence of *MGMT* methylation, and proneural gene expression. Target drugs able to suppress the oncometabolite 2-hydroxyglutarate can be the future adjuvant therapeutic modality.

RESUMO

Astrocitoma difuso e glioblastoma (GBM) constituem um grupo de neoplasias astrocíticas infiltrantes difusas, que mais comumente surgem nos hemisférios cerebrais de adultos. A prevalência da transformação maligna de astrocitoma difuso para astrocitoma anaplásico e GBM varia de 40% a 75% dos casos em diferentes séries. Distintas anormalidades genéticas estão relacionadas com a progressão neoplásica; e as células propensas ao desenvolvimento de neoplasia glial incluem células progenitoras, células-tronco ou células diferenciadas. O GBM primário surge tipicamente de novo*, sem história prévia de uma lesão precursora de baixo grau; o GBM secundário evolui a partir de um astrocitoma de baixo grau, é predominante em pacientes mais jovens e com frequência exibe mutações de isocitrato desidrogenase (*IDH*) 1 e 2. Os gliomas com mutação de* IDH1/2 *têm sido associados a melhor prognóstico quando comparados a gliomas com* IDH *de tipo selvagem. As mutações de* IDH *são raras nos GBM primários e em gliomas que surgem em crianças. Evidências sugerem que as mutações de* IDH *conduzem a um fenótipo de hipermetilação e representam eventos iniciais na transformação tumoral do sistema nervoso central (SNC) devido à produção do oncometabólito 2-hidroxiglutarato. As mutações de* IDH1 *precedem mutações de* tumor protein p53 *(*TP53*) em cerca de 63% dos casos de astrocitomas difusos e resultam em perda nos cromossomos 10q e 19q. O GBM primário também está associado a alterações na proliferação celular [amplificação/mutação de* epidermal growth fator receptor *(*EGFR*), amplificações de* platelet derived growth factor receptor alpha *(*PDGFRA*) e mutações de* neurofibromin *1 (*NF1*)], índice apoptótico anormal [deleção homozigótica* cyclin dependent kinase inhibitor *2A (*CDKN2A*) e mutação* TP53*] e progressão aberrante na fase G1/S do ciclo celular.*

Unitermos: *astrocitoma; glioblastoma; isocitrato desidrogenase; patologia; prognóstico; cérebro.*

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