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Cellular Regulation and Oncogenesis of Primary Tumors in the Central Nervous System

Regulação celular e oncogênese de tumores primários no sistema nervoso central

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Abstract

The World Health Organization's system for classifying and grading primary tumors of the Central Nervous System conjectures the clinical-biological course of the oncogenic process based on morphological, genetic, histological, and immunohistochemical parameters. These principles are fundamental for a progression in the classification of these tumors, to guarantee the promotion of a more precise diagnosis. In this sense, it is important to understand the process of oncotic cell formation, which is the result of mutations in intra and extracellular control pathways. In this way, genes that act to induce the cell cycle, under normal conditions, when mutated, can result in a dysregulation of the progress of the cycle, causing alterations in the control factors and, consequently, phenotypic transformations in the cell. Thus, to understand the role of genes in modulating primary tumors in the Central Nervous System, mutations in the genes most prevalently related to Gliomas, Meningiomas, and Medulloblastomas were addressed highlighting their influences on the development of these tumors.

Keywords
- Carcinogenesis
- cell cycle
- phenotype
- genes
- central nervous system neoplasms

Resumo

O sistema de classificação e graduação dos tumores primários do Sistema Nervoso Central da Organização Mundial da Saúde conjectura os cursos clínico-biológicos do processo oncogênico com base em parâmetros morfológicos, genéticos, histológicos e imuno-histoquímicos. Tais princípios são fundamentais para uma progressão na classificação desses tumores, a fim de garantir a promoção de um diagnóstico mais preciso. Nesse sentido, mostra-se relevante o entendimento do processo de formação de uma célula oncótica, resultado de mutações em vias de controle intra e extracelular. Dessa forma, genes que em condições normais atuam induzindo o ciclo celular, quando sofrem mutações, podem resultar em uma desregulação do progresso do ciclo,

Palavras-chave
- Carcinogênese
- ciclo celular
- fenótipo
- genes
- neoplasias do sistema nervoso central

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causando alterações nos fatores de controle e, consequentemente, transformações fenotípicas na célula. Assim, para o entendimento da atuação dos genes na modulação de tumores primários no Sistema Nervoso Central, foram abordadas as mutações nos genes mais prevalentes relacionados com Gliomas, Meningiomas e Meduloblastomas, destacando as suas influências no desenvolvimento desses tumores.

Introduction

The cell division process can be understood as a sequence of phases, essentially resulting in the duplication of genetic material and cell division, steps that are essential to the cell's activities.[1]

To these operations to take place, there is the need for various means of regulating internal control, such as growth, protein synthesis, nutrients, and cell adhesion; and of external control, as the activation of external cell membranes and activation or inhibition of genes; which, jointly, are essential to the occurrence of the cell cycle sequencing.[1,2]

Therefore, the entirety of the cellular factors mentioned contribute to the regulation of the cell cycle, which is fundamental for the functioning of the cell. Thus, specific mutations in the genes that transcribe proteins that control cellular physiology, contribute to the development of defects in protein expression, providing a possibility for the advent of oncogenesis.

Within this reasoning, Gliomas, Meningiomas and Medulloblastomas are the primary tumors of the Central Nervous System that present a greater expression of mutant genes.[3]

In this context, the tumor is a condition in which there is a change in cellular phenotype, resulting in a genetic modification transmitted in the process of cell division. For this change in the cell to occur, it is necessary, for the tumor structure, to remodel several compensatory mechanisms, to avoid any means of cell destruction, such as apoptosis.[1]

This article has the purpose to describe the physiology of cell division control, relating it to possible mutations in genes most relevant to the development of oncogenic cells in the most prevalent primary tumors of the Central Nervous System.

Material and Methods

This article is an integrative review of various other scientific projects that have contributed to the enrichment of neuroscience. To execute this work, several other articles were selected through the scientific research platforms: Medline, PubMed, SciELO and Google Scholar, with emphasis on those in English and Portuguese, to provide a better foundation on the subject. The following keywords filtered in the "Descritores em Ciências da Saúde" (DeCS) and "Medical Subject Headings" (MeSH) systems were used as search parameters: Carcinogenesis; Cell Cycle; Phenotype; Genes; Central Nervous System Neoplasms. The articles obtained had, as a selection criterion, data related to the theme: Cellular Regulation and Oncogenesis of Primary Tumors in the Central Nervous System, and those that did not conform to the theme presented were discarded.

Regarding primary tumors of the Central Nervous System, only three were selected for a systemic approach: Gliomas, Meningiomas and Medulloblastomas. This decision was based on a comparison of the primary tumors in relation to the mutant gene expression expressed in each type, with a greater expression of mutant genes in the tumors. This analysis was carried out using the 5th Edition, Volume 6 of the classification of primary tumors of the Central Nervous System elaborated by the World Health Organization in 2021.[3]

Regarding genes, the following genes were selected for systemic identification of the impact of their mutations: Tumor Protein p53 (*TP53*), Isocitrate Dehydrogenase (*IDH*) and Telomerase Reverse Transcriptase (*TERT*). They were chosen due to their prevalence in the tumors and their respective impacts on modulation of the primary oncogenesis process in the Central Nervous System. The 5th Edition, Volume 6 of the classification of primary tumors of the Central Nervous System elaborated by the World Health Organization in 2021 was also used for this selection.

There was no restriction in relation to data from other works for the preparation of this article, therefore, articles were selected that were relevant to the subject from different periods.

Results

Cellular Regulation

The process of cell division can be understood through a sequential progression of four phases: G1 → S → G2 → M. In this way, the G1, S and G2 phases are the period of Cell Interphase, which can be understood as a interval of intense growth in the cell's activities; while the M phase is characterized by the stages of Mitosis and Cytokinesis, in which the cell division actually happens. Furthermore, it is important to notice that between these periods of cell division there is the cell cycle control system, taking place in three regulation points, so that only in this way it is possible for the cell to progress to the next phase of cell division.[1]

In this sense, the cell cycle control system can be interpreted in three checkpoints. Firstly, the Start or Restriction Point, which is at the end of the G1 phase, is responsible for

the occurrence of cell consolidation so that there is, consequently, chromosome duplication and, only then, is the cell allowed to enter the cell cycle. Secondly, the transition from G2 to M is verified, resulting in chromosomal alignment to the mitotic axis in the Metaphase phase. Finally, the cycle of checks ends with the third stage of the transition from Metaphase to Anaphase, consolidating in the separation of the sister chromatids, thus concluding Mitosis and Cytokinesis.[1] (►**Fig. 1**)

In regard to the regulation of the checkpoints stages, this control is positively regulated through extracellular and intracellular response pathways that contribute to the modification of target proteins in the cellular environment to process the progression of cell cycle phases. The main protein complexes responsible for these activities are cell surface receptors, retinoblastoma proteins, Bax proteins and, fundamentally, a series of protein-enzymatic complexes called cyclin-dependent kinases.

Cyclin-CDK Complex

Therefore, worth mentioning the main structure responsible for the cell cycle control system, the cyclin-dependent kinases (CDKs) enzymes. These structures perform their regulatory functions by varying their activity as the cell progresses through its cycle, and these oscillations are regulated by the activity of a family of proteins, the cyclins. The cyclins are regulatory proteins that are associated with kinase enzymes, promoting, by binding to these enzymes, the activation of the cyclin-CDK complex so that, only in this way, can the development of the cell cycle be made possible.[1]

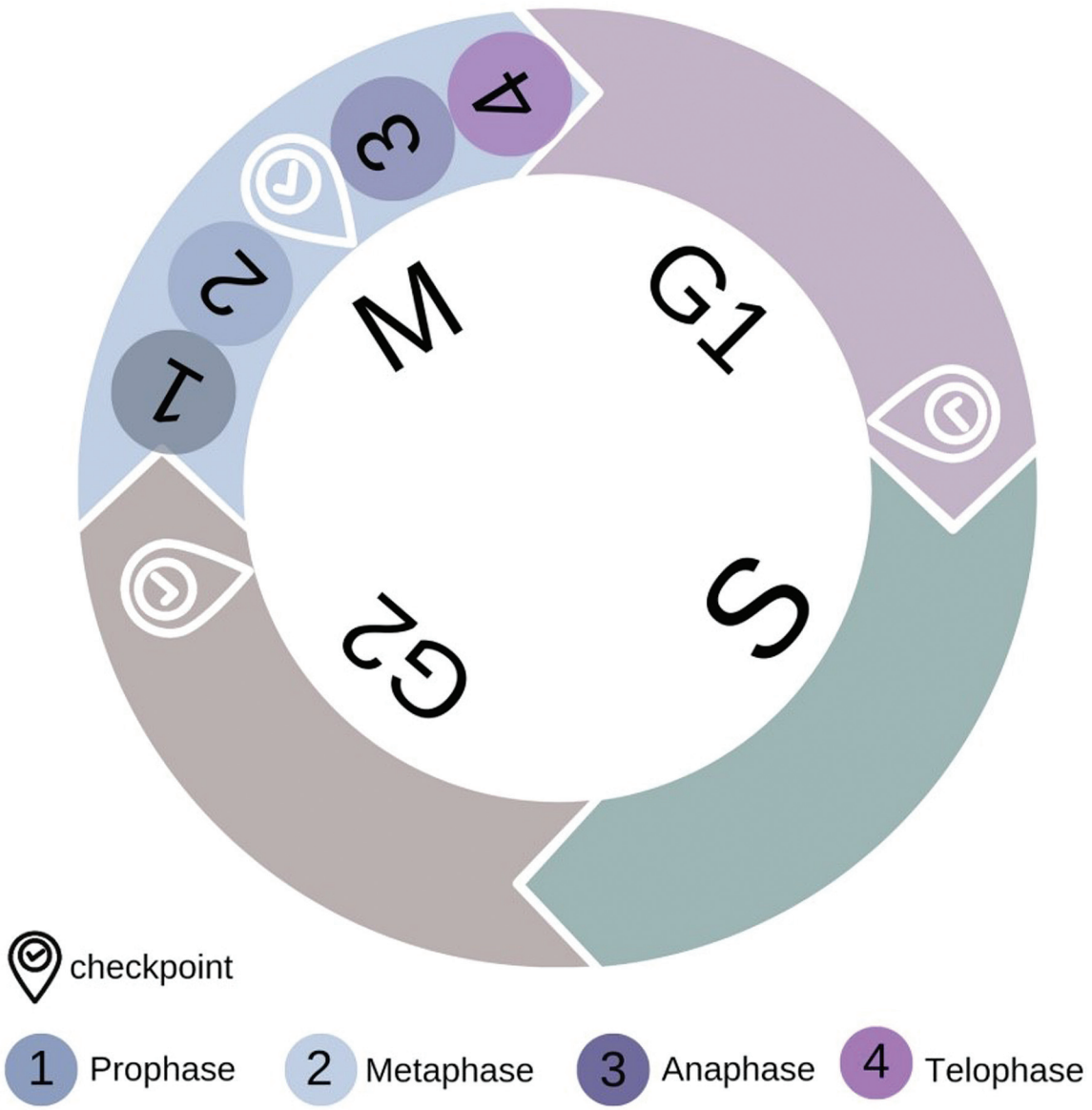

Fig. 1 Illustrative representation of the stages of the cell cycle. The symbol was used to represent the checkpoints present in the G1, G2 and M phases. The arabic numbers in the M phase represent the stages of Mitosis, dividing it neatly into 1-Prophase; 2-Metaphase; 3-Anaphase and 4-Telophase.

In this context, the formation of the cyclin-CDK complex, initially, occurs in the active site of the CDK enzyme, which exhibits, in this location, an inhibitory control protein loop that, upon binding to the cyclin, stimulates its withdrawal. Thus, with the displacement of this protein loop, there is the possibility of partial activation of CDK and, consequently, of the cyclin-CDK complex. Therefore, the full activation of this complex will only occur when there is a process of phosphorylation of the CDK active site, this activity being carried out by the cyclin-CDK activating kinase (CAK) enzyme, which will promote the phosphorylation of an amino acid close to this active site. This process causes a structural change to occur in CDK, ensuring, for both it and cyclin, more efficient ways to synthesize their target proteins to induce cell cycle progression.[1]

Furthermore, cyclin-CDK complexes have the relevance of synthesizing different sets of substrate proteins at each stage of the cell cycle, and for this reason there is a need to have specific cyclin-CDK complexes for each phase of this process, namely: G1-CDK → G1/S-CDK → S-CDK → M-CDK.[1]

Thus, according to the order of the cell cycle phases, the G1-CDK complex, which is associated with cyclin D, is active in cells from the start of the G1 phase as a regulator of its successive complex. Sequentially, the G1/S-CDK complex, together with cyclin E, acts to regulate target proteins to help process the transition from G1 to S phase. In addition, the S-CDK complex, which is linked to cyclin A, incites chromosome duplication after entry into the cycle, helping to control the replication of genetic material during the S phase and preparing the cell for the Mitotic phase. Finally, the M-CDK complex, together with cyclin B, stimulates the passage of the cell from the end of the G2 phase to the beginning of the Mitosis phase, acting in various stages to promote this process, such as inducing the formation of the mitotic spindle, disintegration of the nuclear envelope and rearrangement of the cytoskeleton; there is a progressive decrease in its concentrations halfway through this stage of the cell cycle.[1] (►**Fig. 2)**

Regulation of the Cyclin-CDK Complex

Once the cyclin-CDK complex was explained, its regulated both by the different levels of cyclin throughout the cell cycle and by other physiological processes, such as the suppression of this complex by inhibitory phosphorylation and the action of the cyclin-dependent kinase inhibitor (CKI) protein. In this way, the process of inhibitory phosphorylation occurs from a kinase enzyme called Wee1, which adds a phosphate group to the cavity of the active site of the CDKs, inhibiting their activity and, conversely, their dephosphorylation is succeeded by a dephosphorylation protein known as Cdc25, which increases the action of the CDKs by removing the phosphate group. Thus, this phosphorylation and dephosphorylation mechanism is extremely important, especially in the regulation of M-CDKs, given the need to synthesize various substrate proteins to help promote the cell phase of mitosis. Furthermore, in relation to the CKI protein, it acts to inactivate CDKs by stimulating the structural rearrangement of its active site, consequently suppressing cyclin-CDK complexes.[1]

Rb Protein

In parallel to the cyclin-CDK complex, the retinoblastoma protein (Rb protein) is a protein transcribed by the *Rb* gene that is present in most of the body's cells.[1] This structure is responsible for the intrinsic regulation of the cell cycle through the activation of a transcription factor that acts as a signal transducer, allowing control of the expression of genes that mediate cell progression during the replication of genetic material in the S phase, and therefore, it is involved in tumor suppression.[2]

Therefore, the physiological activity of the Rb protein must be presented in two states of action, acting in the presence and absence of stimuli for the Mitosis phase. Therefore, when the cell receives mitogen stimulation, through cell surface receptors, there is the activation of a main intracellular signaling pathway that is conducted through the monomeric Ras GTPase enzyme, leading to the activation of the mitogen-activated protein kinase (MAPK) which, in turn, increases the production of proteins that regulate cellular transcription, notably Myc.[1]

In this context, among the Myc mechanisms that promote entry into the cell cycle, there is an increase in the expression of genes that encode cyclins present in the G1-cyclin phase, cyclins D, which, as a result, also increase the activity of G1-CDK. Thus, the main function of the G1-CDK complex is to promote the activation of a group of gene regulatory factors called E2F proteins. Thus, the E2F protein is responsible for binding to various gene promoter regions in the DNA that encode proteins, such as G1/S-cyclin and S-cyclin, which are necessary for progression to the S phase of the cell cycle.[1]

Based on this, it is possible to understand the action of the Rb protein, since in the absence of mitogenic stimulus, it interacts with the E2F protein, inhibiting its gene expression and, consequently, preventing the progression of the cell cycle. On the other hand, when there is a mitogenic stimulus, the G1-CDK complex promotes phosphorylation of the Rb protein, reducing its binding to E2F and thus allowing expression of the protein's target genes.[1]

Bax Protein

In the context of cell cycle control, the Bax protein plays an important role, being a pro-apoptotic function in the intrinsic pathway and one of the main effectors of the BCL2 family of proteins. This structure acts in conjunction with another BCL2 family protein, Bak, since at least one of these proteins must function for the intrinsic apoptosis pathway to develop.[1]

In terms of their functionality, Bax proteins are inactive in the form of monomers or dimers and are predominantly concentrated in the cytosol due to their constant translocation from the mitochondria to the cytoplasm. On the other hand, following apoptotic stimuli in cells under oxidative stress, Bax accumulates in the mitochondrial outer membrane (MOM) to be activated by interaction with the pro-apoptosis BH3-only proteins, which allow both the insertion

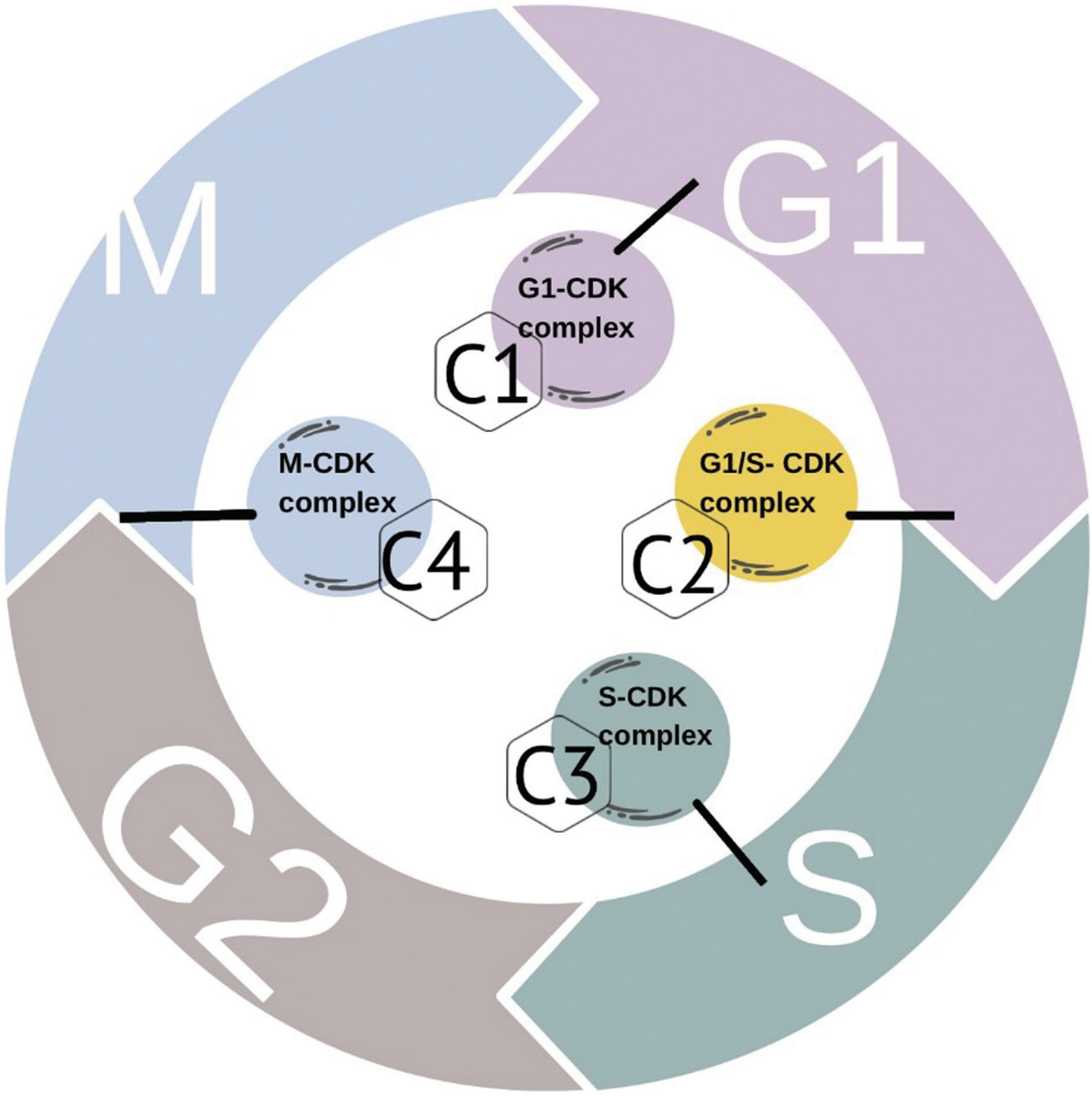

Fig. 2 Illustrative representation of the action of cyclin-CDK complexes present in the cell cycle. In the G1 phase, there is the G1-CDK complex associated with cyclin D (C1). At the transition from G1 to S phase, the G1/S-CDK complex is found associated with cyclin E (C2). In the S phase, the S-CDK complex is associated with cyclin A (C3). At the transition from G2 to M phase, the M-CDK complex is found associated with cyclin B (C4).

of Bax into the MOM and the transient exposure of the BH3-binding domain of the Bax protein. Following this logic, the Bax protein aggregates to the outer mitochondrial lipid bilayer in the form of oligomers so that it is possible to promote an accumulation of proteins in the leaflet of this membrane, increasing its stress and tension, thus, resulting in the opening of pores that allow the permeabilization of the MOM and the release of cytochrome C from the mitochondria into the cytosol.[4]

Thus, during apoptosis, this release occurs through the action of a protein called "dynamin-related protein 1", which contributes to the formation of essential platforms for calcium transfer. As a result of this calcium mobilization, cytochrome C is released from the mitochondria into the cytosol.[4]

In this way, cytochrome C is responsible for transporting electrons from Mitochondrial Complex III to IV during the process of oxidative phosphorylation, promoting, as a result, the synthesis of adenosine triphosphate (ATP). Due to the relevance of ATP for promoting the metabolism of several cell pathways, occasional inadequate transcriptions of the Bax protein by the *BCL2* gene can impede the synthesis of this compound, causing cell death due to hypoxia and acidification of the environment. This process is due, respectively, to the absence of electrons for the bond with oxygen and the formation of H^+ in the intracellular environment; both adversities are caused by the absence of cytochrome C and ATP molecules in the cell.[1]

Therefore, once the importance of cellular control to guarantee successive cell division is understood, there is a need to address oncogenic factors to understand the successive manifestation of tumors in the Central Nervous System (CNS).

Oncogenic Factors

Modifications in genes that stimulate cell division can affect the cell due to intense and/or deregulated regulatory signals, which come from intrinsic and extrinsic sources, such as, respectively, results from the metabolism of deoxyribonucleic acid (DNA) and irradiation, thus configuring in mutations in the genes responsible for the transcription of proteins acting in the "checkpoints" stages.[5] Furthermore, this mutant process it may result from a resistance on the part of these mutant cells to the apoptosis process, which contributes to causing oncogenic cellular products, giving the cell growth advantages and phenotypic transformations in relation to other functional units.[2,6] However, under normal physiological conditions, the genes that act positively in inducing the cell cycle are called proto-oncogenes, because, if they present mutations, there is the possibility of becoming oncogenic; while the genes influential in protecting and blocking the cell cycle are called tumor suppressor genes.[2]

In this sense, to systematize an explanation about the impact of these types of genes on oncogenic modulation in primary CNS tumors, the following stand out: Tumor Protein p53 (*TP53*), Isocitrate Dehydrogenase (*IDH*) and Telomerase Reverse Transcriptase (*TERT*).

TP53 Gene

The *TP53* gene is a tumor suppressor gene that is predominantly associated with Gliomas, but can also be associated with Medulloblastoma.[7] It can be understood as a great detector of damage to genetic material, as its transcription factor coordinates the expression of several genes that act in different cellular responses to conditions of oxidative stress in the cell.[8] Like these cellular control factor pathways, there is predominantly DNA repair through the association between the *TP53* gene and the p21 protein. This repair occurs through the elevation of *TP53* levels because of the perception of any cellular stress, inducing the transcription of p21. This activation contributes to the promotion of DNA repair, since, when activated, p21 performs its function of preventing the cyclin-CDK bond from being made, which, consequently, inhibits the phosphorylation of the Rb protein, thus allowing, a repair of genetic material.[2]

Therefore, due to its important reparative role, abnormalities in the *TP53* gene can compromise cellular repair and can induce the cell to synthesize proteins related to negative control of the cell cycle. Thus, this mutant process can be understood by the acetylation of *TP53* in response to possible cellular stress, which results in a selective induction of the inhibition of pro-apoptotic genes, such as the *BCL2* gene, with the possibility of preventing apoptosis of the mutant cell, which can result in a change in the cellular phenotype, establishing the primary tumor.[9]

IDH Gene

The *IDH* gene is a proto-oncogene that is predominantly found in its mutant form in Gliomas, which are one of the main types of primary tumors of the CNS.[7] In this context, the role of this gene is in the transcriptional synthesis of the isocitrate dehydrogenase (IDH) enzymes, which are divided into three types according to the transcription of their respective genes, namely: "IDH1" enzyme - transcribed by the *IDH1* gene, is located in the cytoplasm and in the peroxidase; "IDH2" enzyme - transcribed by the *IDH2* gene, is located in the mitochondria; and "IDH3" enzyme - transcribed by the *IDH3A*, *IDH3B* and *IDH3G* genes, also located in the mitochondria.[10] Thus, these enzymes are responsible for catalyzing, in the third stage of the citric acid/tricarboxylic acid cycle, the oxidative decarboxylation of isocitrate into α-ketoglutarate and carbon dioxide, synthesizing, at the end of this process, Nicotinamide Adenine Dinucleotide Phosphate (NADPH).[10–12]

In this sense, of the three enzymes mentioned, the IDH1 enzyme stands out, as it can be a factor in preventing cellular damage because of its regulation of epigenetic modifications and the stabilization of demethylated histones that result from oxidative stress to the cell, thus promoting control of cell proliferation.[12]

Thus, a mutation in the IDH1 enzyme by the *IDH1* gene can compromise the synthesis of NADPH, preventing the restoration of glutathione, which is a tripeptide with important antioxidant action in the cell. This effect of inhibiting glutathione synthesis is the advent of an accumulation of free radicals in the cell, due to the decrease in antioxidant agents and the increase in the generation of oxidizing substances, reflecting, in the structure, a state of oxidative stress that can favoring lesions at the levels of DNA bases, which may lead to the establishment of a primary tumor.[12]

In this way, in addition to the aforementioned adversities, specific mutations in the *IDH1* gene contribute to a modification in its active site, resulting in the loss of the ability of its transcribed enzymes to decarboxylate isocitrate and the synthesis of an onco-metabolite product called 2-hydroxyglutarate (2-HG).[13] This mutant metabolite is involved in several tumor biological changes, notably blocking the histone demethylase enzyme, resulting in DNA hypermethylation and, consequently, changes in gene expression.[14,15] Furthermore, another important factor to be highlighted is that 2-HG can affect the function of non-tumor cells that are around this tumor, thus emphasizing neurons and immune cells, given, again, the prevalence of this gene mutant in the Gliomas.[16]

TERT Gene

The *TERT* gene is a proto-oncogenic gene that is, predominantly, associated with Gliomas and Meningiomas.[7] Thus, this gene acts in the transcription of the telomerase reverse transcriptase enzyme or, simply, telomerase; which has the function of acting in the maintenance of telomere length, which is an extremely relevant factor for the cell, since telomeric length correlates with the process of cellular

senescence, which is characterized by the arrest of cell division due to the absence of telomerase enzyme.[17]

Furthermore, the eventual shortening of these structures is promoted at the end of the entire cell cycle, impacting the cell in a stage of aging so that, only then, it is possible to enter the senescence phase. This process occurs through the continuity of Mitosis cycles, since for each of these phases there is a progressive loss of telomeres. Thus, when telomeres reach their critical shortening stages, the cell loses its replicative capacity and undergoes apoptosis, this phenomenon being called the Hayflick Limit.[18]

Thereby, tumor cells can avoid their Hayflick Limit due to the fact that there is a mutation in the *TERT* gene that leads to overexpression of telomerase.[19] This increase in expression is due to mutations in certain locations of this gene that result in new binding sites for a family of proteins called E-twenty-six (ETS). Therefore, with the possibility of greater connections between *TERT* and ETS, there is, as a result, a maintenance of positive regulation of the gene in its mutant state, contributing to the conservation of telomere length in tumor cells.[18]

In this sense, even in a state of senescence, cancerous structures can reactivate their telomerases, giving them cellular dysregulation, making it possible to impede the apoptosis process and, consequently, the continuation of mutant cell division.[19]

Classification of CNS Tumors

Tumors in the CNS can be classified according to their grades of clinical-biological behavior, being idealized by histological, immunohistochemical, cytogenetic patterns and, recently, by molecular biomarkers.[20] These standards contribute to evaluating and classifying the grades of tumor variation, which can range from 1 to 4.

In that regard, to exemplify these grades of classification, a subdivision of Gliomas, Astrocytomas, was used as a representation, given their best definition in terms of the presence of biological indicators, such as necrosis and cell proliferation.

Thereby, grade 1 tumors have lesions with low proliferative potential with a high possibility of cure after treatment. The grade 2 proliferates slowly and may or may not invade adjacent brain tissue. The grade 3 has a high rate of proliferation and invasion of normal tissue, with a high rate of recurrence. Finally, grade 4 tumors correspond to tumors with higher rates of mitotic activity, with a tendency to form necrosis and/or microvascular proliferation, with the possibility of infiltration into the surrounding tissues and craniospinal metastasis.[21]

This structuring in grades of variation was designed, mainly, to provide greater flexibility of use in relation to the type of tumor, highlight biological similarities and adapt CNS tumors to other tumors that did not belong to that location.[7]

Failures in cellular control processes result in conditions favorable to a greater expression of primary tumors in the CNS. Among primary CNS tumors, Gliomas, Meningiomas and Medulloblastomas are the most prevalent and stand out for the highest expression of mutant genes.

Gliomas

Gliomas can be understood as tumors that affect Glial cells, ranging from grade 1 to grade 4. This group of tumors includes oligodendrocytes (oligodendrogliomas), ependymal cells (ependymomas) and, predominantly, astrocytes (astrocytomas). Its epidemiology is predominantly composed of adult men, with, due to the presence of 4 types of grades, a wide rate of variation in the survival of this sample space.[22] Thus, such cellular structures, together with clinical-biological behaviors, contributes to the recognition of the division of Gliomas into 6 defined Molecular types, namely: Adult-type diffuse gliomas, Pediatric-type diffuse low-grade gliomas, Pediatric-type diffuse high-grade gliomas, Circumscribed astrocytic gliomas, Glioneuronal and neuronal tumors; and Ependymomas.[7]

Adult-type Diffuse Gliomas

Adult-type diffuse gliomas are subdivided into 3 types: Astrocytoma, *IDH*-mutant; Oligodendroglioma, *IDH*-mutant, and 1p/19q-codeleted; and Glioblastoma, *IDH*-wildtype.[7] (►**Fig. 3**)

Pediatric type Diffuse Low-Grade Gliomas

In reference to Pediatric-type diffuse low-grade gliomas, they are subclassified into 4 types: Diffuse astrocytoma, *MYB*-altered or *MYBL1*-altered; Angiocentric glioma; Polymorphous low-grade neuroepithelial tumor of the young; and Diffuse low-grade glioma, MAPK pathway-altered.[7] (►**Fig. 3**)

Pediatric type Diffuse High-Grade Gliomas

Pediatric-type diffuse high-grade gliomas are sub-related into 4 types: Diffuse midline glioma due to histone 3 (H3) alteration in the *K27* gene (Diffuse midline glioma, H3 *K27*-altered); Diffuse hemispherical glioma due to H3 mutation in the *G34* gene (Diffuse hemispheric glioma, H3 *G34*-mutant); Diffuse pediatric-type high-grade glioma, H3-wildtype and *IDH*-wildtype; and Infant-type hemispheric glioma.[7] (►**Fig. 3**)

Circumscribed Astrocytic Gliomas

Circumscribed astrocytic gliomas are segmented into 6 types: Pilocytic astrocytoma; High-grade astrocytoma with piloid features; Pleomorphic xanthoastrocytoma; Subependymal giant cell astrocytoma; Chordoid glioma; and Astroblastoma, *MN1*-altered.[7] (►**Fig. 4**)

Glioneuronal and Neuronal Tumors

Glioneuronal and neuronal tumors are fragmented into 14 types: Ganglioglioma; Desmoplastic infantile ganglioglioma/Desmoplastic infantile astrocytoma; Dysembryoplastic neuroepithelial tumor; Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters; Papillary glioneuronal tumor; Rosette-forming glioneuronal tumor; Myxoid glioneuronal tumor; Diffuse leptomeningeal glioneuronal tumor; Gangliocytoma; Multinodular and

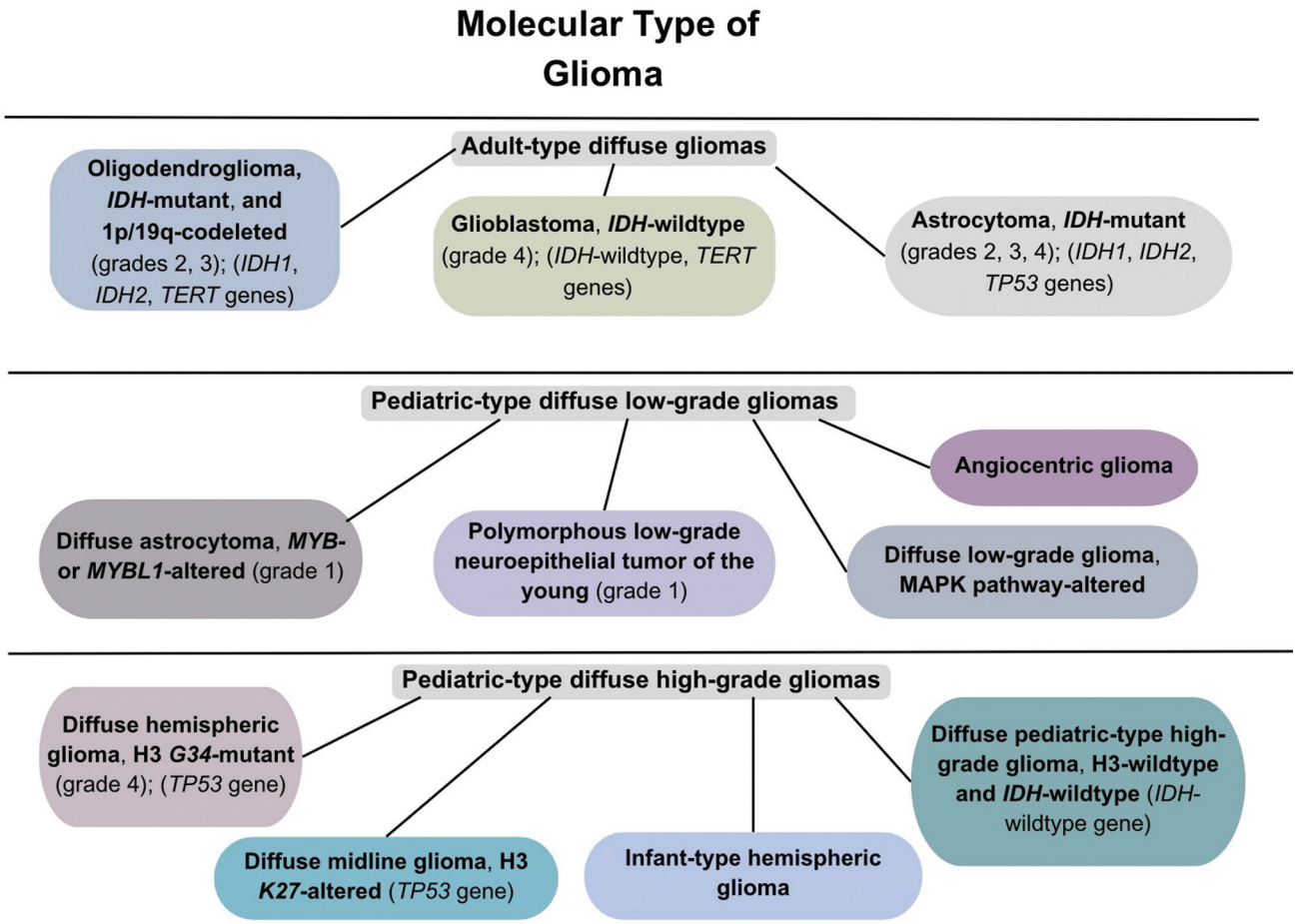

Fig. 3 Illustrative representation of the Molecular type of Glioma: Adult-type diffuse glioma, Pediatric-type diffuse low-grade glioma, Pediatric-type diffuse high-grade glioma. For certain types of gliomas, there are still no definitive grade classification criteria. Tumors that mention the *TP53*, *IDH* and *TERT* genes have a direct mutation relationship with them.

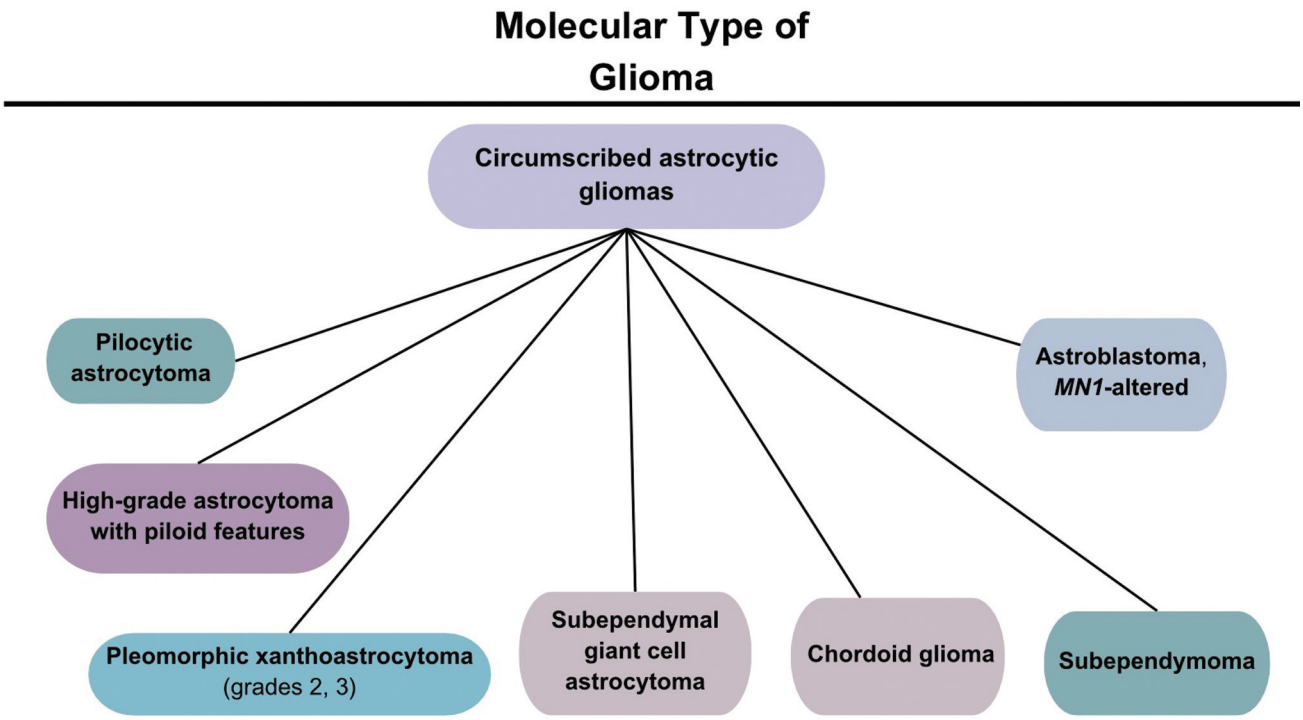

Fig. 4 Illustrative representation of the Molecular type of Glioma: Circumscribed astrocytic glioma. For certain types of gliomas, there are still no definitive grade classification criteria.

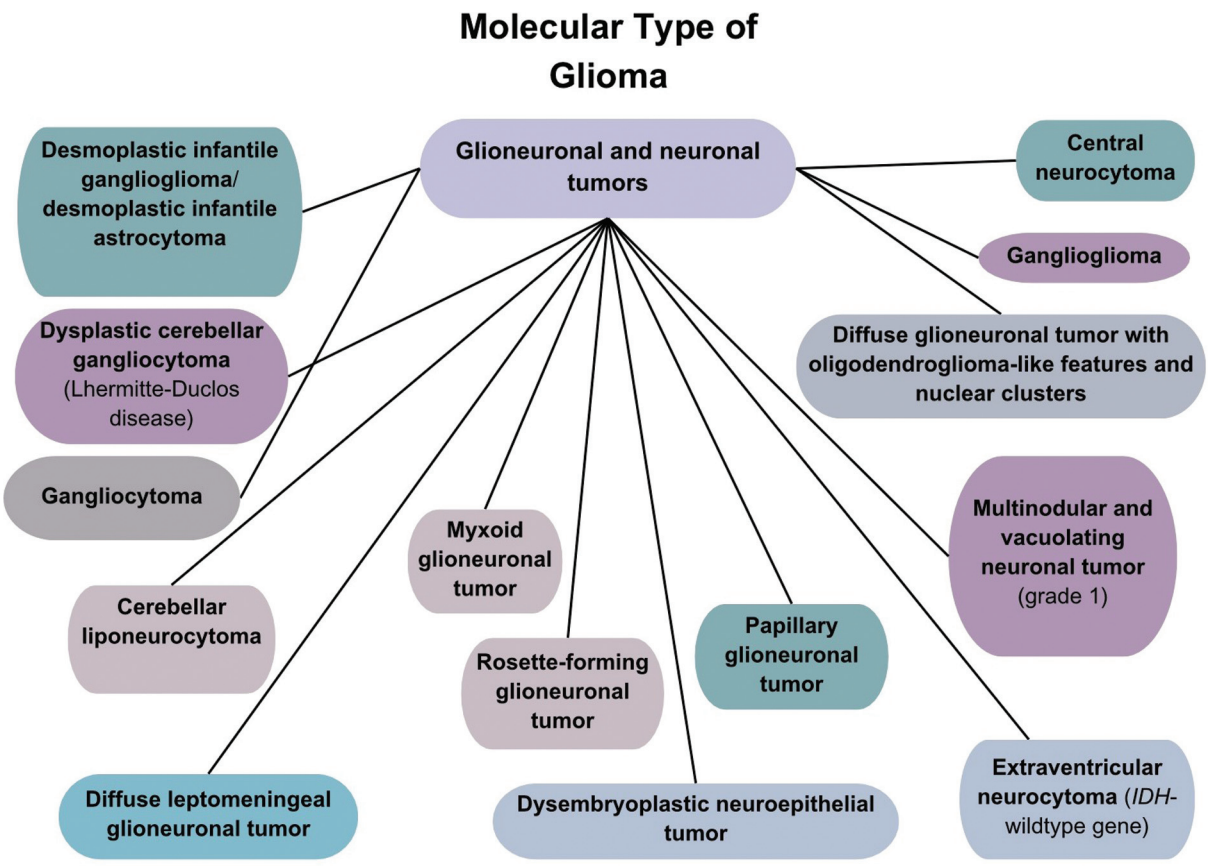

Fig. 5 Illustrative representation of the Molecular type of Glioma: Glioneuronal and neuronal tumors. For certain types of gliomas, there are still no definitive grade classification criteria. Tumors that mention the *IDH* gene have a direct mutation relationship with it.

vacuolating neuronal tumor; Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease); Central neurocytoma; Extraventricular neurocytoma; and Cerebellar liponeurocytoma.[7] (►**Fig. 5**)

Ependymomas

In reference to Ependymomas, they are sub-fractionated into 10 types: Supratentorial ependymoma; Supratentorial ependymoma, *ZFTA* fusion-positive; Supratentorial ependymoma, *YAP1* fusion-positive; Posterior fossa ependymoma; Posterior fossa ependymoma, group *PFA*; Posterior fossa ependymoma, group *PFB*; Spinal ependymoma; Spinal ependymoma, *MYCN*-amplified; Myxopapillary ependymoma; and Subependymoma.[7] (►**Fig. 6**)

Meningiomas

Meningiomas are the most prevalent representatives of primary CNS tumors. Its epidemiology is mainly composed of adults over 65 years of age, being twice as common in womans.[20] Thus, Meningiomas can only classify their grades of variation from 1 to 3; therefore, they are interpreted as tumors that affect the meninges, encompassing Dura mater, Arachnoid mater and Pia mater.[7]

Such tumors are classified according to their clinical-biological characteristics into just one Molecular type, which is the Meningioma itself, which has a direct mutation relationship with the *TP53* gene; however, due to its broad morphological spectrum, it is reflected in several Histological subtypes, notably Meningiomas: Meningothelial, Fibrous, Transitional, Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Atypical, Chordoid, Clear cell; and Anaplastic. Of these histological subtypes mentioned, the only one considered malignant is Anaplastic, as it has a grade of variation of 3.[23] (►**Fig. 7**)

Medulloblastomas

Medulloblastomas are the most prevalent primary malignant tumors in pediatric cases, representing around 20% of tumors for this sample space; being predominantly located in the cerebellar region.[24]

In this context, Medulloblastomas, as well as the other tumors mentioned, can be classified according to their clinical-biological behavior into 4 defined Molecular types, namely: Medulloblastoma, Wntless (WNT) protein-activated (Medulloblastoma, WNT-activated); Medulloblastoma, Sonic Hedgehog (SHH) protein-activated and *TP53*-wildtype (Medulloblastoma, SHH-activated and *TP53*-wildtype); Medulloblastoma, SHH-activated and *TP53*-mutant; and Medulloblastoma, non-WNT/non-SHH. Furthermore, in relation to its histological classification, it can be presented as "Histologically defined Medulloblastoma", encompassing 4 subtypes: Classic; Desmoplastic; Medulloblastoma with extensive nodularity (MBEN); and Anaplastic. It is worth mentioning that all these Medulloblastomas mentioned have

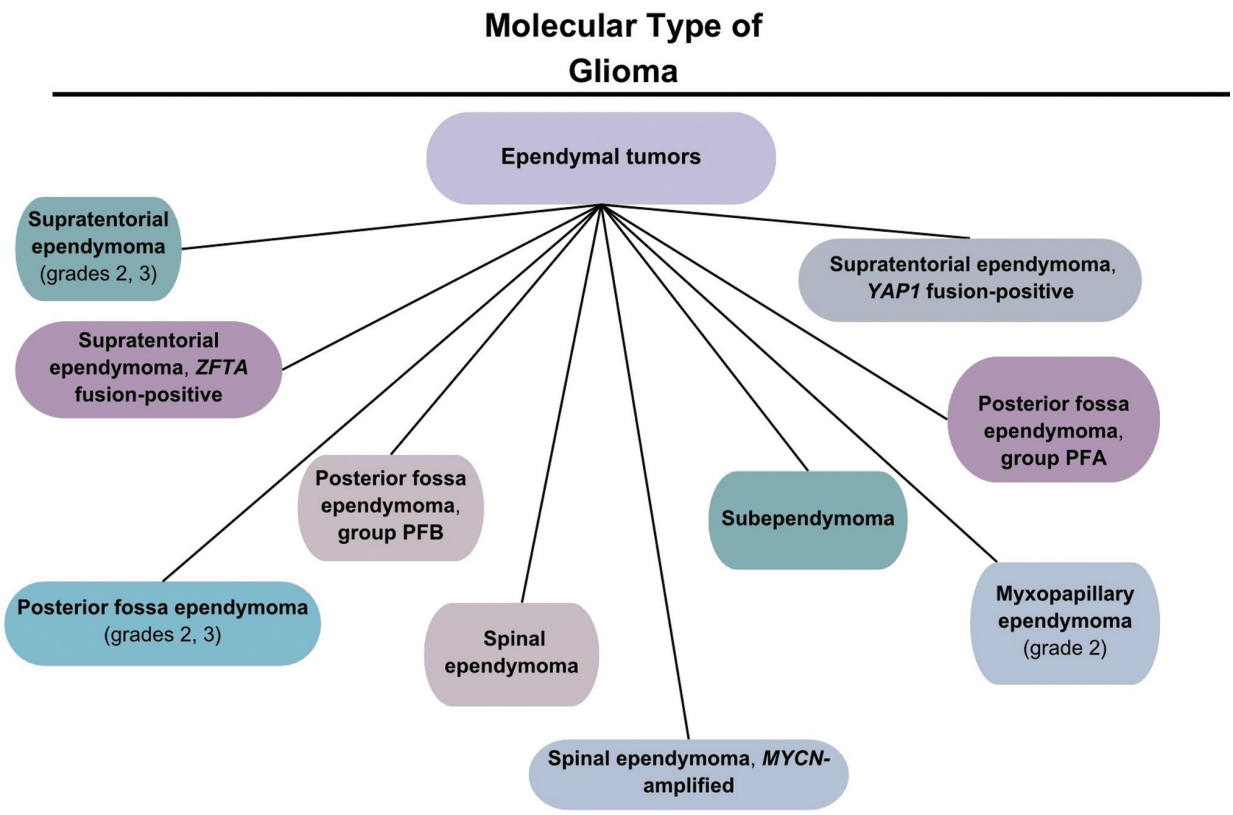

Fig. 6 Illustrative representation of the Molecular type of Glioma: Ependymomas. For certain types of gliomas, there are still no definitive grade classification criteria.

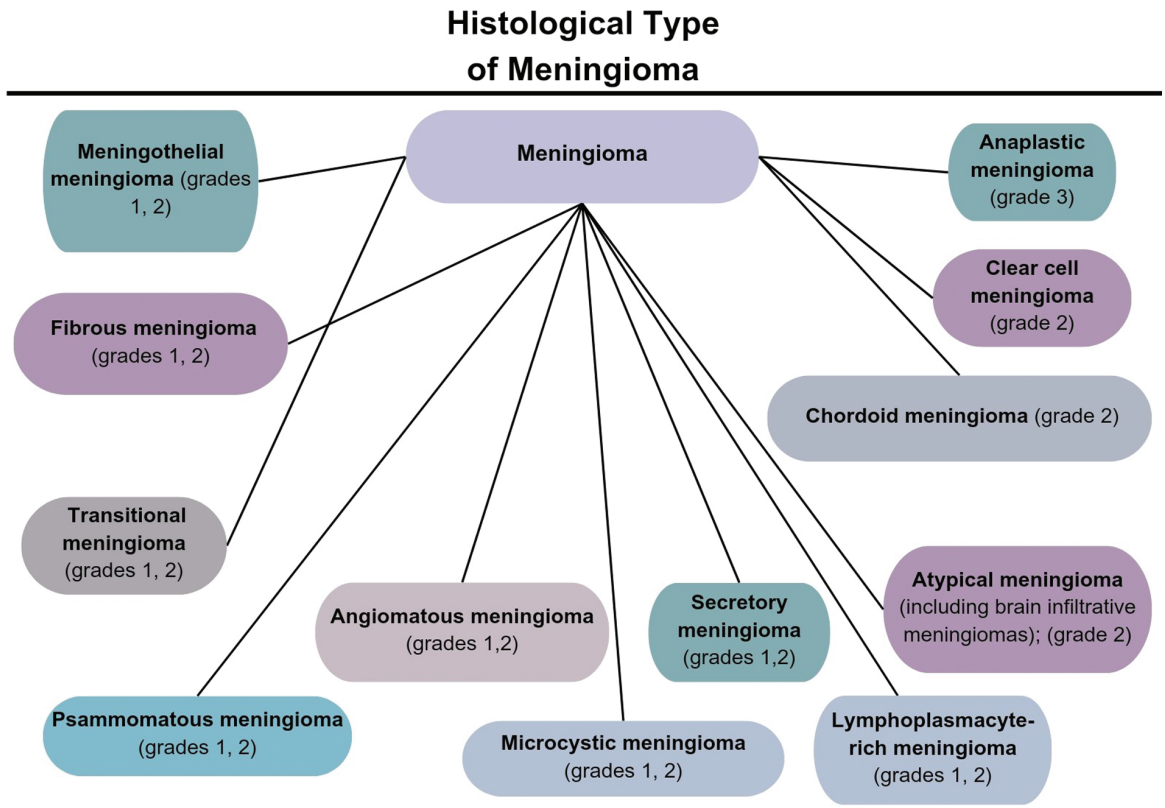

Fig. 7 Illustrative representation of the Histological type of Meningioma: Meningothelial, Fibrous, Transitional, Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Atypical, Chordoid, Clear cell and Anaplastic. All types of Meningiomas have a direct mutation relationship to the *TERT* gene.

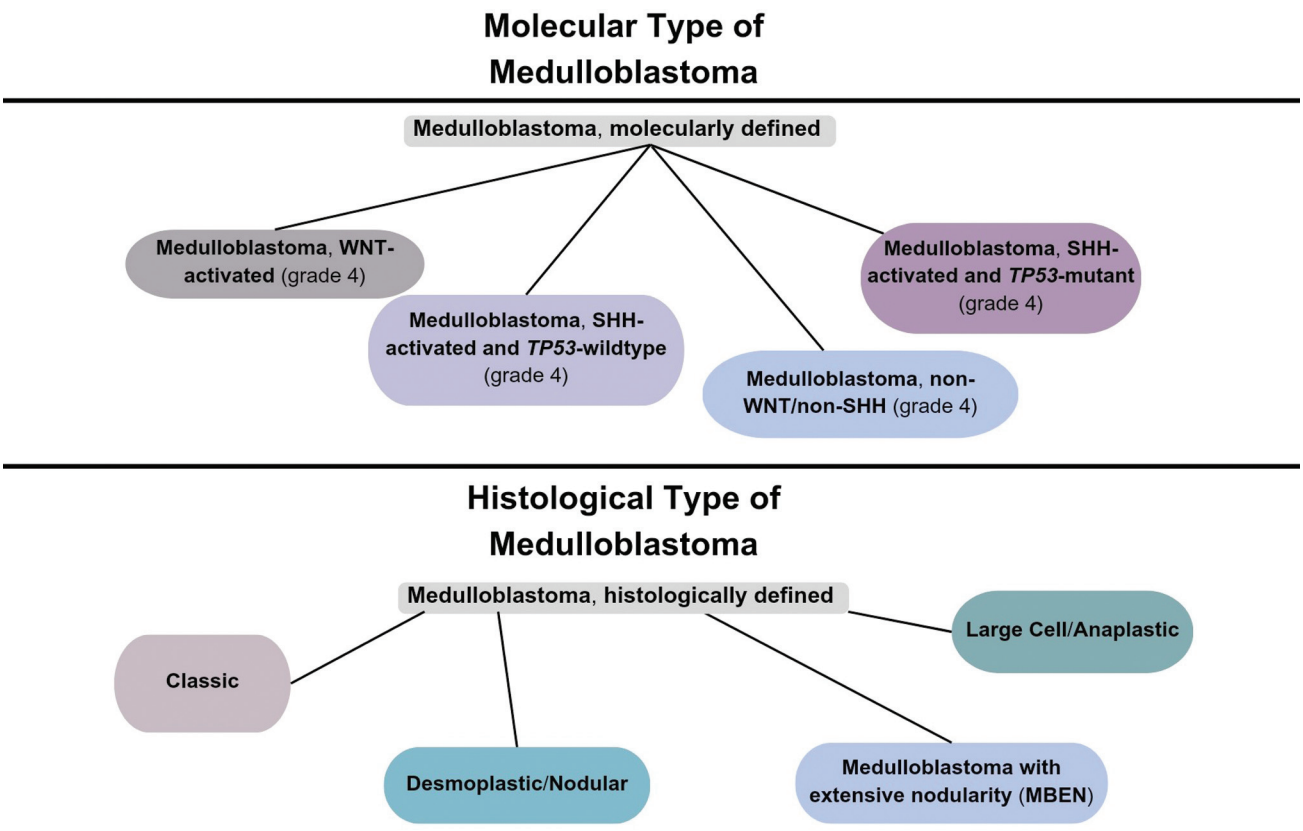

Fig. 8 Illustrative representation of the Molecular and Histological types of Medulloblastoma. For the Molecular type there are: Medulloblastoma, WNT-activated; Medulloblastoma, SHH-activated and *TP53*-wildtype; Medulloblastoma, SHH-activated and *TP53*-mutant; and Medulloblastoma, non-WNT/non-SHH. For the Histological type there are: Classic, Desmoplastic, Medulloblastoma with extensive nodularity (MBEN) and Anaplastic. Tumors that mention the *TP53* gene have a direct mutation relationship with it.

a grade 4 variation, making them extremely susceptible to the oncogenic process of metastasis.[7] (►**Fig. 8**)

Discussion

Furthermore, in relation to the types of Gliomas mentioned, these 7 types stand out: Astrocytoma, *IDH*-mutant; Oligodendroglioma, *IDH*-mutant, and 1p/19q-codeleted; Glioblastoma, *IDH*-wildtype; Diffuse midline glioma, H3 *K27*-altered; Diffuse hemispheric glioma, H3 *G34*-mutant; Diffuse pediatric-type high-grade glioma, H3-wildtype and *IDH*-wildtype; and Extraventricular neurocytoma. Such caveats were recommended, since these tumors are directly related to the mutant genes, such as the *IDH*, *TERT* and *TP53* genes. Given this reasoning, it is possible to relate the mutations occurring in these genes to the types of primary tumors mentioned, which thus develops the respective carcinogenic mechanisms of these structures. For example, there is the "Diffuse midline glioma, H3 *K27*-altered" and the "Diffuse hemispheric glioma, H3 *G34*-mutant", due to the fact that these present mutations in the *TP53* gene.[7] Thus, as already discussed, mutations in this gene can compromise cellular repair, inducing the cell to synthesize proteins related to negative control of the cell cycle, such as inhibition of the apoptosis process.[8]

In this sense, Meningiomas have a prevalent mutation in the *TERT* gene, since the increase in the frequency of mutations in this gene is directly proportional to the increase in the degree of variation in the tumor.[25] This fact can serve as an impact to result in the carcinogenic mechanisms mentioned, such as preventing the action of the telomerase enzyme in the shortening of telomeres, preventing the cell from entering the state of senescence, which, consequently, allows the continuation of the process of cellular replication of the mutant structure.[17] Furthermore, another adversity that has been recognized in Meningiomas that can cause an increase in expression in the *TERT* gene is hypermethylation in the DNA site called cytosine-phosphate-guanine (CpG). Thus, CpG hypermethylation may be associated with the inactivation of several tumor suppressor genes, such as *TP53*, which is a possible explanation for why there is an increase in the expression of the proto-oncogenic genes, like *TERT*.[26] Therefore, the presence of mutations in the *TERT* gene can be considered as biomarkers for therapeutic interventions, since these genetic changes are associated with greater risks of tumor recurrence and progression.[27]

Thereby, it is observed that Medulloblastomas are more susceptible to mutations in the TP53 gene, with the following molecular types standing out for this condition: Medulloblastoma, SHH-activated and *TP53*-wildtype; and Medulloblastoma, SHH-activated and *TP53*-mutant.[7] Thus, these mutant adversities may be associated with the epidemiology of Medulloblastomas, since the mutant state in the *TP53* gene is commonly observed in pediatric cases and, rarely, in adult

cases. Furthermore, because of this relationship between the *TP53* mutation and Medulloblastoma, there is, for pediatric cases, a frequent association of "Medulloblastoma, SHH-activated" with Li-Fraumeni syndrome, conferring a worse prognosis for carcinogenesis.[28]

Conclusion

Therefore, it is concluded that the process of carcinogenesis in the CNS is determined by the advent of failures in cell cycle control processes, with mutations in genetic factors being a direct result of this process. Such genetic mutations, evidencing those of the *TP53*, *IDH* and *TERT* genes, are dominant conditions for the development of Gliomas, Meningiomas and Medulloblastomas, causing, due to the phenotypic alteration of the affected cells in the locations of these primary tumors, the modification of cellular parameters morphological, genetic, histological and immunohistochemical; thus, demonstrating a deregulation of the clinical-biological behavior of the cellular structures.

Conflict of Interests
The authors have no conflict of interests to declare.

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