Gene Mutation and Epigenetic Modification Origin in Glioma Initiation: Are the GDNF and SOX1 Overexpression the Causes of Its Initiation?

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ABSTRACT

The extrinsic and intrinsic factors are essential in glioma initiation. Many extrinsic factors (UV, radiation, food, etc.) and intrinsic factors (proteins, hormones, ageing, DNA and RNA damages, etc.) was reported to being responsible for glioma initiation and progression. However, the cell responsible for glioma origin is still unknown. Many research papers have reported that glioma stem cells, senescent cells, injured cells, and death neurons are the cells of glioma origin. However, gene mutation and oncogene protein overexpression doesn't occur only in cancer but during life evolution. The source of genetic mutations has become a fundamental issue in understanding its role in the initiation of glioma. The glioma is the precise coordination of several distant factors that work together in the initiation and development of glioma. However, the role and effects of the genes (GDNF and SOX1) on cancer cells are well known, but their gene mutation origin is controversial. Several models and theories have been proposed to explain the origins of GDNF and SOX1 genetic mutations and epigenetic modification related to cancer. Our aim in this review

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is to clear that incertitude about glioma origin (gene mutation and epigenetic modifications) and those factors involved in glioma initiation and recurrence.

Keywords: GDNF, SOX1, CAFs, senescence, aging cell, methylation, tumour, and glioma

INTRODUCTION

Glioma is the deadliest tumour of the central nervous system. The increasing number of patients suffering from glioma and the complex risk factors have shown that this disease evolves and changes form [1]. Despite the advanced discovery on cancer initiation and their manifestations in the study of cancer stem cells, the mechanism of action and the origin of glioma is still a holy grail of cancer research [1-4]. However, many brain cells was reported as being responsible for glioma initiation through a strange physiological and genetic phenomenon that occurs in one cell and induces the transformation of other multitude cells [5]. Genetic materials in the cells undergo a constant modification for the implementation of some tasks depending on the body's needs. These modifications guide, direct, and attribute the cells towards a specific function. Gene modification can be physically mutation (deletion, addition) of sequence or nucleic base during DNA and RNA maturation (splicing), and epigenetic changes especially the addition of molecules without altering the DNA or RNA sequence how a single cell accumulate, all genetic and epigenetic mutations are still not well known. The overexpression of oncogenes during embryogenesis, inflammations, and other diseases (meningitis, wound, etc.) during life processes not always lead to glioma or other cancers, prompting questions about the initiation of the glioma. Can glioma be due to an exaggerated increase in a specific oncogene expression or due to niche modification? In this review, we will briefly discuss and highlight the origin of

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gene modification and epigenetic modifications on GDNF and SOX1 genes during embryos development to adults in which their overexpression affects the brain neurons function due to a perpetually changes in cell protein levels according to the body needs.

Eukaryotic cell and genetic mutation origin

Eukaryotes are the type of cells characterized by the presence nucleus in which the chromosome containing the genetic materials. The main molecular systems and machinery of Eukaryotes are found in Prokaryotes, most especially, Archaea. The simplest interpretation is to consider the Eukaryotic cell as the result of successive symbioses between Archaea and Bacteria. The eukaryotic cell, like we know today, has originated for many centuries as a result of the symbiotic association between a host cell and microorganism according to the evolution theory. This symbiosis includes the fusion of genetic information and physical elements of two cells into a single cell. After the apparition of the first eukaryotes, life started to evolves from a single cell to an association of many cells to form one organism (metazoans) such as a human. During this process of evolution, many modifications occur in the management of the DNA and RNA sequence of a species, which is essential for the adaptation of such animals and plants concerning their environment [6-9]. All metazoans originate from a single pluripotent eukaryotic stem cell in which many phenomena occur. The genetic materials fusion promote the apparition of novel characteristic and behavior that the first eukaryote cells don't have such as the cell structure modification, ability of cells to communicate each other, novel proteins expression and fecundation [9].

It was reported that genetic mutations and disorders occur during the process of cancer initiation [1, 4]. The mechanism related to the accumulation of all

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these genetic mutations in a single cell is still not clear. A lot of oncogenes are activated in glioma through DNA or RNA damages, gene sequence depletion, and epigenetic modifications (methylation, acetylation) [4]. All these genetic matters showed clearly that glioma initiation, aberrant oncogene amplification, and proteins overexpression, uncontrollable proliferation, malignancy, evolution plasticity of glioma cells, and their resistance to immune reaction are associated to genetic alteration. The complexity of genetic mutation in cancer is so much that even two daughter cells derived from the same cancer cell have a different genetic sequence; This explains the heterogeneity within tumour cells [10] and the various results derived from the same experiment (technology). Sometimes the researcher has to repeat the experiment many times before to get the expected results even sometime without success. These genetic modifications depend on the type of cells and the microenvironment where the cells are located.

Moreover, chow et al., 2011; Alcantara et al., 2016 [5, 11] reported that the glioma initiated cells would be a Neuronal stem cell (NSC) that can differentiate into other types of brain cancer cells. The reasoning is logical because neuron cells are all derived from a single stem cell capable of differentiating into various kinds of neuron cells, but it is not sufficient to conclude the origin of glioma cells. The first initiated cell is not always a stem cell or a neuron stem cell. All the cells can become a cancer cell, but the persistent and strong resistance of cancer stem cells is generally due to their ability to differentiate into several types of cells. Glioma cell origin or initiation largely depends on their microenvironment and extrinsic factors rather than intrinsic factors. However, all these factors are linked and influence each other. Cancer-associated fibroblasts (CAFs) and supporting cells such as glial cells are more exposed to extrinsic factors because they have more contact with other cells because their environment is prone to

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perpetual change and also benefit immune cells protection. The concept of glioma cell origin depends on a specific point that the researcher wants to highlight. There are no criteria to determine the cell responsible for the origin of gliomas. Stem cells are targeted for more perspective (resistance, differentiation) towards an eventual therapy. To understand glioma origin, we should go back to the source of the first eukaryotic cell.

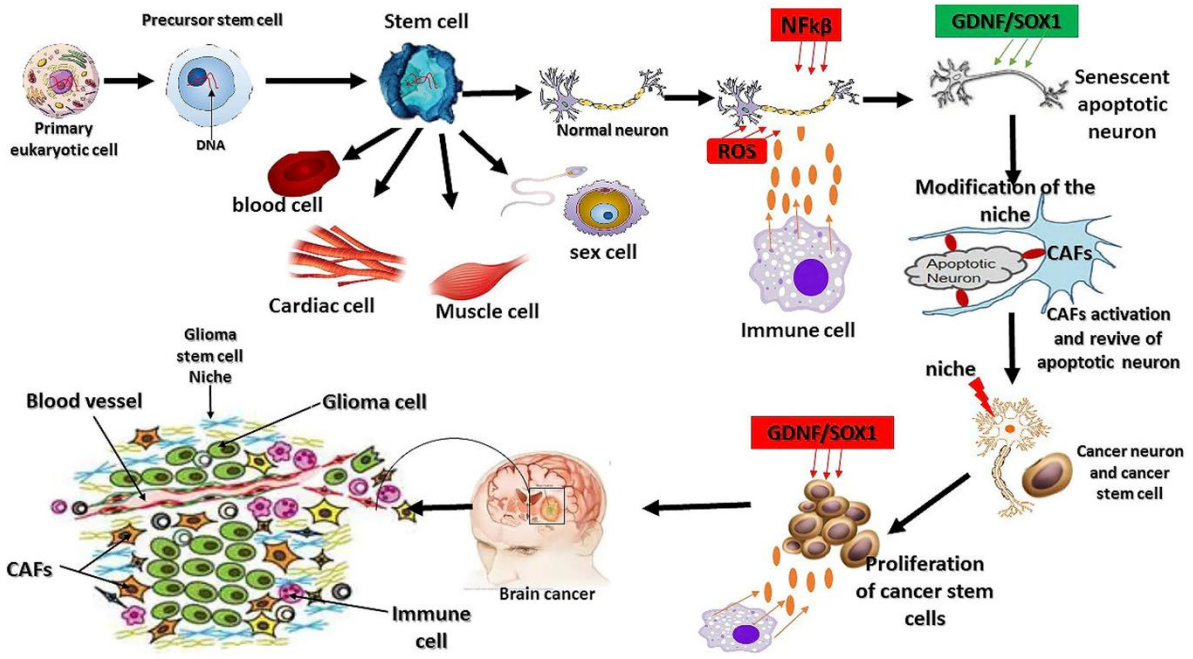

Figure 1: The origin of glioma cell mutations: senescent cell and the extrinsic factor promotes glioma cell and glioma stem cell initiation. *During life evolution, it was demonstrated that the eukaryotic cell like we know today originates from the symbiotic association between a host cell and microorganism. This physic association is also followed by a genetic mutation of the DNA, synthesis of some protein and modification of the cell structures. Cancer or glioma cells also behave like primary eukaryotic cells by modifying their structure, gene mutations, high synthesis of a novel oncogene. The extrinsic factors involved in the oxidative stress reaction which promote the overexpression of NFkβ and interleukin 1α to promote cell death and senescence. The response to*

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the oxidative stress reaction is the synthesis of certain oncogene such as GDNF, SOX1… and the activation of fibroblast cell to revive the senescent and death cells leading to the dysfunction of the revived neurons and the voluntary of the organism to maintain them alive via the overexpression of GDNF and SOX1 because of their neuroprotective effect and their protection by immune cells. This will allows the single revive neuron to proliferate, and their dysfunction ability can isolate other neurons and promote glioma progression. Stem cells are the origin of the organism tissue via their differentiation into many types of cells, but stem cells are not the origin of mutations involved in glioma because it is a legacy that inherited to the primary eukaryotic cell. The only factors which oriented the stem cell differentiation are the niche and other extrinsic factors.

a. Cancers trigger: the genetic mutation during species evolution promotes cell communication and adaptation.

The gene modifications during the transformation of a host cell into eukaryotic cell trigger a new behaviour "heterotrophy" which push eukaryotic cells to communicate and organize themselves to increase their survival rates. The necessity of this communication and survival behavior leads to a symbiosis between the primary eukaryotes and the bacteria, which drives the mitochondria to perform the metabolic machinery [6, 9]. This novel function and the abundance of nutrients trigger the necessity of cellular division for more dissemination and to mimic the extinction of species [9]. It is this necessity of the cell to divide that will cause the "**boom of gene mutation**" because of the old way of cell division "**scissiparity,**" which is the separation of a single cell into two identical clones, which was not the secure and efficient way for eukaryotes dissemination. To compensate these scissiparity limits, eukaryotic cells have to neglect asexual reproduction for sexual reproduction, which is a boon to their

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survival with a very high rate of spread and heterogeneity. This mixing of genetic pieces of information has reinforced communication between cells because sexual reproduction requires the communication and the fusion of two cells of the opposite sex, which was not the case with scissiparity. For this fusion of sex cells to be effective, eukaryotes have developed a new strategy called "chemotactic," which makes it possible to attract gametes to each other through genetic manipulation and protein synthesis. The success of this process has been the key to the development and evolution of species through gene manipulation and also marks the beginning of diseases linked to defective genes (cancer) [12] and malformation (trisomy 21).

b. Genetic mutation and gene overexpression during fecundation and embryo development is a precursor of glioma initiation

Fecundation is a crucial stage of life evolution and improvement in living beings [13, 14]. An error in these processes can lead to fatal or vital consequences in an individual. The increase in the expression of specific genes does not necessarily initiate cancer but participates step by step in its establishment throughout life by increasing the risk factors.

The fecundation and embryonic machinery development are activated and regulated by many genes and hormones that have oncogenic proprieties to let the egg cells to proliferate into an entire independent organism. In the early stage of embryonic development, many genes are activated, and their expression increases. Glial cell line-derived neurotrophic factor (GDNF) and sex-determining region box 1 (SOX1) are among the first proteins expressed in embryonic development during ectoderm and neural tube differentiation [1, 2, 15]. GDNF and SOX1 play an essential role in the nervous system (central and peripheral nervous system) differentiation. It was reported that GDNF and SOX1

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are highly overexpressed in glioma and promote glioma stem cell proliferation, invasion, and migration [2, 15]. However, the increase in the expression of GDNF or SOX1 is not necessarily followed by glioma or other types of cancer but can be a distant cause of its initiation. During embryonic development, the exaggerated increase in the expression of GDNF and SOX1 allows the proliferation of embryonic cells and their differentiation into several categories of specific neurons adapted to the future functions that will be assigned to them; it also enables the activation of the connections between neurons, their protection, and survival during the development processes. The role played by the growth factors and neurotrophic factors in cancer is undeniable, but their main function would be to ensure the integrity of the body and keep it in shape. This explains the increase in their expressions during the wound healing process and repairing infected tissues through their abilities to regenerate tissues. Glioma cancer cells took advantage of these proteins to proliferate and develop as in the case of an embryo to form a stable and resistant tumour. Therefore, the discoveries reported by (Lin LF et al. .1993 and Ayanlaja, A. A. et al. .2018) and (Archer, T. C.et al 2011 and Nitta, K. R. et al. 2006) [2, 15-17] are contradictory in terms of the role of SOX1 and GDNF overexpression in glioma initiation (trigger) but are consistent in terms of the properties of these proteins (GDNF and SOX1) on neuronal cell proliferation, invasion, and interconnection.

c. Genetic mutations and epigenetic modification of glioma cells regulate genes (GDNF and SOX1) expression.

- **GDNF/SOX1 methylation and histone acetylation**

GDNF gene is localized on chromosome 5 at p12-p13.1 and contains two promoters (I and II) and five exons [1]. SRY (SOX1) gene is localized on chromosome Y, but other researches also reported SOX1 gene to be located on the biggest chromosome 13 (chr13:112,067,599-112,071,706) and have 4,108

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bases in its sequence [2, 15, 18]. Recent studies demonstrated that epigenetic silencing of the tumour suppressor's gene promotes the overexpression of oncogenes to regulate cancer geneses, maintenance, and progression [18, 19]. The high expression of GDNF and SOX1 is due to epigenetic modifications that occur in the genome.

The methylation is a process in which a "methyl" group attaches itself to the carbon chain of another main molecule. In the case of epigenetic modifications, the "methyl" group binds itself to histone and lysine residues K4, K9... sometimes also to arginine [20, 21]. Methylation, in general cases, always occurs in chromatin in collaboration with some specific enzymes such as histone methyltransferases, which play a crucial role in the methylation process. Many types of research done in our laboratory and other research articles demonstrated the epigenetic modifications (methylation and acetylation), which occur in GDNF high expression in glioma [1, 22, 23]. In SRY superfamily, especially SOXB1, the case of methylation is almost the same as in TGFβ. Methylation or hypermethylation of the SOX1 gene is involved in glioma initiation and progression [24-27]. Lai, H. C. et al. [27] demonstrated that the methylation of PAX1/SOX1 in human papillomavirus (HPV) also increases the risk of cancer, especially in glioma and promotes GSC proliferation [28, 29]. Histone H3K9 is highly involved in GDNF gene methylation. In the case of SOX1, the Histone H3K4 methylation/acetylation is responsible for SOX1 overexpression and GSC initiation and proliferation by interacting with OCT4 [11, 30]. SOX1 gene methylation is not well known because some details remain not evident. The epigenetic modifications involved in GDNF and SOX1 are almost the same, but only the location of methylation is different, H3K9 for GDNF and H3K4 for SOX1. Glioma initiation is a continuous process of transformation in the brain cells. During nervous system differentiation, the brain neurons inherit the mutations

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from the neuronal stem cells that originate from the fecundation via mitosis. However, the origin of mutations and epigenetic modification in the brain cells is not well known. The neurons are derived from the neuronal stem cells, while the neuronal stem cell originated from the embryo egg cells and so on to the formation of primary eukaryotic stem cells which is the cell of origin for all metazoans. So the source of gene mutation started to the first eukaryote cell (stem cell).

The transmission of gene mutation generation by generation exposes some individuals rather than other related to the family genealogy. Two chromosomes express SOX1; chromosome 13 and chromosome Y. SOX1 overexpression due to chromosome 13 genetic sequence modification cannot be transmitted to the future generations, and the risk of getting nervous system cancer is not high but depend on the metabolism and environment of each descendant. Gonosomal chromosome Y SOX1 overexpression can only be transfer to males but not females. Gonosomal SOX1 expression increases the risk of cancer, but their initiation to glioma depends on the metabolism and microenvironment of the cells. These two cases show that the risk of glioma is lowest in autosomal than in gonosomal SOX1 expression. The significant factors of glioma initiation mainly depend on the microenvironment and other extrinsic factors. The niche plays a critical role in stem cell differentiation and their destiny.

All brain cells are susceptible to become brain cancer cells depending on the brain cell microenvironment. However, the genetic sequence of the body cells is different; the only factors that can change is the cell niche, microenvironment, which determines the big part of the function, metabolism, and future (differentiation, proliferation, apoptosis). The brain senescence cell stimulates the other brain neuron to produce more GDNF and SOX1 for their survival and

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proliferation, therefore trigger glioma initiation. During oxidative stress response (ROS), NFkβ, and interleukin one alpha (Il-1α) overexpressions promote inflammation to modify the cell microenvironment changes leading to the initiation of neurons senescence and death. During the senescence, GDNF and SOX1 play an essential role in reviving the apoptotic cells to initiate glioma [17]. This explains the fact that the increase in GDNF and SOX1 during embryogenesis doesn't promote glioma but just ectoderm and neural tube differentiation. The factors which regulate glioma initiation is more extrinsic (microenvironment, niche) rather than intrinsic (genetics); however, both factors are essential in glioma initiation.

1. **Genes mutations: one of the main trigger of glioma initiation**

a. **The gene mutation promotes niche modification and cancer-associated fibroblast (CAFs) activation**

The usual niche is composed of fibroblast, immune, endothelial and perivascular cells, extracellular matrix (ECM), cytokine network, and growth factor [31, 32]. The niche composition contributes to tumour cell heterogeneity and tumour progression, genetic diversity, and epigenetic modifications [33, 34]. Any changes in the niche composition affect stem cell renewal and differentiation ability. The overexpression of GDNF and SOX1 during human being development and diseases affect the niche fibroblast cell by promoting their proliferation as well as increases their metabolism. Fibroblast cell proliferation result from the reduction in the quality (low) of the niche and microenvironment, therefore, cause loss of protection of the fibroblast cell against apoptosis and promote the immune cells fusion to become like a "cement," i.e., unify the fibroblast into "**symbiotic colony**" a mass of tumour precursor cells. The fibroblast "**symbiotic colony**" can survive for a long time, thus waiting for an advantageous occasion

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(overexpression of growth factors, inflammation, injury) to grow and transform the surrounding cells and neurons into a tumour. It is well known that injury and inflammation cause DNA damage that can lead to the overexpression of the P53 gene to repair the DNA during which the DNA polymerase cut and join the DNA sequences leading to DNA methylation and acetylation [1, 17]. The methylation and acetylation of the DNA will activate the GDNF and SOX1 genes and increase their expression levels in the fibroblast colony microenvironment and likewise activate primary glioma tumour initiation and progression. At this stage of glioma, these primary glioma cells are not resistant and benefit from the protection by the immune system via the synthesis of interleukins (IL-6 and IL-8) and cytokines that make the tumours to adapt themselves to an immune reaction and start to develop their resistance. These clusters of cells acquired their resistance by adapting to their environments and the cytokines released by immune cells. A structural rearrangement of the DNA supports this phenomenon of adaptation by targeting and blocking the genes involved in sensitivity to these cytokines thus leading to structural reorganization of the plasma membrane at the level of hormone and protein receptors by reducing their sensitivity as much as possible. These clusters of cells being refractory to immune responses are free to manage their proliferation. This precursory phase becomes very resistant and almost indestructible thanks to glioma stem cells, which are cells capable of differentiating into several types of brain cells. The invasion of glioma stem cells in various kinds of tissue due to their ability to multiply, migrate, resistance, and extended life span properties.

In glioma, GDNF, a growth factor expression significantly increases [17]. The overexpression of GDNF promotes the recruitment and activation of Cancer-Associated Fibroblast (CAFs), leading to the initiation of inflammation and activation of an immune response [35]. These promote the synthesis of

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interleukine-6/8 (IL-6/8), and CD113 by T-cells to overcome and heal the injury [36]. CAFs will activate immune reaction and promote the overexpression of growth factors like CXCL12, IL-6, IL-8, Wnt /Notch to induce the differentiation of epithelial non-stem cells into tumor-initiating stem cells (TISC) and changed their phenotypes [37, 38]. The proliferation of CAFs cells affects glioma stem cell morphology, modification microenvironment, mesenchymal stem cells, and their implications in glioma stem cell proliferation and metastasis [37, 39]. Glioma stem cell proliferation promotes immunosuppression in the niche by adapting themselves to cytokine, chemokine, IL-6, and Transforming growth factor β (TGFβ), which will inhibit the immune cell receptors [36, 38].

b. The modification of the niche and microenvironment regulate cell to cell contact

Cell to cell interaction is indispensable to their survival. A single isolated cell eventually loses its functional capacity and dies by apoptosis because it is no longer receives stimulation (hormones, proteins) from its origin tissue. This situation increases the risk of cancer by increasing metalloproteinase-3 (MMP3) gene expression, which leads to genomic instability and causes tumour formation and GSC proliferation. A little modification in the niche significantly affects cell-cell contact and tumour initiation via secretion of the GSC marker, such as SOX1 [40].

The environment where the cell is located plays a crucial role in that particular cell survival in its tissue. A physical separation between cells and their tissue or niche increases the risk of its transformation into a cancerous cell, which can then circulate in the body through fluids, blood, lymph and cause damage to other parts of the body (migration, metastasis). The overexpression of GDNF may improve cell adherence and communication within the tissue via the

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synthesis of collagen regulated by fibroblast cells. Collagen overexpression promotes tumour cell contact, the ability to form a colony and resistance to immune cell attack. The overexpression of GDNF increases SOX1 expression level, which will interact with β-catenin to regulate the microtubule and actin filament by promoting α and β tubulin binding, the overexpression of F-actin and the extension of intermediate filament in extracellular microenvironment. Through these extensions, CAFs will bind to the epithelial-mesenchymal cells and initiate their transformation into tumour cells [39, 41].

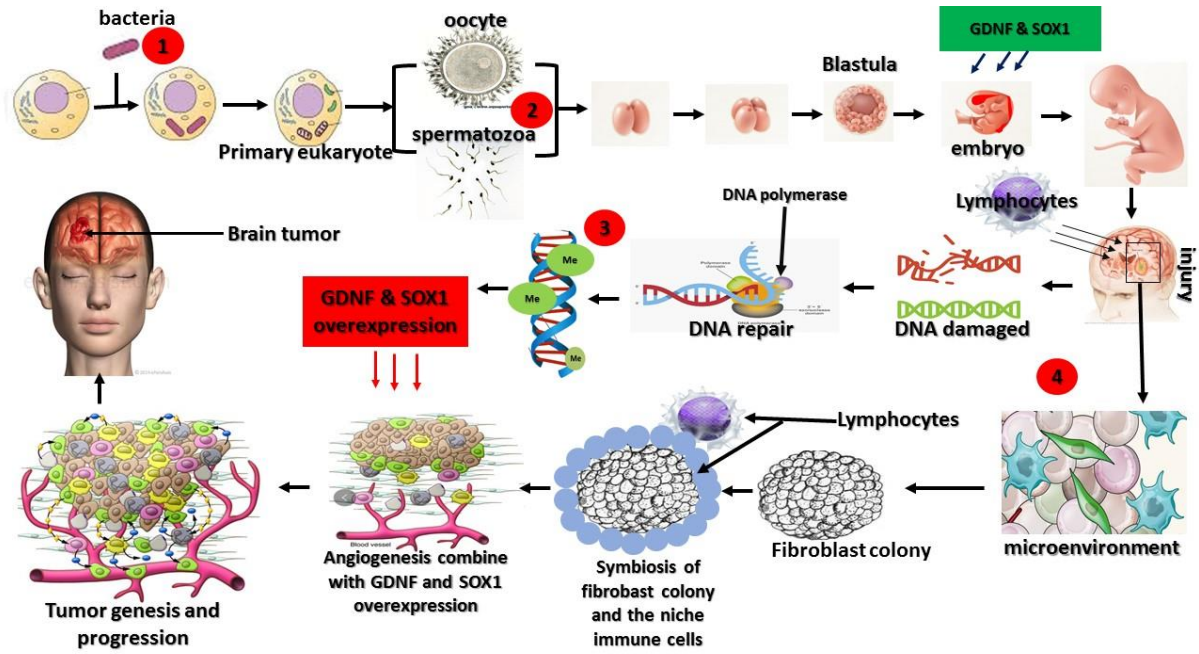

Figure 2: gene mutation and species evolution in glioma initiation and progression. *The origin of the eukaryotic cell by a symbiosis of a host cell with bacterial archaea is the first step of genetic mutations. From fertilization and gamete fusion to embryonic development, the modification and adjustment (mutation, methylation, and acetylation) of the DNA allows the differentiation of organs, during which the expression of specific genes increases considerably. Among the genes, GDNF and SOX1, which together play an essential role in the differentiation of the central and peripheral nervous system. Without external*

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causes such as infections, brain diseases (meningitis), the genetic information of specific brain cells such as neuronal cells cannot be damaged. The healing process of infections is also followed by the plugging of the damaged DNA strand which would be the cause of the epigenetic changes and the starting point for the transformation of these cells and their initiation to glioma. During the healing process, essential elements of the microenvironment (fibroblast, immune cells, etc.) undergo structural reorganization to complete the lack and loss of cells that have died from necrosis. These cells and immune cells will fuse (not physically) and proliferate to form fibroblast "colony" cells. This colony will persist until a further increase in the expression of GDNF and SOX1, which will lead to the transformation of these fibroblast colonies into cancerous fibroblast colonies hence the origin of the glioma. (1), (2), (3) and (4) on the figure showed the critical phenomenon of gene mutation and epigenetics modification.

Tumour recurrence after therapy: feedback control of GDNF and SOX1.

These modifications (methylation and acetylation) over-activated the target gene transcription, increases the activity of the proteins, and at the same time, activates a cascade of reactions that will affect (promote or silence) other gene expressions. Through the usage of next-generation sequencing (NGS) technology, research done in our lab showed that the overexpression of only GDNF in glioma stem cells (human and mouse) promotes a lot of genes overexpression. During that period, we also found that the increase in the expression of GDNF and SOX1 is also followed by the overexpression of other associated genes in which the expression depends on the GDNF and SOX1 gene [2, 15]. So glioma cell initiation started earlier since the apparition of eukaryotes and during embryo development (neurectoderm differentiation) in which genes mutation and epigenetic modification begin. During and after embryo

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development into an adult organism, many phenomena occur (disease due to virus, bacteria, infection, wound healing, vaccination, etc.) promoting genetic mutation and cell structure modification. During that period, the contracted disease, virus, bacteria RNA, and DNA can be associated with cell DNA leading to genomic mutations. All these genetic disruptions associated and accelerated by extrinsic factors such as UV, dugs, food, age will induce gliomas. Glioma and cancers have their origin and cause so far, but their development depends on triggers and accelerator factors.

The healed neuron cells after injury or inflammation can also transfer their mutations and epigenetic modifications (histone acetylation and methylation) to their daughter cells via mitosis. This will affect the neuroendocrine signaling leading to the overexpression of the oncogenes that was previously promoting glioma maintenance. The neuroendocrine system plays a critical role in glioma recurrence due to epigenetic modifications and genetic mutation, which enable feedback control of oncogenes expression and glioma initiation via the regulation of protein vesicles and neurotransmitters synthesis. Aging neurons can also cause the disorder and troubles in neuroendocrine and synapses system. The proliferation of aging neuron cells and the spread of damaged DNA via mitosis and the alteration of the central nervous system synapses is also one of the causes of tumour recurrence. The alteration of the neuroendocrine and synapses significantly affect neuron microenvironment and cancer-associated fibroblast initiation. This environment is favorable for glioma initiation or tumour recurrence after surgical resection.

CONCLUSION

Glioma is a long process of transformation and modification of brain neurons, and the gene mutation is one of the triggers of its initiation and malignancy. The

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gene mutation and epigenetic changes cannot induce glioma without the support of extrinsic factors. During every human being's development and life, the oncogene expressions perpetually increase because of the mutation of the gene sequences, but not all humans get cancer or glioma. Each individual is unique and genetically new to its progenitors; it is clear that genetic mutation only makes us more resistant or adapts us to our environments where we live by modifying our DNA to increase our chances of survival (evolution). Glioma cells would use this opportunity in their favor to diversify. Genetic mutations play a crucial role in the longevity of cancer cells but are unlikely (very low) to trigger glioma. Extrinsic factors (UV, radiation, pharmaceuticals, packaged food, etc.) are more dominant in the glioma initiation process. CAFs cells play a critical role in glioma initiation and spreading in the body, regarding the transformation linking CAFs to the first transformed cancer cells. The problem related to genetic materials showed that our cells are predefined to cancer even after fecundation, there is no cell of origin of glioma [42]. However, all the body cells are potent cancer cells, but only the trigger factors expose some cells more than others to become tumour initiated cells. This explains the recurrence of tumour cells after therapy or clinical resection and the ability of cancer cells to adapt themselves to the environment and drug [17]. The role of GDNF and SOX1 respective family groups is vital in the nervous system differentiation but also cancer initiation and progression [2, 15]. The protective effect of high GDNF and SOX1 on neurons and neuron progenitor cells is a solid proof that all the cells are defined to cancer, and cancer initiation is more a gradual than spontaneous process [17]. Both extrinsic and intrinsic factors mutually influence each other, but external factors are more involved in cancers (glioma) initiation. The best way to overcome glioma and cancers is to develop a better therapy approach targeting the damage cancer cell (DNA & RNA) and its microenvironment (fibroblast, support

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cells, immune cells) simultaneously. The treatment of cancer cells only by using stem cells without treating the external factors (niche/microenvironment) such as fibroblast cells and extracellular elements would be a failure.

List of abbreviations and their meanings

Glioma stem cell (GSC); Neuronal stem cell (NSC), *glucose transporters (GLUT1/4); glial cell line-derived neurotrophic factor (GDNF); sex-determining region box1 (SOX1), oxygen stress response (ROS), Temozolomide (TMZ); signal transducer and activator of transcription 3 (STAT3);* DNA methyltransferase (DNMT), calcium ions (Ca^{2+}), next-generation sequencing (NGS), metalloproteinase-3 (MMP3), extracellular matrix (ECM), cancer-associated fibroblast (CAF), tumor-initiating stem cells (TISC), Catenin Alpha 2 (CTNNA2), interleukin (IL-6).

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