Elucidating the pathogenic and biomarker potentials of FOXG1 in glioblastoma

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Abstract

Glioblastoma (GB) is an extremely pugnacious brain cancer originating from neural stem (NS) cell-like cells. Forkhead box G1 (FOXG1; previously recognized as BF-1, qin, Chicken Brain Factor 1, or XBF-1 and renamed FOXG1 for mouse and human, and FoxG1 for other chordates) is an evolutionary preserved transcription factor driven from the forkhead box group of proteins FOXG1 modulates the speed of neurogenesis by maintaining progenitor cells in a proliferative mode as well as obstructing their differentiation into neurons during the initial periods of cortical formation. FOXG1 has been implicated in the formation of central nervous system (CNS) tumors and precisely GBs. Pathophysiology, joint actions of FOXG1 and phosphatidylinositol-3-kinases (PI3K) intermediate in intrinsic resistance of human GB cells to transforming growth factor-beta (TGF-β) stimulation of cyclin-dependent kinase inhibitor 1(p21Cip1) as well as growth inhibition. FOXG1 and NOTCH signaling pathways may functionally interrelate at different stages to facilitate gliomagenesis. Furthermore, FoxG1 actively contributed to the formation of transcription suppression complexes with corepressors of the Groucho/transducin-like Enhancer of split (Gro/TLEs). Also, FOXG1 was stimulated by Gro/TLE1 and abridged by Grg6. FOXG1 silencing in brain tumor-initiating cells (BTICs) also resulted in diminished secretion of markers characteristic undifferentiation natural neural stem/progenitor cells (NSPC) states, such as Oligodendrocyte transcription factor (OLIG2), (sex determining region Y)-box 2 (SOX2) and B lymphoma Mo-MLV insertion region 1 homolog (BMI1). This review therefore focuses on the pathogenic and biomarker potentials of FOXG1 in GB.

Introduction

Glioblastoma (GB) is an extremely pugnacious brain cancer originating from neural stem (NS) cell-like cells.1 Several studies have shown that, the transcriptional as well as epigenetic machineries that regulates the stimulation and continuation of NS as well as progenitor cells are captured and derestricted in GBs.1,2 Forkhead box G1 (FOXG1; previously identified as BF-1, qin, Chicken Brain Factor 1, or XBF-1 and renamed FOXG1 for mouse and human, and FOXG1 for other chordates) is an evolutionary preserved transcription factor driven from the forkhead box group of proteins.4-8 The name forkhead was coined out because these proteins were first observed in Drosophila.5,9 Studies have shown that, in vertebrates, FOXG1 is fundamental for the growth of telencephalon, cell movement, and cerebral cortex modeling as well as layering.6,8 It is proven that, both up-regulation and down-regulation of FOXG1 are interconnected with cancer evolution.4 In 1993, the association between FOXG1 (with the name quin) and cancer was established, exhibiting that FOXG1 is an effective oncogene.6,7

Studies have shown that, in GBs, FOXG1 over-secretion inhibits the transcription of cyclin-dependent kinase inhibitor 1 (p21Cip1) as well as instigates anomalous cellular productions resulting in poor outcomes.4,9,10 Nevertheless, the FOXG1 gene encrypts a growth-related transcription factor with repressor actions and it was secreted at initial phases of telencephalic growth.11-13 Furthermore, it was secreted inadequately by differentiated astroglial cells, and FOXG1 alteration leads to up-regulation of astroglial differentiation genes.14 Also, transcriptomic reporting in The Cancer Genome Atlas (TCGA) GB cohort revealed that elevated FOXG1 mRNA concentrations is prognostic of unfavorable sequel in multivariate investigation.11,15 Another study demonstrated that, secretion of FOXG1 is appreciably poorer in the analytically uncomplimentary K27-mutant midline cancers than in all other glioblastoma subgroups.16 Therefore, FOXG1 secretion is a fundamental consequence in the advent of GBs. This usually transpire either early in gliomagenesis or later, leading to ancillary modification of a low-grade glioma.11,15 This review focuses on the pathogenic and biomarker potentials of FOXG1 in GBs.

Function of FOXG1

Studies in rats have shown that, during the initial periods of cortical formation, FOXG1 modulates the speed of neurogenesis by maintaining progenitor cells in a proliferative mode as well as obstructing their differentiation into neurons.4,17 It is also proven that, FOXG1 was very vital in exact development of the inner ear,
the olfactory gland as well as correct axonal formation in the evolving retina.\textsuperscript{18-20} Also, FOXG1 was capable of maintaining accurate balance during cell replication and differentiation although the precise mechanisms via which it regulates these fundamental procedures are essentially undetermined.\textsuperscript{4} Therefore, further studies are needed in this direction.

On the other hand, FOXG1 has been implicated in the formation of central nervous system tumors and precisely GBs.\textsuperscript{4,14,15} It was proven that, during typical brain formation in mice, FOXG1 contributes significantly to the formation of the forebrain, more precisely the telecephalon. Also, FOXG1 modulated angiogenesis within the forebrain which typically arise from pial vessels that emerge early in formation of the brain at E9.\textsuperscript{21-23} Studies have shown that, these may account for the fraction of normal vessels in Tgfb2-cKO forebrains since FOXG1-driven-secretion is comparatively weak in the initial phases of forebrain formation but intensely upsurges with high E9.5.\textsuperscript{21,24} Hellbach \textit{et al.} demonstrated that, Foxg1\textsuperscript{cre-/-}; Tgfb2\textsuperscript{flox/flox} mice can act as a model to innovative comprehension of the interface between neural and angiogenic cells during brain formation.\textsuperscript{21} Nevertheless, FOXG1 also function as a transcriptional repressor, not only during initial brain formation, but also in the matured brain. Thus, in a matured brain, FOXG1 modulates neuronal survival.\textsuperscript{25,26} A detailed literature search revealed that no studies have been conducted on the effects of FOXG1 on angiogenesis during the pathogenesis of GBs. Therefore, further research should focus on these post-translational roles of FOXG1.

**Post-translational modification of FOXG1**

FOXG1 is about 58-kDa and it is mainly located in the nucleus as well as the cytoplasm. It was proven that, the intracellular part of FOXG1 was modifiable post-translationally and it alternates between the nucleus and the cytoplasm.\textsuperscript{4,27} More Precisely, FOXG1 was restrained mainly in the nucleus and precisely in zones with ongoing neurogenesis during the formation of the mouse brain, while the cytoplasmic portion was associates with initial neuronal differentiation zones.\textsuperscript{27} Furthermore, in the nucleus, FOXG1 functions as a transcriptional repressor and thus targets fibroblast growth factors (FGFs), sonic hedgehog homolog (SHH), as well as cell-cycle inhibitors like p21Cip1.\textsuperscript{4,10,28} On the other hand, in the cytoplasm, FOXG1 functions as a transforming growth factor-beta (TGF-\(\beta\)) blocker by binding to receptors like mothers against decapentaplegic homolog 3 (Sma3).\textsuperscript{10,28} It is shown that, FOXG1 can be imported from the nucleus and cytoplasm into the mitochondria resulting in further proteolization within the matrix.\textsuperscript{4} Also, the full-length protein can be partly proteolized in the cytoplasm with the production of a 45-kDa fragment that partly remain in the cytoplasm and partly imported into the mitochondria. Nevertheless, this 24-kDa C-terminal fragment of FOXG1 is entirely generated within mitochondria.\textsuperscript{4} Pancrazi \textit{et al.} demonstrated that, in isolated mitochondria, cell lines, prime cell cultures, and mouse cortical extracts, the fraction of FOXG1 is confined to the mitochondrial matrix.\textsuperscript{4} Thus, a distinctive domain sited between amino acids 277 and 302 is accountable for its mitochondrial targeting. They indicated that full-length, mitochondrial, and cytosolic categories of FOXG1 influence cell growth, differentiation, and mitochondrial functions.\textsuperscript{4}

Studies have shown that, mitochondria modulate vital activities during neuron formation as well as neuroplasticity such as differentiation of neurons, formation of axons and dendrites. Also, mitochondria are responsible for the development and reformation of synapse.\textsuperscript{5,28-31}

Nevertheless, the \textit{in silico} study indicated that FOXG1 is deficient in the typical N-terminal mitochondrial targeting structure but has an inner one sited downstream its forkhead domain.\textsuperscript{4} Interestingly, FOXG1 undergoes a multifarious as well as comparatively slow post-translational modification, with insignificant disparities based on the cell type. Pancrazi \textit{et al.} observed an obviously dissimilar proliferation/differentiation-stimulating action of over-secreted both nuclear and mitochondrial (FL-FOXG1), solely mitochondrial (mt-FOXG1) as well as solely cytoplasmic (cyt-FOXG1) exhibiting a dispersed intracellular localization.\textsuperscript{4} They indicated that While FL-FOXG1 facilitated mitochondrial fission and cellular proliferation, mt-FOXG1 promoted mitochondrial fusion as well as early neuronal differentiation. In literature, little is said about these post-translational changes associated with FOXG1.\textsuperscript{4} Therefore, further research should focus on these post-translational roles of FOXG1.

**FOXG1 and neural cell apoptosis**

FOXG1 possesses an extremely preserved DNA-binding domain, which binds to precise DNA successions and modulates gene communication. Also, FOXG1 over-secretion \textit{in vivo} was interrelated with neural progenitor cell over development as a result of FOXG1 DNA-binding as well as repressor action.\textsuperscript{32} Furthermore, FOXG1 acts to preserve the natural neural stem/progenitor cells (NSPC) genre at the expense of neural cell differentiation. Also, its inactivation triggered an intense perturbation of cerebral cortex formation due to premature NSPC differentiation. Nevertheless, FOXG1 protein functions partially by establishing transcription suppression complexes with other modifying proteins.\textsuperscript{32} Several studies have demonstrated that, FOXG1 over-secretion stimulates overgrowth of NSPC via neutralizing signaling triggered by cytosstatic factors like TGF-\(\beta\) and BMP4 through the suppression of transcription cyclin-dependent kinase inhibitors p15Ink4b and p21cip1. It also decrease the rate of normal programmed cell death or apoptosis (Figure 1A).\textsuperscript{32,33} The apoptotic roles of FOXG1 in neurons as well as GBs still need further investigation. It is proven that, FOXG1 interference blocked glioma cell U118 proliferation and initiated cell apoptosis in time-depend manner.\textsuperscript{32} Furthermore, Dastidar \textit{et al.} discovered a pro-survival function of FOXG1 and TLE1 in healthy neurons.\textsuperscript{34} Dali \textit{et al.} demonstrated that FOXG1:TLE1 facilitates glioma cell survival partial via the inhibition of the pro-apoptotic roles of Chac glutathione-specific \(\gamma\)-glutamylcyclotransferase 1(CHAC1) (Figure 1A).\textsuperscript{35} Several studies have demonstrated that, silencing of FOXG1 in cultured brain tumor initiating cells (BTICs) results in reduced sphere-forming (SF) capability and BrdU amalgamation, with a contemporaneous up-codification genes linked to cell cycle exit as well as replicative senescence like p21cip1, Growth Arrest and DNA Damage (GADD45A), and \(\beta\)-galactosidase, whose action is recognized to upsurge in senescent cells (Figure 1A).\textsuperscript{33,36,37} Studies have also demonstrated that, FOXG1 has the ability to restrain cell death in rat cerebellar culture programed to undergo apoptosis, while inhibition of FOXG1 secretion triggers apoptosis in normal neurons.\textsuperscript{3} \textsuperscript{34}

**FOXG1 and Groucho/transducin-like enhancer of split in glioblastoma**

Several studies have implicated transcription factors like the Groucho (Gro)/transducin-like Enhancer of split (TLE) family to...
partakes in several of growth pathways in invertebrates and vertebrates. Precisely, Gro/TLE1 was associated with machineries that negatively modulated the production of postmitotic neurons from undifferentiated neural precursors in the telencephalon. It is proven that, without ancillary proteins, Gro/TLE proteins cannot function alone because they are deficient in DNA-binding action. Furthermore, they become conscripted to specific gene modulating strains in context-determined fashion by establishing complexes with several DNA-binding transcription factors. Several studies have demonstrated that, FOXG1 actively partakes in the formation of transcription suppression complexes with corepressors being the Gro/TLEs.

Studies have proven that, Gro/TLE-related gene product 6 (Grg6), a transcription repression-inept, antagonize the roles of FOXG1: TLE complexes. Furthermore, Marçal et al. established that, Grg6 exhibits about 60% preservation during the introduction of Gro/TLEs at the level of the WD40 repeat (WDR) domain. This resulted in the facilitation of Gro/TLE binding to FOXG1 but however exhibits only a partial connection at the level of its N-terminal domain. Nevertheless, the failure of Grg6 to bind to Gro/TLEs was as a result of its deficiency in two preserved N-terminal leucine zipper-like motifs that are capable of intermediating Gro/TLE oligomerization. On the other hand, it is likely that, a solitary recognized leucine zipper-like motif at its N terminus was enough in the intermedation of Grg6 homodimerization but not interface with Gro/TLEs. Conversely, the structural components that trigger Grg6 homodimerization is still a matter of debate. Therefore, further studies are warranted in this direction. Also, Grg6 and Gro/TLEs are capable of interacting with FOXG1/BF-1, but only Gro/TLEs bind to hairy and enhancer of split-1 (HES1) with high affinity.

Furthermore, studies have proven that, Grg6 and Gro/TLE display analogous biochemical features but intermediate dissimilar operative effects. However, they both interrelate with FOXG1 transcriptional suppression and their facilitation by FOXG1 is stimulated by Gro/TLE1 and abridged by Grg6. Marçal et al. demonstrated that, Grg6 secretion was down-regulated in GBs and up-regulated in normal brain, analogous to the extreme secretion of both FOXG1 and TLE in GBs. They further indicated that, Grg6 binds to FOXG1 via its WD-40 repeat domain with analogous affinity to that of TLE. Nevertheless, Grg6 fails to bind to, or interrelates very feebly with numerous other TLE-binding associates as evidence in literature. Also, Grg6 does not possess the amino-terminal Gln-rich domain via which TLE is capable exhibiting protein-protein interaction. Therefore, Grg6 is not a typical antagonist to the entire roles of TLE. Its limited protein-protein communication competes makes Grg6 a more selective dominant-blocker of transcription multiplexes associated with FOXG1 and, perhaps, other FOXG1-interconnected proteins.

Several studies have demonstrated that, the ability of FOXG1 to modulate cortical progenitor proliferation is assumed to be inter-mediated via protein-protein communications, rather than FOXG1’s own DNA-binding capability. Nevertheless, FOXG1 necessitates a complete DNA-binding domain to block neuronal differentiation of telencephalic precursor cells. Nonetheless, either via its own DNA-binding capability or via communications with other DNA-binding proteins the conscription of FOXG1 to DNA is assumed to result in transcriptional suppression of the targeted genes. Several studies have demonstrated that, FOXG1 is co-secreted with Gro/TLEs in the formation of the telencephalon and Gro/TLEs actively function as a transcriptional corepressor for FOXG1. Therefore, exogenous Gro/TLE1 secretion in cortical progenitor cells results in buildup of proliferating cells as well as reduction in the quantity of progenitors that differentiate into neurons. This further indicate that, FOXG1 works jointly with Gro/TLEs to avert premature precursor cell cycle exit and differentiation in the telencephalon.

Figure 1. An illustration showing the mechanisms via which FOXG1 facilitates glioblastoma cell survival (A) as well as gliomagenesis (B).
FOXG1 and brain tumor-initiating cells

Many studies have demonstrated that, between the most feebly differentiated GB cells are cells bestowed with stem-like features, explicitly capable of preserving lengthy self-renewal. These cells also propagate precipitously proliferating progenies, hypothetical for multi-lineage differentiation, as well as ability to contribute to cancer proliferation due their resemblance to parental cancers.\textsuperscript{45-48} GB cells with these physiognomies are hypothesized to function as tumor-forming cells and are usually named brain tumor-initiating cells (BTICs).\textsuperscript{45,46} Furthermore, BTICs are postulated to possess numerous features with NSPCs, such as assiduous self-renewal capacity, pluripotency, as well as tissue repopulating abilities. Nevertheless, they vary from NSPCs with features such as the existence of genetic anomalies and atypical gene secretion repetitions, capacity to proliferate autonomously of mitogens, diminished differentiation ability, as well as tumor-forming capability.\textsuperscript{49} This therefore means that, the gliomagenic capabilities of BTICs comes from the perturbation of molecular machineries that typically modulates the equilibrium between proliferation and differentiation in NSPCs.\textsuperscript{49}

Also, BTICs have been implicated in GB relapse because of their aptitude to re-amass cancer cells after surgical resection of the primary GB. Thus, BTICs are postulated to epitomize the chemotherapy-resistant cell group inside GBs because of their slow proliferation quotient as well as a more efficient drug resistance ability. This often makes them recalcitrant to anti-mitotic medications.\textsuperscript{14,47,48} Therefore, BTICs epitomize a curatively striking target for GB management schemes. Several studies have demonstrated that, knockdown of FOXG1 in cultured BTICs led to reduced SF aptitude. Also, BrdU amalgamation with a contemporaneous up-codification of genes linked with cell cycle exit and replicative senescence like p21Cip1, GADD45A, and β-galactosidase resulted in augmentation of senescent cells.\textsuperscript{14,33,36,50} Nevertheless, FOXG1 silencing in BTICs also resulted in diminished secretions of markers characteristic undifferentiated NSPC states, such as Oligodendrocyte transcription factor (OLIG2), (sex determining region Y)-box 2 (SOX2) and B lymphoma Mo-MLV insertion region 1 homolog (BMI1) (Figure 1B). Also, endogenous FOXG1 was conscripted to the facilitators of both SOX2 and BMI1 in BTICs.\textsuperscript{14} A body of evidence indicated that FOXG1 binds to the BMI1 facilitator in medulloblastoma stem-like cells (MSIC) and silencing of FOXG1 resulted in diminished BMI1 transcription in these cells (Figure 1B).\textsuperscript{51}

Nonetheless, the reduced secretion of NSPC markers as a result of FOXG1 knockdown in BTICs was linked with an inverse up-regulation of three genes normally seen in maturing or matured astrocytes, such as GFAP, S100β, and glutamine synthetase (Figure 1B). Furthermore, endogenous FOXG1 binds to facilitators of these genes, directly involving FOXG1 in the transcriptional modification of GFAP, S100β, and glutamine synthetase in BTICs. Verginelli et al. established participation of mouse FOXG1 in NSPC conservation and blockage of astrocyte differentiation.\textsuperscript{14} They further indicated that, FOXG1 was associated with conservation of undifferentiated state as well as inhibition of astrocyte cell lineage differentiation in BTICs.\textsuperscript{14} Also, studies with in vivo orthotopic transplantation revealed that, brain cancers triggered by FOXG1-knockdown BTICs are tinier than cancers triggered by non-knockdown BTICs, leading to persistent host survival. This implies that FOXG1, performs significant functions in BTIC-propagated brain cancers formation.

On the other hand, a study established that, augmentation of FOXG1 secretion in the evolving mouse brain results in forebrain hyper-cellularity leading to the augmentation of progenitor cell expansion as well as deferred differentiation.\textsuperscript{52} It is proven that, stimulation of p21Cip1 facilitator in a feedback reaction to TGF-β signaling resulted in FOXG1 inhibitory trans-stimulation action

![Figure 2. An illustration showing the pathways via which FOXG1 is able to inhibit gliomagenesis.](image-url)
and thus antagonized cytostatic consequence of TGF-β (Figure 1B). Nonetheless, it appears incongruous that, FOXG1 facilitates BTIC conservation and gliomagenic capability by antagonizing TGF-β signaling (Figure 1B). Furthermore, FOXG1 contributes to TGF-β’s ability to augment proliferation as well as averts differentiation in BTICs. This therefore implies that, FOXG1 and TGF-β signaling abilities to conserve BTICs still warrants further studies. Nevertheless, FOXG1 was essential in sustaining BTIC proliferation via inhibiting the secretion of genes that facilitates termination of proliferation as well as replicative senescence.

FOXG1, transducin-like enhancer and brain tumor-initiating cells

TLE proteins are global transcriptional corepressors that partakes in machineries that preserve stem/progenitor cell state as well as restrain differentiation in different tissues. It was proven that, FOXG1 was secreted by GBs but its participation in gliomagenesis is still not well studied. It is further proven that, FOXG1 and TLE are co-secreted and form a complex with BTICs resulting in brain cell proliferation. Functionally, blockade of FOXG1 and TLE resulted in reduction of BTIC ability to trigger gliomagenesis. Correspondingly, both FOXG1 and TLE binds to conjoint domains in the GADD45A and β-galactosidase facilitators. Furthermore, the negative consequence of FOXG1 knockdown on the proliferative capability of BTICs can be phenocopied by TLE1 or TLE2 silencing. This implies that, the roles of FOXG1 in BTICs includes the development of transcription suppression complexes with TLE proteins. Nonetheless, FOXG1 and TLE complex was confine to p21Cip1 facilitator on BTICs and knockdown of FOXG1 or TLE resulted in analogous up-regulation of p21Cip1 secretion. Several studies have demonstrated that, FOXG1 forms complexes with the transcriptional corepressor TLE in BTICs during rodent and amphibian forebrain formation. Studies have established that, FOXG1 and TLE1 suppress the secretion of genes linked to the formation astroglial phenotype like GFAP, S100b as well as glutamine synthetase. Also, the roles of FOXG1 and TLE1 complexes in GBs proven via the isolation of CHAC1 as a direct FOXG1:TLE1 target gene.

Signaling pathways FOXG1 and glioblastoma

Seoane et al. demonstrated that, Forkhead box O (FoxO) proteins are fundamental associates of Smad3 and Smad4 in the TGF-β-determined production of a p21Cip1 stimulation complex. FoxO factors are also associates of the Forkhead box (FOX). They have been implicated in the modulation of cell and organismal growth, development, metabolism, as well as survival. Studies have demonstrated that, FoxO factors are negatively influenced by phosphorylation of the Ser776 domain in the GADD45A and β-galactosidase facilitators. It is evidenced that in reaction to mitogenic signals, growth, development, metabolism, as well as survival. 25,54,55 This therefore implies that, FOXG1 and TGF-β signaling abilities to conserve BTICs still warrants further studies. Nevertheless, FOXG1 was essential in sustaining BTIC proliferation via inhibiting the secretion of genes that facilitates termination of proliferation as well as replicative senescence.

FOXG1 as biomarker in glioblastoma

Engström et al. demonstrated that FOXG1 was one of the most constantly over-secreted genes in their study involving primary cultures of GB-derived NS (GNS) cells and genetically normal NS cells. Verginelli et al. also indicated that, FOXG1 was genetically augmented in GB and FOXG1 mRNA concentrations in primary GBs are contrariwise associated with patient outcome. Liu et al. established that, the oncogenic EGFR truncation (EGFRvIII) is elevated substantial in typical subtype of GBs as a result of FOXG1 over-secretion. Nevertheless, data from 363 evaluated GB samples revealed a substantial upsurge in mean FOXG1 identifying indicators in astrocytic cancers with augmenting WHO grade. This signifies that FOXG1 actively participated in astrocytic malignancy. Verginelli et al. evaluated 58 glioma specimens by FOXG1 immunohistochemistry and found an analogous upsurge in median of up to 50% FOXG1-positive cancer cells in GBs. Although this did not correlate well with a specific GB subtype, they depicted FOXG1 positive cells molecularly as inadequately differentiated astrogial cells.

Schäfe et al. demonstrated that the quantity of FOXG1 positive nuclei in oligodendroglioma was analogous to IDH mutant astrocytoma (grade II-III) but appreciably decreased compared to the IDH-wildtype GB cohort, again signifying prognostic potentials of FOXG1. Furthermore, stratification of brain tumors into significant molecular subgroups indicated that FOXG1 indicators were greater in G34-mutant cancers compared to K27M-mutant gliomas of the midline. Sturm et al. demonstrated that FOXG1+/Olig-2 negative patterns were representative of G34-mutant cancers in their limited immunostained studies. Also, FOXG1 over-secretion was implicated in medulloblastoma and interrelated with gliomagenesis as evidenced in the Non-SH/Non-WNT cohorts. This markedly support the function of FOXG1 up-regulation as an unfavorable prognostic factor in brain cancers. Schäfe et al. detected that cancers with FOXG1 labelling index below partitioning-analysis resolute cutoff (FOXG1 low indices) had a considerably enhanced patient outcome during their univariate study.
It is proven that, transcriptomic profiling of TCGA dataset confirmed an extreme FOXG1 mRNA concentrations which correlated well with poor survival. It was further postulated that FOXG1 maintains cell proliferation via p21Cip1 suppression and thus may aid in gliomagenesis. Schäfe et al. demonstrated that K27M-mutant cancers possess FoxG1 low/Olig-2 high and G34-mutant cancers display a FoxG1 high /Olig-2 low profile in their H3F3A-mutant glioma cohort. Sturm et al. earlier indicated that, in their experiment involving 8 K27M-mutant cancers with Olig-2+/FoxG1-immonofluorescence and 6 G34-mutant cancers with Olig-2-/FoxG1+ profile. Schäfe et al. concluded that nuclear FOXG1 in glioma correlated well with WHO tumor grade in astrocytic/oligodendrogial cancers. FOXG1 outcomes in univariate analysis (low FOXG1 indices) also correlated with other auspicious prognostic markers like IDH mutation and ATRX secretion. Further studies are still needed in this direction to further validate FOXG1 as a biomarker in G Bs.

Conclusions

This review established that, mutual actions of FOXG1 and PI3K intermediate in intrinsic resistance of human GB cells to TGF-β stimulation of p21Cip1 as well as growth inhibition. Also, FOXG1 and TLE1 are co-secreted and form a complex in BTICs and thus augmented cell proliferation. Furthermore, FoxG1 actively partakes in the formation of transcription suppression complexes with corepressors of the Gro/TLEs. Also, FOXG1 is stimulated by Gro/TLE1 and abridged by Grg6. FOXG1 silencing in BTICs also resulted in diminished secretion of markers characteristic undifferentiated NSPC states, such as Olig2, SOX2 and BMI1. Moreover, FOXG1 was genetically augmented in GB and FOXG1 mRNA concentrations in primary GBs are contrariwise associated with patient outcome. Transcriptomic profiling of TCGA dataset confirmed an extreme FoxG1 mRNA concentrations correlated with poor survival. This review therefore elucidated the pathogenic and biomarker potentials of FOXG1 in GBs.

Abbreviation list

ChaC glutathione-specific γ-glutamylcyclotransferase 1= CHAC1, cyclin-dependent kinase inhibitor 1 = p21Cip1, Glioblastoma =GB, Growth Arrest and DNA Damage = GADD45A , Hairy and enhancer of split-1= HES1, Neural stem=NS, Forkhead box G1 =FOXG1, Phosphatidylinositol-3-kinases =PI3K, Transforming growth factor-beta =TGF-β, Groucho/transducin-like Enhancer of split =Gro/TLEs, Gro/TLE-related gene product 6 = Grg6, Brain tumor-initiating cells =BTICs, Neural stem/progenitor cells =NSPC, Fibrolast growth factors =FGFs, Sonic hedgehog homolog =SHH, Mothers against decapentaplegic homolog 3 =Smad3, Nuclear and mitochondrial =FL-FOXG1, Mitochondrial =mt-FOXG1, Cytoplasmic =cyt-FOXG1, Sphere-forming =SF, WD40 repeat =WDR, Medulloblastoma stem-like cells =MSC, Forkhead box =FOX, Delta and NOTCH-like epidermal growth factor-related receptor =DNER, GB-derived NS =GNS, The Cancer Genome Atlas =TCGA.

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