Novel Pathogenic, Biomarker and Therapeutic Potentials of Foxm1 in Glioma

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ABSTRACT

Gliomas embody entirely prime brain tumors of glial cell or neuroepithelial derivation. Glioma is still one of the lethal human cancers notwithstanding contemporary innovations in both diagnostic techniques and therapeutic schemes. Also, glioma carries the lowest survival rate as compare to other cancers 5 years after definitive diagnosis. FoxM1 was initially identified as HFH-11, WIN, MPP2, as well as Trident. It’s an evolutionary well-maintained, with common winged helix DNA-binding domain. FoxM1 actively participates in gliomagenesis via several pathways like, FoxM1/MELK/EZH2 signaling, FoxM1/BMI-1/Ink4a/Arf/Ink4b signaling, FoxM1/IP07/H3 signaling as well as FoxM1/PLAGL2/Wnt/β-catenin signaling. FoxM1 also augments’ the stimulation of Akt as well as secretion of survivin, cyclin E, and cyclin D1. Furthermore, FoxG1 contributes to glioma invasiveness via MMPs especially MMP-4 and MMP-9. Nevertheless, FoxM1 contributes to glioma angiogenesis via VEGF and transcription stimulators like HIF-1 and STAT3 have been implicated as VEGF facilitators. FoxM1 has also proven to a promising diagnostic and prognostic biomarker in glioma. Moreover, FoxM1 has therapeutic potential in glioma either alone or in combination with other agents. This review therefore focuses on the novel pathogenic, biomarker and therapeutic potentials of FoxM1 in Glioma.

Key Words: Glioma, pathogenic, biomarker, therapeutic, prognosis, diagnosis

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Introduction

Gliomas embody entirely prime brain tumors of glial cell or neuroepithelial derivation (Liu et al., 2006). Glioma are classified into lowest-grade tumors, lower-grade tumors, higher-grade malignancies, and highest-grade malignancies according American Association of Neurosurgeons (Surawicz et al., 1998). Astrocytoma, which is the most frequent human glioma is further classified by WHO into four grades. Grade I embody pilocytic astrocytoma, grade II; low-grade astrocytoma, grade III; anaplastic astrocytoma while grade IV embodies glioblastoma multiforme. Grade I arise mostly in children and has minimal transformation potentials into Grade II-IV. On the other hand, grade II or III are often associated with malignant transformations into grade IV(Surawicz et al., 1998; Liu et al., 2006; Siegel et al., 2013).

Glioma is still one of the lethal human cancers notwithstanding contemporary innovations in both diagnostic techniques and therapeutic schemes (Liu et al., 2006; Cheng et al., 2013). Also, glioma carries the lowest survival rate as compare to other cancers 5 years after definitive diagnosis (Surawicz et al., 1998; Siegel et al., 2013; Seidu et al., 2017; Su et al., 2017). FoxM1 gene which has been identified recently is implicated as a human proto-oncogene (Myatt and Lam, 2007; Li et al., 2012). Studies have demonstrated that FoxM1 is primarily secreted at the mRNA level in fetal tissue, while its secretion is...
overshadowed in differentiated cells (Yao et al., 1997; Ye et al., 1997; Liu et al., 2006).

Up regulation of FoxM1 has been reported in various cancers like skin, liver, breast, lung, prostate, colon, pancreas, ovarian as well as brain (Wang et al., 2010; Li et al., 2012; Wang et al., 2015). This review therefore focuses on the novel pathogenic, biomarker and therapeutic potentials of FoxM1 in Glioma.

**Structure and function of FoxM1**

FoxM1 was initially identified as HFH-11, WIN, MPP2, as well as Trident. It is an associate of the Fox transcription factor group of genes (Yao et al., 1997; Ye et al., 1997; Liu et al., 2006). Studies have shown that it's an evolutionary well-maintained, with common winged helix DNA-binding domain (Yao et al., 1997; Liu et al., 2006). Modification of FoxM1 protein secretions has been associated with cell growth, cycling dysregulation as well as carcinogenesis (Kalin et al., 2011; Koo et al., 2012; Wang et al., 2015). Furthermore, this protein has also been implicated in the modulation of diverse metabolic as well as growth in diverse species including human beings (Laoukili et al., 2005; Wang et al., 2005; Wang et al., 2015). Nevertheless, the human FoxM1 gene comprises of 10 exons of which two are alternatively intertwined. Moreover, these intertwine occurrences contribute to three dissimilar modifications like FoxM1A, B as well as C. Functionally, FoxM1A has been implicated as a transcriptional repressor while FoxM1B and FoxM1C are both transcriptional activators (Kalin et al., 2011; Koo et al., 2012). Studies have shown that FoxM1 contains an NH2-terminal domain, a preserved forkhead box domain (residues 232–332), an NLS domain (residues 350–366), as well as a COOH-terminal domain (Fig. 1) (Park et al., 2008; Zhang et al., 2011).

**FoxM1 and Cell cycle regulation**

It has been indicated that FoxM1 secretion is progressively augmented from G0-phase and peaks at late G1 or early S-phase. Also, the concentrations of FoxM1 are constant up to the end of G2-phase and it precipitously declines during mitosis. Furthermore, transformations in the secretion of FoxM1 chaperoned by cell cycle modification emphasizes that the key roles of FoxM1 is modulation of cell cycle (Yao et al., 1997; Surawicz et al., 1998; Laoukili et al., 2005; Li et al., 2012). Studies have proven that FoxM1 is fundamental in modulating G1 to S phase as well as G2 to M phase during cell cycle (Fu et al., 2008; Anders et al., 2011; Alvarez-Fernández and Medema, 2013). Nevertheless, silencing of FoxM1 in cells led to G2 phase interruptions as well as extensive mitotic features resulting in dysfunction of chromosomal separation and genomic instability (Wang et al., 2010; Li et al., 2012; Seidu et al., 2017). Several studies have demonstrated that FoxM1 regulators the secretion of genes prerequisite for both G1/S and G2/M modification and it is crucial for mitotic entry and advancement as well as warranting the conservation of chromosome stability (Fig. 2) (Laoukili et al., 2005; Wang et al., 2005; Koo et al., 2012). Also, its transcriptional endeavors are firmly modulated during the entire cell cycle process via multi-locus phosphorylation of diverse kinases as well as its responding phosphatases, resulting in its peaking at G2 phase of the cell cycle (Laoukili et al., 2008; Alvarez-Fernández et al., 2010; Alvarez-Fernández and Medema, 2013).

Additionally, FoxM1 is able to modulate the secretion of Skp2 protein resulting in facilitated mortification of p27Kip1 during anomalous cell cycle as well as gliomagenesis (Fig. 2). Furthermore, FoxM1’s secretions at both mRNA and protein stages, is cell cycle-modulated (Fig. 2) (Laoukili et al., 2008; Park et al., 2008; Alvarez-Fernández and Medema, 2013). Moreover, FoxM1 influence cell cycle via its activities on the secretion of genes like Nek2, KIF20A, CENP-A, CENP-F, CDC25A, CDC25B, p27Kip1 and cyclin D1 which are necessary for chromosomal stability as well as segregation (Ye et al., 1997; Laoukili et al., 2005; Dai et al., 2007; Alvarez-Fernández and Medema, 2013).

Also, FoxM1 triggers the secretion of cyclin A2, JNK1, ATF2, CDC25A phosphatase and restrains the stability of p21Cip1 and p27Kip1 proteins during G1/S modification and DNA replication (Fig. 2) (Wang et al., 2005; Li et al., 2012). Nonetheless, FoxM1 also modulates the secretion of numerous G2/M-precise genes, like CDC25B, AURKB, PLK1, CENP-A, CENP-B, CDC25A, and the stability of p21Cip1 and p27Kip1.
the concentrations of nuclear β-catenin (Liu et al., 2006; Zhang et al., 2011). Zhang et al demonstrated that Wnt3a augmented β-catenin nuclear buildup in MD11 and MD20s cells as compared to control shRNA (Zhang et al., 2011). Furthermore, secretion of either of the two shRNAs anti-FoxM1 inhibited Wnt3a-stimulated β-catenin nuclear but not cytoplasmic buildup. They concluded that FoxM1 does not only influence β-catenin concentration but is prerequisite for β-catenin nuclear buildup in cancer cells (Zhang et al., 2011). Studies affirmed that FoxM1 bind directly to β-catenin resulting in the triggering of β-catenin nuclear restriction as well as transcriptional endeavors (Zhang et al., 2011; Li et al., 2012).

Nuclear and cytoplasmic transactivation of FoxM1

It is proven that FoxM1 has both cytosolic and nuclear domains or sites, and cytosolic FoxM1 actively partakes in β-catenin nuclear translocation (Zhang et al., 2011). Studies have implicated nuclear FoxM1 in the conscription of β-catenin to the β-catenin/TCF4 transcription stimulation multiplex via Wnt target-gene facilitator (Zhang et al., 2011; Chen et al., 2016). It is also proven that nuclear FoxM1 directly interrelated with nuclear β-catenin resulting in the secretion β-catenin from ICAT which then triggers the conscription of β-catenin via Wnt target gene facilitator leading to augmented secretion of Wnt target gene (Chen et al., 2016). Therefore, Wnt stimulation amplifies FoxM1 protein stabilization as well as nuclear buildup (Chen et al., 2016).

Studies have shown that silencing of FoxM1 with FoxM1-siRNA, or via two neutral FoxM1-shRNAs in MD11 and MD20s cells markedly diminished the concentrations of nuclear β-catenin (Liu et al., 2006; Zhang et al., 2011). Zhang et al demonstrated that Wnt3a augmented β-catenin nuclear buildup in MD11 and MD20s cells as compared to control shRNA (Zhang et al., 2011). Furthermore, secretion of either of the two shRNAs anti-FoxM1 inhibited Wnt3a-stimulated β-catenin nuclear but not cytoplasmic buildup. They concluded that FoxM1 does not only influence β-catenin concentration but is prerequisite for β-catenin nuclear buildup in cancer cells (Zhang et al., 2011). Studies affirmed that FoxM1 bind directly to β-catenin resulting in the triggering of β-catenin nuclear restriction as well as transcriptional endeavors (Zhang et al., 2011; Li et al., 2012). Furthermore, FoxM1 enhances glioma stem cells self-renewal of as well as triggers glioma development via its interaction with β-catenin (Zhang et al., 2011).

Xue et al demonstrated that FOXM1 modulates nuclear confinement of glioma-associated oncogene homolog 1 (GLI1) in a DNA binding-determined fashion (Xue et al., 2015). This implies that, the transcriptional action of FOXM1 is a prerequisite...
for nuclear confinement of GLI1 (Xue et al., 2015). Also, FOXM1 stimulates the Hh pathway via the triggering of nuclear confinement of GLI1 resulting in up-regulation of IPO7 secretion (Xue et al., 2015). Studies have shown that FoxM1B over-secretion in glioma cells results in diminished p27Kip1 protein concentrations in the nucleus but did not modify the p27Kip1 mRNA concentration (Xue et al., 2014; Xue et al., 2015). This means that FoxM1 perhaps modulated p27Kip1 protein secretion indirectly via Skp2 secretion (Xue et al., 2015).

**FoxM1 and signaling pathways in glioma pathogenesis**

Several studies have indicated that Wnt signaling modulates numerous activities essential for gliomagenesis (Zheng et al., 2010; Zhang et al., 2011; Clevers and Nusse, 2012; Wang et al., 2015). It is further proven that β-catenin is a strategic molecule for Wnt signaling and Wnt stimulation augments β-catenin protein steadiness (Huang and He, 2008; MacDonald et al., 2009; Clevers and Nusse, 2012). Studies have also confirmed that Wnt/β-catenin signaling is associated with the modulation of migration, invasion, as well as proliferation of malignant glioma cells (Mirza et al., 2010; Clevers and Nusse, 2012). Nevertheless, FoxM1 and β-catenin are both confined in the cytoplasm as well as the nucleus. It is affirmed that Wnt3a stabilized both proteins and augmented their nuclear buildup in glioma cells, signifying that FoxM1 is involve in the down-regulation of Wnt in the Wnt signaling pathway (Chen et al., 2016). Furthermore, FoxM1 modulates Wnt/β-catenin signaling pathway via facilitation of β-catenin nuclear translocation (Zhang et al., 2011; Koo et al., 2012). Also, FoxM1 triggers the facilitator ability of β-catenin target genes c-Myc and cyclin D1 (Gong and Huang, 2012). It is affirmed that the concentration of FoxM1 is interrelated with the pursuit of Wnt/β-catenin signaling in glioma inducing cells (Gong and Huang, 2012; Chen et al., 2016).

Studies have shown that over-secretion of FoxM1 results in the up-regulation of Wnt/β-catenin target genes Axin2, c-Myc, cyclin D1 as well as facilitates glioma cells formation during gliomagenesis in nude mice (Fig. 3) (Zhang et al., 2011; Gong and Huang, 2012; Wang et al., 2015). Also, silencing of FoxM1 or β-catenin with shRNA in glioma cells appreciably blocked glioma formation in nude mice (Fig. 3) (Zhang et al., 2011;}

![Figure 3](image-url)
Wang et al., 2015). Studies have shown that PLAGL2 is an effective protooncogene during malignant glioma pathogenesis because it able to block cell differentiation resulting in self-renewal of NSC/progenitor cells as well as glioma inducting cells (Zheng et al., 2010; Gong and Huang, 2012). Also, the differentiation oppressive functions of PLAGL2 is as a result of the stimulation of Wnt/β-catenin signaling. Moreover, PLAGL2 augmentation is interrelated to the amplification of β-catenin concentration in glioma experiments (Zheng et al., 2010; Gong and Huang, 2012). Additionally, the effects of FoxM1 on PLAGL2 either solitary or via Wnt/β-catenin signaling (Fig. 3) (Gong and Huang, 2012).

In glial to mesenchymal transition (GMT), one of the most fundamental signaling pathways is the TGF-β-determined signaling (Wang et al., 2015). It is proven that TGF-β facilitates EMT of glioma cells via the triggering of phosphorylated Smad2/3 resulting in an amplified secretion of MMP-2, Snail, as well as MMP9 in glioma cells (Fig. 3) (Mahabir et al., 2013). Wang et al. indicated that FoxM1 modulates TGF-β signaling (Wang et al., 2015). Furthermore, TGF-β stimulates it signaling transduction via Smad3 phosphorylation. Also, phosphorylated Smad3 forms a multiplex with Smad4 and then translocate to nucleus to modulate the secretion of down-regulated target genes (Wang et al., 2015). Conversely, TGF-β signaling pathway is negatively modulated by particular inhibitory factors like TIF1γ. It is affirmed that TIF1γ inhibits TGF-β signaling pathway via mono-ubiquitination of Smad4, resulting in the breakdown of Smad3/Smad4 transcriptional multiplex and compulsory egress of Smad3 from the nucleus (Wang et al., 2015).

It is proven that FoxM1 interrelates with Smad3 and restrains TIF1γ from binding to Smad4, resulting in the blockade of TIF1γ-stimulated mono-ubiquitination of Smad4 (Xue et al., 2014). Therefore, FoxM1-Smad3 signaling facilitates Smad3 binding to Smad4 resulting in the confinement of Smad3 in the nucleus, which in turn results in an augmentation of TGF-β1 signaling (Fig. 3) (Wang et al., 2015). Studies have also demonstrated that FoxM1 actively partakes in gliomagenesis via up-modulating the secretion of NEDD4-1, an E3 ligase of PTEN thus down-modulating the concentrations of PTEN (Fig. 3) (Dai et al., 2010; Wang et al., 2015). On the other hand, inactivation of the pRb pathway and over-secretion of FoxM1 occur in more than 80% of gliomas as while inactivation of p53 occurs in 30% of gliomas (Westphal and Lamszus, 2011; Gong and Huang, 2012). It is also proven that FoxM1 over-secretion influence the loss of p53 and pRb as well as their ability to trigger cellular transformation and gliomagenesis in normal human astrocytes (Fig. 3) (Zheng et al., 2008; Dai et al., 2010; Gong and Huang, 2012). Also, FoxM1 intermediated astrocyte transformation and gliomagenesis via machineries like augmented stimulation of Akt as well as secretion of survivin, cyclin E, and cyclin D1 (Fig. 3) (Gong and Huang, 2012).

Maternal embryonic leucine-zipper kinase (MELK) is a serine/threonine kinase and is copiously secreted by glioma cells (Gu et al., 2013; Joshi et al., 2013; Minata et al., 2014; Kim et al., 2015). Perfunctorily, MELK interrelated with oncogenic transcription factors like c-JUN and FoxM1 in GSCs, but not normal cells. This means that MELK has both cancer-specific and survival-facilitating roles (Gu et al., 2013; Joshi et al., 2013). Therefore, FoxM1 is novel cancer-specific substrates for MELK protein (Joshi et al., 2013). Kim et al. demonstrated that the secretory profiles of FoxM1 in gliomas is influenced by EZH2 (Kim et al., 2015). They suggested that signals derived from the MELK/FoxM1 protein complex are both necessary and prerequisite to initiate and maintain the transcriptional roles of EZH2 in GSCs; thus, FoxM1 intermediated MELK-EZH2 signaling axis in GSCs (Fig. 3) (Kim et al., 2015).

The Hedgehog (Hh) signaling pathway is a growth signaling pathway that modulates several developmental activities (Amakye et al., 2013; Xue et al., 2015). This pathway is atypically stimulated in gliomagenesis although it often silenced in normal adult mature glia cells (Rubin and de Sauvage, 2006; Ng and Curran, 2011). It is affirmed that the fundamental machineries of the mammalian Hh pathway comprises of secreted ligands like Sonic hedgehog, Indian hedgehog, and Desert hedgehog. Also, this pathway is associated with a negative regulatory receptor (PTCH), a positive regulatory protein (SMO), and the glioma-associated oncogene transcription factors like GLI1, GLI2, as well as GLI3 (Fig. 3) (Varjosalo and Taipale, 2008; Xue et al., 2015). Xue et al. demonstrated that FoxM1 facilitates the growth and invasion of human glioma cells through the Hh signaling pathway (Fig. 3) (Xue et al., 2015).

Precisely, FoxM1 triggers the transcription of IP07 by binding directly to its three facilitator sites, resulting in nuclear confinement of transcription factor GLI1. This is usually the most imperative indicator of Hh pathway stimulation (Xue et al.,
2014; Xue et al., 2015). Also, FoxM1 over-secretion inhibited oxidative stress-stimulated senescence in mouse fibroblasts (3T3) and this is interrelated with the stimulation of the Polycomb group protein BMI-1, a major negative modulator of the Ink4a/Arf/Ink4b locus that encodes p19Arf as well as the cyclin-dependent kinase inhibitors p16 and p15 (Fig. 3) (Li et al., 2008; Alvarez-Fernández and Medema, 2013). Further studies on this pathway in glioma is warranted.

**FoxM1 contributes to glioma angiogenesis**

It has been indicated that glioblastoma angiogenic phenotype is depicted with argumentation in generation of proangiogenic molecules by glioma cells as well as organ-specific milieu (Folkman, 1995; Zhang et al., 2008; Richard S.A and Su Z.-L, 2017). Studies have shown that glioblastomas depicted with massive proliferation of endothelial cells as well as excessive blood vessel densities. This characteristic histologically extricates grade 4 gliomas from lower-grade astrocytomas (Kleihues et al., 2002; Seidu A. Richard, 2018). Studies have proven that glioblastoma cells over-secrete vascular endothelial growth factor (VEGF). Also, transcription stimulators like hypoxia-inducible factor 1 (HIF-1) and signal transducer and activator of transcription 3 (STAT3) have been implicated as VEGF facilitators(Zhang et al., 2008; Richard et al., 2017d).

Zhang et al showed that human glioma cells fundamentally secrete VEGF and that the concentration of fundamental FoxM1 secretion is extremely interrelated with the concentration of fundamental VEGF secretion(Zhang et al., 2008). In their immunohistochemical studies, they observed that, there is substantial interrelation between FoxM1 over-secretion and high VEGF secretion glioblastoma samples. This implies that FoxM1 modulates VEGF secretion resulting in glioma angiogenesis and gliomagenesis. They concluded that FoxM1 facilitates glioma angiogenesis via up-regulation of VEGF secretion (Zhang et al., 2008). Therefore, FoxM1 transactivates VEGF via direct binding to the VEGF gene facilitators. Furthermore, both clinical and mechanistic confirms that FoxM1 significantly modulates VEGF secretion as well as glioma angiogenesis (Zhang et al., 2008).

Studies with endothelial cell tube formation assays affirms that FoxM1 inhibited cells display appreciably decreased angiogenic capability as compare to controls. Furthermore, FoxM1 actively participated in gliomagenesis by facilitating uninhibited cell proliferation, invasion, as well as angiogenesis via the secretion of p27, Skp2, MMP-2 and VEGF (Dai et al., 2007; Zhang et al., 2008; Dai et al., 2010; Wang et al., 2015). Cheng et al also demonstrated that FoxM1 facilitate glioma cells proliferation, migration, as well as angiogenesis by directly modulating Anxa1 secretion (Cheng et al., 2013). Therefore, FoxM1 facilitates Anxa1 transcription in human glioma cells and Anxa1 is prerequisite for FoxM1-triggered cell proliferation, migration and angiogenesis (Cheng et al., 2013). Studies have proven that hypoxia-intermediated VEGF stimulation requires transactivation of a VEGF facilitator by HIF-1 (Levy et al., 1995; Liu et al, 1995; Zhang et al., 2008). Also, stabilization of VEGF mRNA secretion by proteins that bind to sequences situated in the 3’-untranslated region of VEGF mRNA (Stein et al., 1995; Claffey et al., 1998; Zhang et al., 2008). The end result of the sequencing is angiogenesis.

**FoxG1 contributes to glioma invasiveness via matrix metalloproteinases**

In gliomagenesis, invasion of glioma cells occurs when diseased cells bind to the extracellular matrix (ECM) resulting in the interruption of the ECM machineries and consequent infiltration into neighboring brain cells (Abe et al., 1994; Sawaya et al., 1996; Wild-Bode et al., 2001; Dai et al., 2007; Richard et al., 2017b). This process is intermediated by glioma-secreted matrix metalloproteinases (MMPs) that mortify the ECM at glioma-invasive façades to break through the ECM impediment (Sawaya et al., 1996; Richard et al., 2017c). Studies have proven that higher MMP-2 concentrations interdepend on augmented invasiveness of glioma in a sizable quantity of glioma cell lines (Sawaya et al., 1996; Lampert et al., 1998). Comparatively, MMP-2 secretion is expressively elevated in glioblastomas than in low-grade astrocytomas, anaplastic astrocytomas and normal brain tissue (Abe et al., 1994; Wild-Bode et al., 2001). It is further proven that MMP-9 and MMP-2 the predominant indicators of glioma invasion (Richard et al., 2017a). Several studies have implicated transcription factors like YB-1, Sp1, STAT3 and p53 as the key modulators of MMP-2 secretion (Xie et al., 2004; Richard et al., 2017e).

Studies have shown that FoxM1 has the ability facilitate gliomagenesis as well as metastasis by triggering sequences of oncogenes (Dai et al., 2007; Dai et al., 2013). Dia et al demonstrated that the
molecular machinery via which FoxM1 facilitates glioma invasion embroils the up-regulation of MMP-2 (Dai et al., 2007). They indicated that FoxM1 binds to and triggers the facilitation of the MMP-2 gene. It is also proven that transfection of glioma cell with FoxM1B secreting vector resulted in over-secretion of FoxM1 by glioma cells (Dai et al., 2007). Over-secretion of FoxM1 by glioma cells also resulted in up-regulation of MMP-2 secretion which in turn results in invasiveness of the glioma cells (Dai et al., 2007).

On the other hand, blocked of FoxM1 by transfection of FoxM1-siRNA give contradictory results. Lui et al demonstrated that augmented FoxM1B secretion in glioma cells facilitated gliomagenesis. They affirmed that complied FoxM1B secretion in anaplastic astrocytoma cells resulted in the development of GBMs, which are extremely invasive, in the brains of nude mice (Liu et al., 2006).

Several studies have implicated over-secretion GLI1 in human glioma cells (Carpenter and Lo, 2012; Infante et al., 2015; Xue et al., 2015). Studies have further demonstrated that it directly modulates the secretion of oncoproteins like FoxM1, cyclin D1/2, as well as epithelial-mesenchymal transition-associated proteins, and consequently facilitates the proliferation as well as invasion of glioma cells (Yoon et al., 2001; Gai et al., 2014). Xue et al demonstrated that GLI1 triggers up-regulation of FoxM1 secretion which results in proliferation as well as invasion of brain cells (Richard et al., 2017c). They further confirmed in their functional experiments models that utilizes gain- or loss-of-function that FoxM1/IP07/GLI1 axis facilitates GBM cell proliferation, migration, as well as invasion (Amakye et al., 2013).

**FoxM1 and biomarker in Gliomas**

Studies have shown that FoxM1 levels are significantly elevated in gliomas and thus can contribute to gliomagenesis (Kalinchenko et al., 2004; Kim et al., 2006; Liu et al., 2006; Cheng et al., 2013). Furthermore, it is proven that the secretion of FoxM1 is significantly elevated in gliomas with different grades as compared to normal brain (Liu et al., 2006). Lui et al demonstrated that, in gliomas, only 4% of the low-grade astrocytomas were strongly positive, 4% were moderately positive, and 92% were negative for FoxM1 secretion. Also, 14.7% of the anaplastic astrocytomas were strongly positive, 26.5% were moderately positive, while 58.8% were negative for FoxM1 secretion. In GBM, 36% were strongly positive, 36% were moderately positive, while 28% were negative for FoxM1 secretion. They indicated that FoxM1 secretion in the human glioma tissues is evidently elevated as compared to normal tissue and this over-secretion is directly associated with the grade of the glioma (Liu et al., 2006; Li et al., 2012). In another study they affirmed that augmented secretion of FoxM1 in GBM was considerably linked to poorer prognosis (Li et al., 2012).

Studies have also demonstrated that FoxM1 is primarily secreted at the mRNA stage in fetal tissue, while its secretion is terminated in differentiated cells (Ye et al., 1997; Cheng et al., 2013). Several studies have established that, mRNA and protein concentrations of FoxM1 and Anxa1 were up-regulated in human glioma samples and associated with poor prognosis (Kim et al., 2006; Zhang et al., 2008). Wang et al demonstrated that FoxM1 mRNA and protein whilst not detected in normal brain, were elevated in low grade astrocytoma, anaplastic astrocytoma and GBM (Wang et al., 2015). They further evaluated the concentrations of Skp2 protein secretion and the nuclear concentrations of p27Kip1 protein, the key modulators of G1 to S phase transition, with modifies FoxM1 secretion in diverse glioma cell lines. They found out that, the concentration of FoxM1 secretion differs directly with Skp2 secretion and inversely with p27Kip1 (Liu et al., 2006; Wang et al., 2015). Kim et al demonstrated that MELK, FoxM1, and EZH2 are intensely interrelated to GBM patient prognosis (Kim et al., 2015). Cheng et al demonstrated that Anxa1 secretion is associated with FoxM1 secretion in human glioma tissues and demines prognosis. They also detected a convincing interrelation between the co-secretion of FoxM1 and Anxa1 in glioma patients (Cheng et al., 2013). Therefore, FoxM1 is a promising diagnostic as well as prognostic biomarker in gliomas although further studies are still warranted.

**Therapeutic potentials of FoxM1 in Glioma**

Currently, the gold standard treatment for glioma is extensive surgical resection and subsequently radiotherapy and chemotherapy (Kim et al., 2015). Nevertheless, poor prognosis is still eminent in patient with glioma because these therapeutic modalities does not eradicate a subset of glioma cells that escape from treatment thus leading to recurrence. Kim et al proposed that after irradiation (IR), glioma stem-like cells (GSCs) may utilize the MELK-driven FoxM1/EZH2 signaling which is a promising novel treatment option for GBM (Kim et al., 2015). They argue further that protein kinase
MELK is a key modulator of FoxM1-driven EZH2 signaling in preclinical malignant glioma models. Furthermore, GSCs may promote the advancement of MELK-targeted remedies that result in FoxM1/EZH2 deregulation in malignant gliomas (Kim et al., 2015). Kim et al further demonstrated that the IR-triggered upsurges in MELK as well as EZH2 is because a preferential elimination of non-stem cancer cells and consequent augmentation of GSCs after treatment (Kim et al., 2015). Also, IR-triggered morphological modifications of the treated GBM sphere cells, led to upsurge of MELK and consequently EZH2 via alteration of stress-triggered enzymes (Kim et al., 2015).

Annexin A1 (Anxa1) is classified under the calcium/phospholipid-binding proteins (Cheng et al., 2013). Studies have shown that silencing of Anxa1 in mice was associated with cancer development, angiogenesis, metastasis, as well as wound recovery signifying that of Anxa1 plays crucial cancer modulatory roles (Martin et al., 2008; Yi and Schnitzer, 2009). Furthermore, over-secretion of Anxa1 in knockdown FoxM1 glioma cells demonstrates it capability in glioma development and progressing. Studies have demonstrated that, in glioma, Anxa1 has cancer suppressor functions via the modulation of ERK/MAPK (Alldridge and Bryant, 2003; Martin et al., 2008; Cheng et al., 2013). Also, Anxa1 inhibits cell proliferation via ERK intermediated distraction of the actin cytoskeleton as well as silencing of cyclin D1 secretion (Alldridge and Bryant, 2003; Shen et al., 2006). Further studies are need to elucidate the potentials FoxM1 via either Anxa1 alone or Anxa1/ERK/MAPK axis (Alldridge and Bryant, 2003; Martin et al., 2008).

Monteiro et al demonstrated that FoxM1 deficient MEFs are oversensitive to diverse DNA destructive injuries like epirubicin a topoisomerase II blocker, or γ-irradiation (IR) (Monteiro et al., 2013). This signifies that FoxM1 actively partakes in DNA destruction repair (Monteiro et al., 2013). They indicated further that, FoxM1 is prerequisite for DNA double strand break (DSB) repair via homologous recombination (HR) although unnecessary for non-homologous end-joining (NHEJ) repair (Monteiro et al., 2013). Furthermore, BRIP which is a member of the BRCA1-related BACH1 helicase has been implicated in HR DSB repair. Also, it has been recognized as a direct transcriptional target of FoxM1. Nevertheless, ectopic BRIP secretion has been implicated in destruction FoxM1 and repair of FoxM1 deficient cells (Alvarez-Fernández and Medema, 2013; Monteiro et al., 2013). This signifies that FoxM1 intermediates HR repair via transcriptional modulation of BRIP. Zhang et al indicated that Rad51 is also a prerequisite for effective HR repair. This protein is made up of two forkhead-binding domains. It has proven to be efficient in aiding FoxM1 transcriptional activities in glioblastoma cells (Zhang et al., 2012).

On the other hand, FoxM1 has been implicated in genotoxic drug resistance in GBM (Alvarez-Fernández and Medema, 2013). Also, FoxM1 secretion is associated with poor outcomes in patient treated with alkylator temolozide (Alvarez-Fernández and Medema, 2013). It is further proven that FoxM1-determined chemotherapy resistance is intermediated by augmented secretion of DNA repair genes like BRIP, and Rad51 (Zhang et al., 2012; Alvarez-Fernández and Medema, 2013; Monteiro et al., 2013). Also, apart from DNA repair, FoxM1 as well as other fox members could have aided in chemotherapy resistance. It is affirmed that, FoxM1 is key modulator of recovery during doxorubicin or IR therapy. It is also affirmed that, FoxM1 transcriptional activity is prerequisite in conserving the secretion of pro-mitotic genes like cyclins or Plk1. These gens modulate re-entry of DNA into the cell cycle, after the injury is restored (Alvarez-Fernández et al., 2010; Alvarez-Fernández and Medema, 2013). It is further indicated that FoxM1 blocks DNA damage-stimulated apoptosis via up-regulation of pro-apoptotic Bcl-2 (Halasi and Gartel, 2012).

Also, blockade of both FoxM1 and PARP at same time is a potential in glioma target. Its proven that, PARP polymerases are prerequisite in ssDNA disruptions repair arising during replication. Furthermore, during blockade, unrepaird ssDNA disruptions led to delayed replication forks possibly due to repair carried out by HR. Therefore, blockade of HR via FoxM1 inhibition results in sensitization of glioma cells to PARP blockers (Alvarez-Fernández and Medema, 2013). Anti-FoxM1 blocker, a 26-44 peptide of p19ARF. p19ARF proteins is triggered during glioma initiation resulting in glioma blockade via stabilization of the p53 glioma inhibitor. Its affirmed that the minimum effective form of p19ARF is a 26-44 peptide comprising of nine DArg (Kalinichenko et al., 2004; Li et al., 2012). This peptide has proven to appreciably decrease FoxM1 transcriptional actions as well as FoxM1-stimulated growth of glioma cells(Kalinichenko et al., 2004).
Another promising or potential glioma target is Siomycin A. It is classified under thiopeptide antibiotics. It is made-up of sulfur heterocyclic rings. It is known that Siomycin A has the properties of inhibiting the secretion FoxM1 as well as its phosphorylation resulting in it transactivation behavior (Radhakrishnan et al., 2006; Li et al., 2012). A dose determined reduction of FoxM1 transcriptional action was detected after Siomycin A administration. In vivo studies conducted by Priller et al. revealed that Siomycin A appreciably restraints medulloblastoma development (Priller et al., 2011; Li et al., 2012). They proposed that FoxM1 is an innovative target for medulloblastoma therapy and Siomycin A as a drug target that reiterates the consequences of FoxM1 silencing in mitotic breakdown and growth inhibition (Priller et al., 2011). Nakano et al. established that Siomycin A therapy selectively blocks Stem like GBM cells development via apoptosis as well as blockade of self-renewal (Nakano et al., 2011).

Conclusion

This review clear demonstrates that FoxM1 actively participated in gliomagenesis via several pathways like, MELK/EZH2 signaling, BMI-1/Ink4a/Arf/Ink4b signaling, IPO7/Hh signaling as well as PLAGL2/Wnt/β-catenin signaling. FoxM1 also augmented the stimulation of Akt as well as secretion of survivin, cyclin E, and cyclin D1. Furthermore, FoxG1 contributes to glioma invasiveness via MMPs especially MMP-4 and MMP-9. Nevertheless, FoxM1 contributes to glioma angiogenesis via VEGF and transcription stimulators like HIF-1 and STAT3 have been implicated as VEGF facilitators. FoxM1 has also proven to a promising diagnostic and prognostic biomarker in glioma. Moreover, FoxM1 has therapeutic potential in glioma either alone or in combination with other agents. Further studies are still warranted to explore the biomarker and therapeutic potentials of FoxM1.

References


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