Chapter 5

BMI Transcription Factor as a Novel Target for the Treatment of Brain Tumors

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1. Introduction

Recent studies have hypothesized that brain tumor stem cells (BTSCs) are responsible for the poor survival outcome of brain tumor patients. Sonic hedgehog (Shh) is one of the crucial signaling pathways to regulate stem cell self-renewable capacity. Disruption of this pathway activate Gli transcription factors, which further activate other downstream target genes including BMI1 to promote brain tumor development (medulloblastoma and glioblastoma among other tumors) (Leung *et al.,* 2004; Bruggeman *et al.,* 2007; Godlewski *et al.,* 2008). BMI1 is a polycomb complex protein also known as polycomb group RING finger protein 4 (PCGF4) or RING finger protein 51 (RNF51). BMI1 gene (B cell-specific Moloney Murin leukemia virus integration site 1) is located on human chromosome 10 (10p13). Interestingly, BMI1 showed high expression in medulloblastoma and glioblastoma (Leung *et al.,* 2004; Natsume *et al.,* 2011). Shh treatment induced both BMI1 and Gli1 expression. Gli1 overexpression also promoted high expression of BMI1. High expression of BMI1 in tumor cells indicates high capacity of self-renewing characteristics (Hemmati *et al.,* 2003). Most of the BTSCs showed high expression of BMI1. Inhibition of Gli with specific inhibitor GANT61 and Gli siRNAs mediated knock-down inhibited brain tumor cell proliferation and also decreased the expression of BMI1 in medulloblastoma and glioblastoma (Shahi *et al.,* unpublished). Therefore, all these studies suggest that BMI1 would be a novel therapeutic transcription factor to target BTSCs and enhance the survival of brain tumor patients.

2. BMI1: An oncogene and stem cell marker

BMI1 is one of the crucial genes for the development of various tissues including the nervous system. This gene is located at chromosome 10p13 in humans. BMI1 was initially identified as a murin leukemia viral oncogene [1]. BMI1 was the first gene reported to belong to the Polycomb-group of genes [2]. These genes express the proteins which form a large multimeric structure to silence other genes via modification in chromatin organization [3]. Polycomb repressive complexes are divided into two groups.

Polycomb repressive complex 1 (PRC1)

Polycomb repressive complex 2 (PRC2)

PRC1 includes BMI1, and PRC2 includes enhancer of zeste homolog 2 (EZHZ) to facilitate stable silencing of gene expression [4]

3. Role of BMI1 in normal development

BMI1 polycomb protein is essential for the self-renewal of stem cells of different tissues of the body besides the central nervous system (CNS) [5]. One study showed that Nestin-BMI1-GFP transgenic mice cells increased the development of neural stem cell colonies and the self-renewal capability of fetal and adult CNS cells *(He et al., 2009).* Ink4a and Arf genes encode tumor suppressor proteins p16Ink4a and p19Arf respectively, which are involved in the inhibition of cell cycle progression [6]. Interestingly, BMI1 promotes the maintenance of CNS stem cells from the embryonic stage to adulthood by suppressing Ink4a and Arf genes [5]. BMI1 is also involved in Shh signaling mediated postnatal cerebellar neurogenesis by binding to the promoter of p21waf1/cip1 [7]. Moreover, BMI1 is a crucial gene for the development of embryonic and adult stem cells and brain tumors. Interestingly, selective conditional knockout of BMI1 based on Cre/LoXP in transgenic mouse showed that BMI1 has potential to induce neural stem cells proliferation and self-renewal both *in vitro* and *in vivo* [8]. In this process BMI1 down-regulates both Ink4a/ARF and p21/FoxG1. Moreover, increased ectopic expression of BMI1 in progenitors committed to a neuronal lineage during embryonic cortical development, triggered apoptosis via a survivin-mediated mechanism, and caused a reduction in brain size [8]. However, the self-renewable capability of adult neural stem progenitor cells is independent of FoxG1, while apoptosis resistance of neural progenitor cells depends on high expression of BMI1 [8].

4. Role of BMI1 in glioblastoma development

Gliomas are the most common brain tumors of the central nervous system comprising astrocytic gliomas, oligodendrogliomas, or a mixture of both. The most malignant glioma is glioblastoma multiforme (GBM) (WHO grade IV) comprising about 50% of glioma. Post-

therapy survival rate of GBM patients is 24% for 1 year and 12% for 2 years only [9]. There are ample amount of evidence suggesting that gliomas have stem-like cells called glioma initiating cells (GICs). These cells have self-renewal capability and cause gliomagenesis. The GICs are under the regulation of several signaling pathways including Shh, Notch, Wnt and BMI1. Effective targeting of GICs could become a novel strategy to target glioma [10]. The 10p13 region is highly significant in brain tumorigenesis especially glioblastoma. BMI1 is part of the polycomb repressive complex 1, which epigenetically regulates gene expression by acetylation, methylation, and mono-ubiquitination of histones [11]. These modifications cause transcriptional repression of differentiation and pluripotency of embryonic stem cells [12]. BMI1 is essential for the proliferation and transformation of primary glial cells. BMI1 deficient glial cells have less proliferating and tumorigenic capacities. BMI1 is also involved in pathways including proliferation, adhesion, and differentiation. All these pathways play a significant contribution to stem cell renewal and glioblastoma development [13]. One report demonstrates a high copy number of BMI1 in glioma samples [11]. Even, a murine tumor model showed a role for BMI1 in the genesis of glioma and high fold expression of BMI1 in high-grade gliomas [13]. BMI1 shows functional diversity in different cell types including embryonic stem cells and mature neurons [12]. Moreover, BMI1 sometimes behaves as a tumor suppressor gene or oncogene in different tumors. According to one study most of the glioma samples showed BMI1 gene allelic imbalance. BMI1 negatively regulates p16 in astrocytoma. However, they also suggest that BMI1 is not very significant for prognosis of astrocytic tumors [2]. Interestingly, BMI1 is considered as a transgene, which helps MYC to promote hematopoietic malignancies [14-16]. High expression of BMI1 has been noted in brain tumors irrespective of tumor grades [5]. BMI1 has a role in glioma and glioma stem cell growth which is both dependent and independent of InK4a-Arf [13]. GBM showed an association of BMI1 overexpression and enrichment in CD133+ cells [Xia *et al.*, 2012]. Stable knockdown of BMI1 in GBM reveals that BMI1 prevented the clonogenic nature of GBM cells and also these cells were not able to develop brain tumors *in vivo.* Accordingly, BMI1 is a potent inhibitor of apoptosis in CD133+ cells and of differentiation into neurons and astrocytes [17]. BMI1 is also capable to inhibit alternate tumor suppressor pathways that attempt to compensate for INK4A-ARF/p53 deletion and hyperactivity of the PI3K/AKT pathway [17]. Interestingly, one study suggests that BMI1 causes apoptotic resistance to glioma cells through the activation of IKK-Nuclear factor-kB pathway and could therefore be a good prognostic factor for glioma [20]. IKK-Nuclear factor-kB pathway is very active in high grade GBM and glioma cell lines [18, 19]. High expression of BMI1 protects brain tumor cells from cytotoxic reagents-induced apoptosis, while attenuated BMI1 expression promotes apoptosis inducer factors. BMI1 also controls apoptosis in glioma cell lines by activation of the IKK-NF-kB pathway and promoting anti-apoptotic genes [20]. Co-expression of BMI1 and p65 protein, a subunit of NF-kB in glioma is in favour of BMI1 and NF-kB pathways involvement in glioma chemoresistance. GBM is resistant to all types of therapies. It has been postulated that most CD133+ cells are resistant to gamma radiation via activation of DNA double-strand break (DSB) response mechanism, including the participation of the ataxia-telangiectasia-mutated kinase gene (ATM). After purification of BMI1 with DNA DSB responsive factors and nonhomologous end joining (NHEJ) repair proteins in GBM cells [21], a BMI1 enrichment was observed after irradiation,

being colocalized and co-purified with ATM and histone gammaH2AX. Deficient BMI1 glioma cells showed inactive DNA DSB response, which promoted sensitivity of radiation in glioma cells. Overexpressed BMI1 modulated the neural stem cells radiation resistance by enhancing the ATM activity. Therefore, a combined effect of BMI1 inhibition together with radiation therapy might efficiently target GBM stem cells [21]. Interestingly, a recent report suggested that expression of BMI1 and c-Myc correlated in glioma. This finding further reveals that c-Myc, either directly or indirectly, activates several epigenetic modulators including acetylase GCN5 and polycomb-group (PcG) gene BMI1 [22, 23]. It is interesting to know that BMI1 promoter contains functional E-box and c-Myc binding regions [24, 25]. Moreover, c-Myc was able to activate BMI1; and BMI1 further facilitated the oncogenic expression of c-Myc in glioblastoma development [17]. It has been speculated that c-Myc and BMI1 might be good biomarkers of glioblastoma due to their high expression and involvement in gliomagenesis. Inhibition of both genes could give glioblastoma a greater sensitivity to combined anticancer therapy. A recent study revealed that Tamoxifen (TAM) has the ability to reduce the expression of neural stem cell markers, like Nestin, Bmi1 and Vimentin, in glioma cell lines. Moreover, the action of TAM in glioma cells apotosis is assisted by prostate apoptosis response-4(par-4) [26]. It has been published that AR-A 014418 inhibits GSK3 beta kinase activation which further regulates the cancer escape pathway via downregulation of anti-apoptotic gene BMI1 [27].

5. BMI1 and miRNAs

Low expression of miRNA-128 was reported in GBM samples. High expression of miRNA-128 in GBM down-regulates ARP5 (ANGPTL 6), BMI1 and E2F-3a, factors which are key regulator for brain cell proliferation [28]. miRNA-128 also targets BMI1 and down-regulates its expression. Most of the glioma samples show less expression of miRNA-128. Overexpression of miRNA-128 shows inhibition of GICs proliferation and self-renewable capacity [10]. Normal brain has abundant expression of miRNA-124, however, miRNA-124 expression is diminished during the development of glioma. Interestingly, overexpression of miRNA-124 reduced the formation of neurospheres, the CD133+ cell subpopulation, and the expression of stem cells markers like BMI1, Nanog and Nestin [29]. Smoothened inhibitor NPV-LDE-225 (Erismodegib) inhibits BMI1 in GICs via upregulation of miRNA-128, miRNA-21 and miRNA-200 [30]. Interestingly, NPV-LDE-225 was used in topical cream for basal cell carcinoma treatment and it inhibited the Shh pathway [31]. A recent study suggested that NPV-LDE-225 mediated inhibition of Shh signaling downregulates Bmi1 via upregulation of miRNA-128 [30]. Another study also suggested that polycomb repressor complex BMI1 is targeted by miRNA-128 in glioma stem cells [32]. Another miRNA-218 also inhibited the expression of BMI1 which further retarded glioma invasion, migration, and glioma stem cell renewal capability. Most gliomas showed less expression of miRNA-218 and overexpression of miRNA-128, which further inhibited glioma tumor characteristics. It was assumed that BMI1 is the downstream target gene of miRNA-218. miRNA-218 regulates many genes which are involved in glioma tumorigenesis [33]. Interestingly, we illustrate a model diagram for the role of BMI1 in gliomagenesis (Figure 1).

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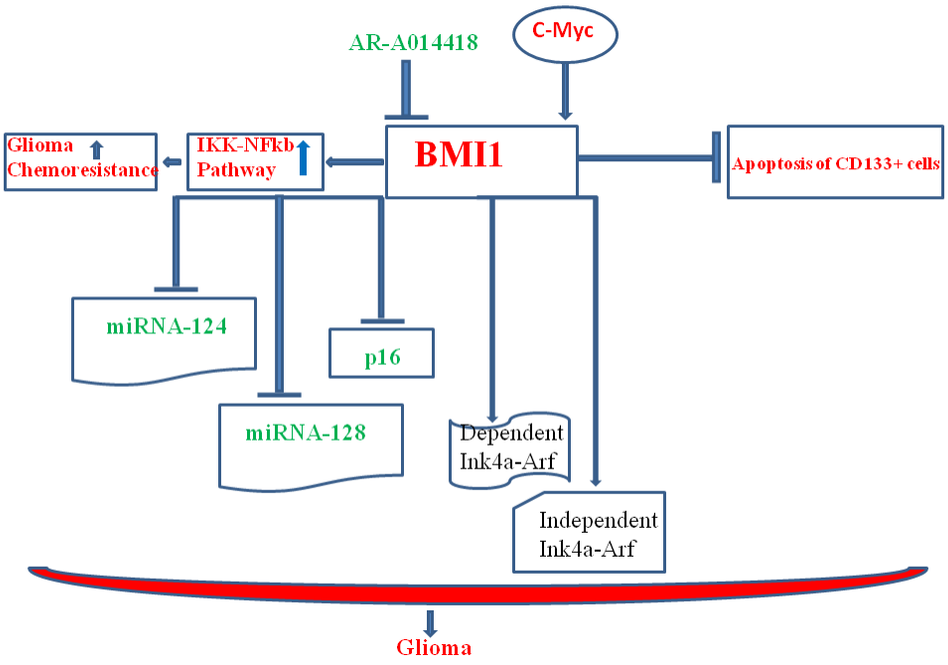

Figure 1. BMI1 networking in gliomagenesis

6. Role of BMI1 in medulloblastoma

Medulloblastoma is a primitive neuroectodermal tumor of the cerebellum. Medulloblastoma is the most common pediatric malignant brain tumor, representing 20% of newly identified CNS tumors in children [34]. Medulloblastoma is driven by several signaling pathways, among which, Shh plays a critical role for the majority of these tumors [35, 36]. Mutations of the Shh pathway regulators are present in about 20-25% of medulloblastomas [37]. Shh-driven medulloblastoma showed high expression of BMI1. A recent study reveals the role of BMI1 in Shh-driven medulloblastoma. Transgenic mice showed the expression of Shh signaling activator SmoA1 with the help of glial fibrillary acidic protein (GFAP) promoter. They found that SmoA1/BMI1+/+; SmoA1/BMI1+/-postnatal mice (p=26) between days P14 to P26 showed prominent potential to develop medulloblastoma compared to SmoA1/BMI1-/-post natal mice (n=6) [38]. Interestingly, cells with BMI1 deficiency BMI1-/- even in the presence of SmoA1 were non-proliferative compared to BMI1+/+ cells [38]. Two down-stream genes which are inversely regulated by BMI1 in Shh-driven medulloblastoma development were reported. Cyclin D1 expression was downregulated and cyclin-dependent kinase inhibitor p19Arf was upregulated. Moreover, it was concluded that BMI1 is crucial for the Shh-driven medulloblastoma development and that BMI1 facilitates medulloblastoma development de novo [38]. During embryonic development Shh signaling pathway regulates proliferation of granular neuron precursors (GNPs). GNPs are progenitors for medulloblastoma development, comprising the transient external granular layer of cerebellum [39]. BMI1 seems to promote the expression of downstream target genes during cerebellum development [40]. BMI1-null mice developed reduced cerebellum and impaired production of granular neurons. Altered

expression of BMI1 in medulloblastoma as well as correlation of BMI1 expression and Shh activation was reported in medulloblastoma [38, 41]. It was suggested that polycomb gene expression could be used as a predictor of poor clinical outcome in medulloblastoma [42]. BMI1 overexpression caused cell proliferation and assisted Shh signaling driven tumorigenesis [43]. BMI1 expression and Shh ligand concentration were positively correlated during development. Chromatin immunoprecipitation experiments revealed that Shh signaling pathway main transcriptional activator Gli1 preferentially binds to the promoter regions of BMI1. Moreover, overexpression and downregulation of Gli1 controls high and low expression of BMI1 respectively. Interestingly, BMI1 is not only a Shh-Gli1 downstream target gene but also promotes a feedback mechanism which further activates Shh-Gli1 signaling. This finding suggested that both BMI1 and Shh signaling pathways are mutually indispensable pathways in brain tumor initiating cells (BTICs) of medulloblastoma [43]. One study reported that overexpressed BMI1 was unable to induce tumors in mice from granule cell progenitors (GCPs). Therefore, it was concluded that overexpression of BMI1 in GCP-derived human medulloblastoma, could promote later stages of tumorigenesis and further sustain tumor cell survival [44]. Apart from cell proliferation other characteristic of tumors include anti-apoptotic nature and sustaining of high metabolic rate, both supported by high BMI1 and low TP53 levels of expression which are characteristic of group 4 human medulloblastoma [44]. BMI1 overexpression alone was not sufficient to induce medulloblastoma; however BMI1 overexpression and loss of p53 induced medulloblastoma in mice, producing similar tumors to group 4 human medulloblastomas [44]. Recently, medulloblastomas have been categorized in 4 subgroups on the basis of prognosis and predicted therapeutics (Kool et al., 2012, Ramaswamy et al., 2013 and Gottardo et al., 2014). Group 1 and group 2 are under the good clinical outcome and regulated by Shh and Wnt signaling, respectively [45]. Groups 3 and 4 medulloblastoma are not Shh/Wnt signaling mediated tumors, have metastatic potencial, and poor patient outcome and lack of known molecular pathways. Current gene expression analysis is unable to detect self-renewal gene and brain tumor-initiating cells (BTIC) in group 3 and group 4 medulloblastoma. BTICs constitute a minority of the tumor mass, and their detection can be difficult in medulloblastoma. High BTIC promoted tumors to increase tumor aggressiveness and poor patient outcome. They investigated the potential stem cells candidate genes among the different subgroups of 251 human medulloblastoma samples from the 4 overlapping MB transcriptional data bases (Amsterdam, Memphis, Toronto and Boston) and 74 nano-string sub-grouped medulloblastoma (Vancouver) [45]. This analysis showed two crucial genes BMI1 and FoxG1, which presented abundant expression in non-Shh/wnt medulloblastoma groups. These genes are responsible to promote MB stem cells and tumor initiation in mice [45]. We also depicted a model for the different group of medulloblastoma development on the basis of cell signaling pathways and gene expression profile (Figure 3). This study also identified a reciprocal promoter in CD15+ medulloblastoma stem cells. The finding could be used as a novel target therapy against BTIC self-renewal. They also found BMI1 is a downstream target of FoxG1 and further promotes tumorigenicity. BMI1 also exerts feedback to FoxG1 expression and facilitates *in vivo* tumor malignancy and enhances in vitro stem cell self-renewal capability. Moreover, high expression of BMI1 can be considered as a strong molecular prognostic marker in pediatric brain tumors. We attempted to show a model for the role of BMI1 in medulloblastoma development (Figure 2).

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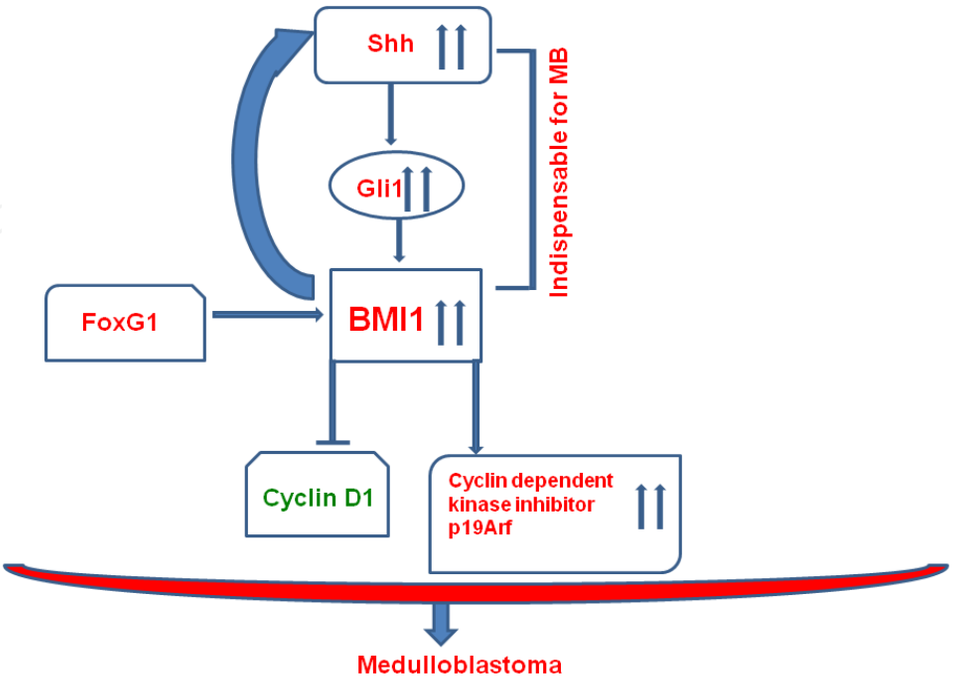

Figure 2. BMI1 networking in medulloblastoma development

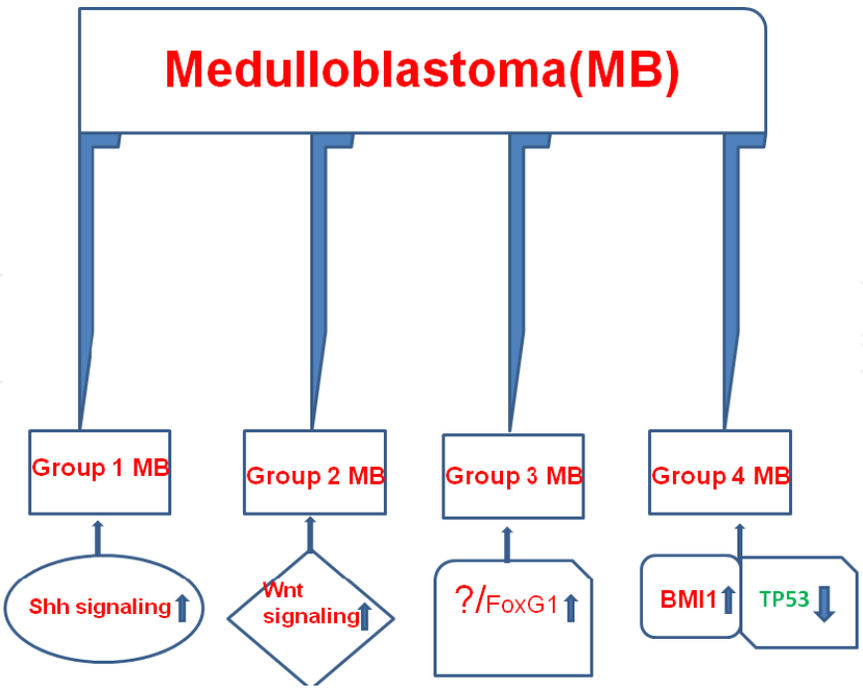

Figure 3. Division of medulloblastoma on the basis of gene and cell signaling expression

7. Conclusion

BMI1 is a very significant stem cell marker gene which contributes to the development of glioblastoma and medulloblastoma. Therefore, the treatment of glioblastoma and medulloblastoma would improve with the addition of BMI1 inhibitors. Moreover, high expression of BMI1 could be used as one of the earliest markers to diagnose brain tumors.

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