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The Class I Histone Deacetylase Inhibitor as a Potent Therapeutic Target for Treating Glioblastoma and Mocetinostat as a Novel Inhibitor in the Induction Death of Cancer Cells

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ABSTRACT

Epigenetic abnormality is one of the hallmarks of glioblastoma cancer cells. Histone deacetylase (HDAC) modification has a crucial role in epigenetic abnormality, which results in the initiation and progression of glioblastoma cancer cells. The selective HDAC inhibitors are well-known epigenetic regulators and promising anti-cancer agents that target specific HDAC enzymes and inhibit the proliferation of many cancer cells. Selective HDAC inhibitors isoform provides a high efficacy as chemotherapy in inhibiting cancer confirmation compared to non-selective HDAC inhibitors. Additionally, selective HDAC inhibitors suppress Class -I HDAC1, HDAC2, HDAC3, and HDAC11. HDAC class I inhibitors induce apoptosis, differentiation, autophagic death cells, and reactive oxygen species (ROS)- induced cell death, inhibit cell migration, invasion, and angiogenesis in cancer cells, while the normal cells showed more resistance to HDAC class I inhibitors. Mocetinostat (MGCD0103), a benzamide histone deacetylase, is a potent anti-cancer therapy for the treatment of several cancer cell lines and induction of autophagy. It has been approved by The Food and Drug Administration (FDA) for the treatment of Hodgkin lymphoma (HL) cell lines. MGCD0103 is a synthesized and selective HDAC inhibitor that has vigorous inhibitory activity against Class-I and IV HDAC. MGCD0103 is well tolerated and has favorable pharmacokinetic properties, pharmacodynamic profile, and fast absorption within 1 hour after oral administration, long elimination half-life, and sustained HDAC inhibition. Therefore, MGCD0103 is expected to be a promising anti-cancer drug for treating several types of human cancer cells.

Keywords: MGCD0103; Apoptosis; Differentiation; Gliblastoma; HDAC; inhibitors.

مثبطات الفئة الاولى Histone deacylase inhibitor علاج قوي لمعالجة الورم الارومي الدبقي Glioblastoma Mocetinostat مثبط جديد لتحفيز موت خلايا السرطانية (MGCD0103):

فراس حميد خضير

الملخص: الشذوذ اللاجيني (Epigenetic Abnormal) هو أحد السمات المميزة للأورم الارومي الدبقي (lioblastoma multiform). تعديل انزيم Histone deacetylase modification (HDAC) امتلكت دوراً مهم في الشذوذ اللاجيني الذي ينشا عنة بدء ونمو الورم السرطاني الأرومي (GBM). مثبطات انزيم(Histone deacetylase inhibitors) (HDACi) الإنتقائية معروفة جيدا كمنظمات فوق جيني ومادة مستقبلية واعدة كمضادة للسرطان التي تستهدف انزيمات (HDAC) الانتقائية وتمنع نمو العديد من الخلايا السرطانية . توفر مثبطات (HDACi) الانتقائية فعالية عالية كعلاج كيميائي في تثبيط تكوين السرطان مقارنة بمثبطات HDACi غير الانتقائية. مثبطات HDACi الانتقائية تمتلك قدرة عالية متخصصة لتثبيط الفئة الاولى لإنزيم HDAC Class I (HDAC11, HDAC3 , HDAC2 , HDAC1) . المثبطات HDACi من الفئة الأولى حفزت موت الخلايا المبرمج والتمايز والتهام الذاتي و مركبات الأوكسجين التفاعلية (ROS) التي تسبب موت ومنع هجرة وغزو الخلايا وتكوين الأوعية الدموية في الخلايا السرطانية. في حين أظهرت الخلايا السليمة مقاومة أكبر لمثبطات الفئة الأولى HDACi مقارنة بخلايا السرطانية. Mocetinostat المعروف أيضًا باسم

الامريكية (FDA) لعلاج خلايا سرطان الغدد الليمفاوية (Hodgkin lymphoma).MGCD0103 هو مثبط انتقائي تركيبي لانزيم HDAC مع نشاط تثبيطي قوي ضد الفئة الاولىClass I والخامسةClass IV لانزيم HDAC. يمتاز MGCD0103 بخاصية حركية دوائية مواتية و مظهر ديناميكي دوائي و جيد التحمل وامتصاص سريع خلال ساعة واحدة بعد تناوله عن طريق الفم وعمر نصف الدواء للتخلص طويل وفترة تثبيطية طويل لعمل HDAC. كل ذلك قد يجعل MGCD0103 عقارًا واعدًا مضادًا للسرطان لعلاج عدة أنواع من الخلايا السرطانية البشرية. واحدة بعد تناوله عن طريق الفم وعمر نصف الدواء للتخلص طويل وفترة تثبيطية طويل لعمل HDAC. كل ذلك قد يجعل MGCD0103 عقارًا واعدًا مضادًا للسرطان لعلاج عدة أنواع من الخلايا السرطانية البشرية.

الكلمات المفتاحية: الفئة الأولى لمثبطات HDACi ، MGCD0103 ، الموت المبرمج للخلايا ، الورم الاروميي الدبقي.

1. Introduction

Histone deacetylase enzymes (HDACs) are a large family of enzymes that remove acetyl groups from lysine-residues of histone proteins, causing transcription repression while histone acetylation enzyme (HATs) catalyzes the addition of an acetyl group to lysine residues in the histone tail that leads to open chromatin and allows gene transcription of histone and non-histone protein [1]. The equilibrium between acetylation and deacetylation of histone and nonhistone proteins significantly contributes to the regulation of gene expression. The impairment in the balance between histone acetylation and deacetylation is usually associated with dysfunction in the expression of tumor suppressor genes and cancer progression [2]. In the human, there are 18 HDAC's divided into four classes on the basis on similarity to yeast proteins: Class I: reduced potassium dependency 3(Rpd3)-like proteins (HDAC1, HDAC2, HDAC3, and HDAC8); Class II: Hda1-like proteins (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, HDAC10); Class III: Sir2 (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6 and SIRT7); and class IV proteins: (HDAC11) [3]. HDACs class I, II, and IV need Zn^{+2} as a cofactor for their enzymatic activity, and HDACs class III or Sirtuins require nicotinamide adenine dinucleotide (NAD) in their active site [4]. In addition to histone substrate, the aberrant activity of HADC enzymes may bind to non-histone protein substrates such as transcription factors, hormone receptors, signal transducers, chaperones and proteins of the cytoskeleton which also lead to the growth and development of cancer cells. [5]

The inhibitory action of these enzymes by HDAC inhibitors (HDACi) significantly contributes to the accumulation of the acetyl group in lysine residues in histone and non-histone proteins. Consequently, these inhibitors induce apoptosis, differentiation, cell cycle arrest, autophagic cell death, and reactive oxygen species (ROS)-induced death of cells [6, 7]. Also, HDAC inhibitors prevent repair of damage of DNA double-strand breaks (DSB) when combined with other cancer therapy such as radiation leading to enhanced tumor cell death in glioblastoma [8]. Histone deacetylase inhibitors (HDACi) are a promising cancer drug that have structural similarities to HDAC acetyl-lysine substrate [9]. There are two types of HDAC inhibitor enzymes: selective and non-selective inhibitors. Non-Selective-HDAC inhibitors, also known as pan-inhibitors represent the majority of HDAC inhibitors that affect the activities of all HDAC enzymes. For example, SAHA and TSA are canonical pan-inhibitors, inhibiting the activity of HDAC(1-9) with almost equivalent effectiveness [10]. Selective histone deacetylase inhibitor (HDACi) is a novel agent to target specific HDAC, either a single HDAC isoform or several isoforms within a single class of HDAC (Bieliauskas and Pflum, 2008). Selective HDACi has a therapeutic efficacy more than non-selective HDAC inhibitors in killing cancer cells because of the high similarity in the structure between them and the active site of the HDAC enzyme family [11]. However, in glioblastoma cells, the overexpression of Class I histone deacetylase (HDAC) has been connected to many biological processes such as cell cycle progression, cell survival, and differentiation. Inhibition of class I HDAC enzymes might be beneficial for the treatment of glioblastoma cancer cells [12].

MGCD0103 is a novel class I iso-selective histone deacetylase inhibitor, which has a broad spectrum in suppressing the growth of cancer cells in both vitro and in vivo [13]. MGCD0103 is highly specific in inhibition of class I and IV HADC enzymes for induction of apoptosis and autophagy in various types of tumor cells [14], and they do not influence the class II HDACs [15]. Recent studies have found that MGCD0103 has a good tolerance and favorable pharmacokinetic and pharmaco-dynamic profile in clinical trials in patients with Hodgkin's lymphoma. The drug also shows safety and low toxicity when treating cancer cells [16, 17, 18]. All these traits of MGCD0103 make them promising anti-cancer drugs. This review will show the inhibitory efficacy of HADC class I in the treatment of glioblastoma cancer cells by different biological activities, including inducing apoptosis and differentiation and inhibition of migration and invasion of glioblastoma as well as showing the efficacy of MGCD0103 as one of the types of histone deacetylase (HDAC) inhibitor class I in induction apoptosis and differentiation in different cancer cells.

2. The Role of the Class I HDAC in Glioblastoma

Epigenetic alteration is an alteration in gene expression without change in the DNA sequences through modulation of specific signaling cascades within the tumor. Histone deacetylases (HDAC's) play critical roles in epigenetic alteration in the human body [19]. The class I HDACs is part of the HDAC's superfamily that has a vital role in several biological activities [20]. Class I HDAC enzymes consist of HDAC1, 2, 3 and 8 with sequence similarity to (Rpd3), a transcriptional regulator found in yeast protein [21]. These enzymes are proteins ubiquitously expressed in human cells, found exclusively in the nucleus for most cells, except in HDAC3 and HDAC8, which are present in both the nucleus and cytoplasm [4, 22]. They show a high enzyme activity on histone substrate and attach with transcriptional repressor and cofactor [20, 23]. Recent studies have started investigating the expression types of HDACs in Glioblastoma Multiforme (GBM). GBM cells and primary GBM tissues showed an increase in HDAC1,3 expression compared to non-neoplastic brain tissues in both the RNA and protein levels [24]. The structure of class I HDAC contains a conserved single deacetylase domain at the N terminus with short amino and carboxy-terminal extensions [20]. Class I HDAC is a classical HDAC family that needs zinc ions (Zn^{2+}) on the active side as a cofactor of enzyme activity [25]. Abnormal HDAC enzyme increases their expression in cancer cells, and it acts as an oncogene causing many types of malignancies in the human body [26], resulting in high dedifferentiation and cell proliferation in the tumor [27].

The overexpression of different families of class I HDAC enzymes is significantly implicated in cancer formation in glioblastoma [28, 12]. A recent study found that class I HDAC increased in high-grade gliomas by different mechanisms [12] (Table 1). The studies observed that overexpression of HDAC1 was correlated with induction cell proliferation in glioma cells through a decrease in the expression of BIM, BAX, Caspase-3, and E-cadherin, as well as an increased level of TWIST, Snail, and Matrix metalloproteinases (MMP) in T98G glioma cell line [29]. Other studies suggested that HDAC1 is remarkable for the induction of high-grade glioma by its interaction with phosphor-special AT-rich sequence-bind protein-1(SATB1). High expression level of Phosphor SATB1 is considered essential in the proliferation and invasion of glioblastoma cells. Phospho- SATB1 associates with HDAC in glioma and induces expression of MMP2 and MMP9 in the U87 and SU3 glioblastoma cells line. Consequently, the interaction between phosphor-SATB1 and HDAC1 is considered key in the regulation of gene expression of glioma cells [30].

HDAC2 is a member of the class I family and is highly expressed in glioblastoma. Recent study investigated expression class I HDAC (1, 2, 3, and 8) in U87, A172, U251, and LN229 cell lines of glioblastoma compared with their expressions in normal cells. The findings found that HDAC2 was upregulated compared with other types of HDAC Class I, and it was involved in cell proliferation, migration, and invasion in glioblastoma via increased mRNA and protein expression of multidrug resistance-associated protein 1 (MRP1) [31]. While Was *et al*. (2019) found that both HDAC 1 and HDAC2 were overexpressed in U87 and LN18 glioblastoma cells, and they are responsible for the aberrant activity of an epigenetic enzyme that causes a decrease in acetyl level from histone H3 and H4 in glioblastoma.

HDAC3 plays an essential role in developing brain function and is associated with the pathological grade of glioma [32]. It also upregulates expression in children's glioma [33]. Overexpression of HDAC3 is observed in glioblastoma and evaluated in both nuclear and cytoplasmic human astrocytic glioma tumors [34]. Norwood *et al*. (2015) observed that HDAC 3 has a crucial role in regulating the development of the adult brain, in which HDAC3 can modulate glial cells growth and deletes HDAC3 from neural progenitor cells leading to an increase in astrocytes through an increased expression of GFAP in the cortex and cerebellum of cKO MICE, while Geo *et al*.(2009) demonstrated that HDAC3 attributed to activation of the CEBPB and JUN transcriptional factors induced HIF-1α that played a critical role in chemotherapy and radiation therapy resistance of glioblastoma under different hypoxia conditions [35]. HDAC3 also induces the proliferation and dedifferentiation of germline stem cells (GSCs) by inhibition of TGF-β pathway induced SMAD7, SOX2 activation [36].

HDAC8 is similar in sequence to HDAC1 and 2 and belongs to class I HDAC. It is different from other classes of HDAC in location on the X chromosome at position q13. The expression of HDAC8 is widespread in the body tissues, especially in the brain, prostate, and kidney [37]. Overexpression of HDAC8 decreases apoptosis and increases cell proliferation in glioblastoma, so it acts as an oncogene in the induction of tumors [38]. It was found that HDAC8 can interact with P53 and inactivate p53 resulting in cell proliferation in neuroblastoma [39]. Besides, HDAC8 causes resistance of glioblastoma cell lines to temozolomide (TMZ) treatment through increased expression of O^6-Methylguanine -Methyltransferase DNA repair enzyme (MGMT). In U87 and T98G glioblastoma cells line, this increase in MGMT expression occurs through interaction HDAC8 with proteasome ubiquitin receptor ADRM1 that lead to promoting cell viability [40]. Other studies also showed that the levels of HDAC2 and HDAC8 dramatically increased in the glioblastoma and caused the induction of proliferation, migration, and invasion through upregulation mRNA and protein expression of multidrug resistance protein 1(MRP1) mediated in increased resistance of glioblastoma to temozolomide (TMZ) [41].

Table 1. The role of class I HDAC in the regulation of proteins involved in different biological activities in glioblastoma cancer cells.

enzymes	Cell proliferation	Differentiation	Invasion
HDAC1	Bim, BAX ↓ Capase3,SATB1 ↓	E-Cadrine ↓	SATB1 ↓
HDAC2	MRP1 ↑	——	MRP1 ↑
HDAC3	JUN , CEBPB ↑ TGF-β ↑	GFAP ↑ SMAD7,SOX2 ↑	——
HDAC8	P53 ↓ ADRM1,MRP1,MGMT ↑	——	MRP1 ↑

3. Potential class I HDAC inhibitor in the induction of apoptosis in glioblastoma cancer cells

HDAC class I inhibitors are new promising antiproliferative agents that induce cell cycle arrest, differentiation, and apoptosis of cancer cells [2, 42] (Figure 1). The inhibitory effects of class I HDAC inhibitors in the treatment of glioblastoma cancer cells occur through multiple mechanisms that lead to the upregulation of tumor suppressor genes, enhancing of immune response, inhibiting oncogenes, and downregulation of oncogenes [43]. The principal function of HDAC class I inhibitor in the inhibition action of HDAC enzymes occurs through binding to the zinc ion in the active site of the HDAC. This leads to the accumulation of histone acetylation, thereby promoting the transcription of histone and non-histone genes [44]. These inhibitors have been classified into four types depending on the structure of HDAC: hydroxamic acid, Benzamide, short fatty acid, and cyclic peptide [45]. HADC class I inhibitors can act against specific types of HDACs (selective- inhibitors) or all types of HDACs (pan-inhibitors) [46].

Recently, some of the class I HDAC inhibitors have been approved by the FDA for treating many types of human cancer cells as Vorinostat, Depsipeptide, and Belinstat, in the treatment of T-cell lymphoma [47,2]. The mechanisms of action of HDAC inhibitors in cancer cells depend on type of cancer cell and doses of drugs [2]. The studies investigated cytotoxic effects for several types of class I HDAC inhibitors, whether selective HDACi such as MC1746, MC2129, and Compound 106, or pan HDACi such as Vorinostat and Valproic acid on cultured human GBM cells [12]. The principal purpose of HDAC inhibitors in glioblastoma is to create a balance between two enzymes (HAT) involved in the transcription of the gene and (HADC)-induced gene silence to kill cancer [48]. In addition, these inhibitors increase cell cycle arrest at the G2/M or G0/G1 phase, and induce DNA fragmentation that leads to apoptosis by increasing the expression of p21, cleaved caspase 3, and Poly (ADP-ribose) polymerase-1(PARP-1) in glioblastoma (Was *et al*., 2019). The inhibitors have a high capability for crossing the Blood-Brain Barrier (BBB) with low toxicity in normal cells [49, 50].

Valproic acid (VPA) is a pan-HDAC inhibitor that can effectively cross the blood-brain barrier (BBB) with a low cytotoxic profile [51, 52]. The effects of valproic acid have also been studied on glioblastoma cancer cells and it was found that it markedly inhibited proliferation of cancer cells because of its high capability to increase the production of reactive oxygen species (ROS), p21, and p27 and downregulation of stress-related molecules such as paraoxonase (PNO2), cyclin-dependent kinase 2(cdc2), and Bcl-XL in U87 and GBM8410 glioblastoma cells line [53].

Entinostat selectively inhibits class I HDAC enzymes and is a potent therapy in the treatment of glioblastoma through direct inhibition of HDAC enzymes. It can reduce cell proliferation and induce apoptosis, cell cycle arrest in the G0/G1 in U89MG, C6, F98 and SMA-560 [54]. Was *et al*. (2009) found that compound 106 specifically inhibits HDAC3 and can be caused an increase in the level of acetyl-H4, and significantly induce p21 and γ-h2ax proteins in U-87 MG cells [12]. Also, histone deacetylase (HDAC8) was inhibited by HDAC8-specific inhibitor PCI3405 when used to treat glioblastoma. PCI3405 decreases MGMT level and increases the level of phosphorylate H2Ax, which represents a DNA damage marker. PCI3405 also reduces the expression of HDAC8 required for cell proliferation of T98Gglioblastoma [40].

Phenylbutyrate (PBA) is considered a pan-histone deacetylase inhibitor classes I (HDAC) and has known effects on glioblastoma. PBA induces cell cycle arrest and apoptosis by upregulating the expression of P21 and downregulating anti-apoptotic BCL2/Bcl-XL without affecting the expression of proapoptotic Bax and Bim in N-229 glioblastoma cells line

[55]. Dacinostat (LAQ824) has been shown to anticancer agent against growth of glioblastoma because ability to blood brain barrier(BBB) permeability [56]. Dacinostat (LAQ824) helps in the promotion of apoptosis in glioblastoma via increasing accumulation of acetylation on histones, inducing cell cycle arrest, and upregulating P21 [57, 58].

Panobinostat (LBH-589) is a pan HDAC inhibitor and is in phase II trials for the treatment of glioblastoma [59]. LBH-589 is used against diffuse intrinsic potent glioma (DIPG), which is one of the deadliest forms of childhood cancer. LBH-589 contributed to the increasing accumulation of H3 acetylation and H3K27 trimethylation. Subsequently, it can stop the growth of brain tumors [60].

Romidepsin is one of the cyclic peptide compounds that has a potent inhibitory effect on glioblastoma cell growth. Romidepsin has been tested in phases I and II for treating patient of glioblastoma cells [61]. Romidepsin (FK228) decreased tumor growth and induced apoptosis in the glioblastoma model by downregulating antiapoptotic proteins Bcl1-XL and increasing expression of the cyclin-dependent kinase inhibitor p21 [62].

The Class I HDAC inhibitor, DWP0016, effectively suppressed the growth and induced cell cycle arrest in U251 glioblastoma cells. DWP0016 causes the induction of transcription and acetylation of tumor suppressor gene p53 by regulating P300, CBP, and PCAF. P53 activation involved BAX and PUMA expression to induce the mitochondrial death pathway [63]. Class, I HDAC inhibitor has been tested not only as a single agent but also in combination with other cancer therapies for the treatment of glioblastoma [64]. SAHA plays a unique role as an HDAC inhibitor alone or combined with N-(4-hydroxyphenyl) retinamide (4HPR) to inhibit the growth of two glioblastoma cell lines C6 and T98G through activating mitochondrial extrinsic and intrinsic pathway-induced apoptosis [65]. Similarly, sodium butyrate (NaB) and quercetin (QCT) synergistically have been tested in C6 and T98G glioblastoma cells line. The data has demonstrated that the combination of NaB +QCT highly enhanced the increase in inhibition of cell proliferation and autophagy formation in two cells line of glioblastoma through activating BAX, Caspase 3, cleavage PARP-induced apoptosis, and the decrease in expression of Beclin-1 and Microtubule-associated protein 1A/1B-light chain 3(LC3II)-induced to autophagy [66]. Valproic Acid (VPA) and radiotherapy (X-ray) significantly downregulate Bcl2 and upregulate BAX protein compared with drug alone in the treatment of C6 glioblastoma [67].

4. Role of Class I HDAC in migration, invasion, and angiogenesis in glioblastoma

During the epithelial-to-mesenchymal transition (EMT) process starting with the migration of cells to other organs of the body by a blood vessel, main extracellular metalloproteases in the degradation of extracellular matrix (ECM) are MMP1 and MMP9, which act as oncogenes and mediate degradation of the extracellular matrix that led to cell migration and invasion of glioblastoma cell [68]. One of the upstream pathways controlling MMP expression is the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PI3K/AKT) pathway [69, 29] Histone modification has a high ability to regulate EMT [70, 26]. Class I HDAC enzymes play an important role in the induction of cell migration and invasion in human cancer cells and the regulation of gene expression of an extracellular matrix-related gene (ECM) [71] by reducing the histone acetyl group from histone protein H3 that may lead to increase expression of MMP9 and paternally expressed gene 1(PEG1) [26]. Class I HDAC enzymes play an important role in the migration, invasion, and angiogenesis of glioblastoma in both tumor and non-tumor cells. HDAC1, which belongs to HDAC class I, significantly increases its expression during tumor progression in glioma cells compared with normal cells causing cell invasion in glioma cells by increasing expression of phosphorylated PI3K/AKT and MEK/ERK signaling pathway in vitro and in vivo [72] involved in secretion of MMP2, 9 expression [73]. Another study found that overexpression of HDAC1 involved in migration and invasion of glioma cells was correlated with increase expression of invasive-related factors (TWIST1, SNAIL, and MMP9) [29]. Zhang *et al*. investigated expression class I HDAC enzymes (1,2,3 and 8) and found that HDAC2 expression was a significantly higher expression in the glioblastoma than the other class I HDAC, and it is responsible for the progression of tumor glioma cells [41]. Few studies show the role of the inhibitor in the suppression of migration and invasion of glioblastoma. Class I HDAC inhibitors induce inhibition of invasion of glioma through decreasing expression of MMP in the glioma cell line [29]. For example, Entinostat a class I HDAC selectively inhibited HDAC 1,3 and has a cytotoxic effect in suppressing the migration of glioblastoma cells. The study suggested that entinostat was the most effective HDACi compared with trichostatin A (TSA) and MC1568 in decreasing the migration and invasion of the U87 glioblastoma cell line that reached 44% as compared to the control that was 100% without a clear mechanism [74, 75] demonstrated that Panobinostat may act as an anti-invasive agent in the reduction of the Epithelial-mesenchymal transition (EMT) that causes potential cell migration to nearby tissues. The results found that Panobiostat alone or in combination with temozolomide caused decreased migration in the LN405 glioblastoma cell line through increased expression of N-cadherin that represents mesenchymal marker and increased the level of E-cadherin protein. SAHA (vorinostat) alone or in combination with 4HPR significantly limited migration and invasion in the glioblastoma and identification as an anti-invasive compound by suppressing pI3K/Akt activity and downstream its target transcription factor (*Nuclear factor kappa B* (NF-kB) and p38 involved in activation MMP9 and MMP2 responsible for invasion cells in both cell line C6 and T98G glioblastoma cells line [65]. Also, the studies observed that sodium butyrate inhibits migration and invasion of C6 glioblastoma cells [76], while Nakagawa *et al*. found that sodium butyrate suppresses cell invasion in human GB A172 cells by increasing the phosphorylation of Focal Adhesion Kinase (pFAK) that is a key regulator of adhesion and motility in cancer and normal cells [77].

Further, Glioblastoma multiform (GBM) progression can express a transcription factor called hypoxia to induce factor-1 (HIFα-1) and (HIFα-2) that has an influential role in GBM

development and progression regulates angiogenesis [29]. HIFα-1 stimulates several genes including Vascular endothelium growth factor (VEGF) mediates angiogenesis in glioblastoma [78]. The epigenetic therapy that targets the epigenetic alternation by multiple mechanisms also causes inhibition of angiogenesis [79]. HDAC enzymes that can remove acetyl groups from histone significantly increase the expression of HIFα-1 [80]. Histone deacetylase inhibitors help in the suppression of angiogenesis of GBM via inhibiting growth factors (VEGF, EGFR) production or by blocking vascular channels in GBM [81]. There are many studies indicating the role of class I HDAC inhibitors in the suppression of angiogenesis through accumulating hyperacetylation of histone and regulating heat sock protein 90 induction of HIFα-1 of histone [82]. Yao *et al.* (2017) examined the mechanisms of Panobinostat (LBH589) on angiogenesis activity of glioblastoma invitro and in vivo, The results found that LBH589 causes disruption of heat protein 90/HDAC6 complex and inhibits expression of HIFα and VEGF in U87 glioblastoma cell lines [59]. Other groups of HDAC inhibitors including SAHA, TSA, and FK228, have also been reported as anti-angiogenic activity in glioblastoma cells line [65, 62].

5. Role of class I HDAC inhibitors in Differentiation

Neural differentiation of human pluripotent stem cells (hPSCs) inducing human embryonic stem cells (hESC) and human induced pluripotent stem cells (hPSCS) leads to differentiation into cell types of three germ layers [83]. Neural progenitor cells (NPCs) generated from hPSC and finally convert NPC into neuronal or glial cells [84]. Astrocytes are the most common types of glial cells and play a vital role in the function and development brain [85]. Astrocytes have subtypes of glial fibrillary acidic protein (GFAP-positive cell) in the human brain, while there are two subtypes in rodents [86]. Epigenetic alteration of DNA and histone plays a crucial role in regulating gene transcription of neural cells [84] HDAC deacetylase (HDAC) is the main agent for regulating the development of cancer by removing the acetyl group from histone and other histone proteins thereby preventing transcription gene that can cause deacetylation a variety of proteins responsible for cell growth, differentiation, and apoptosis (Di marcotullio *et al.*, 2011). Overexpression of class I HDAC involved in dedifferentiated tumor [27]. The Class I HDAC inhibitors are a group of short-diverse molecules in structure and function known as anticancer therapy in the induction of differentiation [88]. HDAC inhibitors cause the accumulation of acetyl on both the histone and nonhistone proteins resulting in differentiation, apoptosis, and cell cycle arrest [89]. SAHA promotes the differentiation of glioblastoma stem cells and the development of an astrocytic morphology through upregulating glial fibrillary acidic protein (GFAP) and TUBB3 that represent differentiation in glioblastoma and downregulating both PROM1 and nestin that is dedifferentiation in glioblastoma. Also, other studies found that some HADC inhibitors can inhibit class I HDAC and induce differentiation [90]. Svechnikova *et al.*, 2008) investigated the inhibitory effect of two types of the histone deacetylase inhibitor trichostatin A (TSA) and 4-phenylbutyrate (4-PB). They observed that these inhibitors promote and induce differentiation in GBM-29, U-343MG, and U-343MGa glioblastoma cells line. The inhibitors TSA and 4-PB separately increased the expression of differentiation marks (GFAP) and decreased the expression of vimentin and nestin involved in the dedifferentiation of glioblastoma [88].

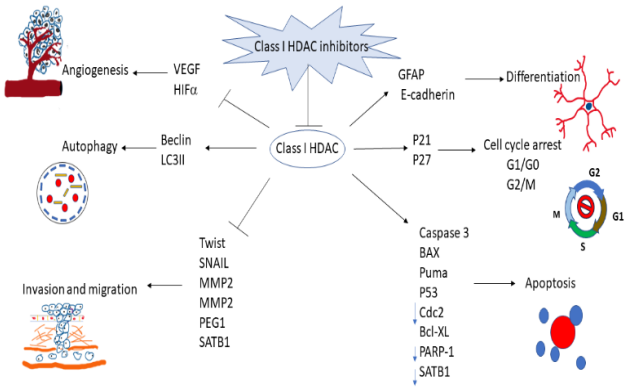

Figure 1. The role of class I HDAC inhibitor on a variety of biological activities in glioblastoma.

6. Mocetinostat (MGCD0103)

6.1 Structure and Function of MGCD0103

The chemical name of MGD0103 is [N-(2-aminophenyl)-4-[(4-pyridrin-3-3ylpyrimidin-2-yl)2amino] methyl] benzamide. MGCD0103 was developed by a Methyl Gene company in Canada [15]. The molecular weight is 558.27 [91]. It is small molecular, chemically synthesized, and orally available in treatment of cancer (Buglio *et al.*, 2010). MGCD0103 is a non-hydroxamate HDAC inhibitor, consists of a benzamide group instead of the hydroxamate group present in SAHA, Lbh589. MGCD0103 has various mechanisms in the inhibition action of HDAC enzyme different from that of hydroxamate acid inhibitor. The carbonyl oxygen and the ortho-NH2 group directly attach with the ZN^{+2} ion. These two groups also form potential hydrogen bands with the side chains of several amino acids inactive side.

The empty cavity of the arilide ring is partially filling the 14 A hydrophobic cavity adjacent to the catalytic site causing beneficial interaction [13] (Figure 2).

Mocetinostat drugs may be beneficial for the remedy of health problems for patients such as cancer, cardiovascular disorders, and brain disorders. MGCD0103 showed a high ability to increase induction of anti-proliferation p57 gene expression and block cardiac fibroblast cell cycle progression to prevent the formation of cardiac fibrosis, which is the excess deposition of extracellular matrix in heart dysfunction [92]. Furthermore, MGCD0103 has an important role in regular cardiovascular homeostasis through the increase of expression NPr1 gene transcription via suppressing of HDAC1/HADC2 activity,

reducing the interaction of SP1 promoter with HDAC1 /2, promoting attachment SP1 with p300, and p300/CAMP bind protein-associated factor to NPr1 promotor so that MGCD0103 may be a helpful therapy in the treatment hypertension and renal pathophysiological condition [93]. MGCD0103 significantly regulate glucose level in the blood, which showed a high ability to protect the pancreas from streptozotocin (STZ) mediate in induction type I diabetes and hyperglycemia through increasing expression Superoxide Dismutase 1,2,3(SOD1,2,3) antioxidation enzymes and increase in the histone acetylation level of a specificity protein 1 (SP1) transcription factor on the promoters of the gene encode SOD. consequently, MGCD0103 can protect pancreatic B-cell from STZ-induced oxidative stress (ROS) and β cell death in the pancreas that leads to type I Diabetes [94]. For people that have weak memory and difficulty in learning, Mocetinostat also showed significant neuroprotective effects and contributed to improving short-term and long-term memory in patients with Alzheimer's disease through reduction neuroinflammation, the accumulation of β-amyloid (Aβ), and downregulation of Tau protein. In addition, it can increase the number of noradrenergic neurons and the expression of synaptophysin protein [95].

Mocetinostat (MGCD0103) Is an isotype-selective class I Histone deacetylase inhibitor (HDACi) that binds and inhibits Class I HDAC 1,2,3, and 11 [96], and but does not have any effect on class II HDACs [15]. Mocetinostat shows vigorous inhibition of HDAC 1 with little inhibition against HDAC 2, 3, and 11 [97]. It has been trialed in phases I and II trials for patients with acute leukemia [99, 98]. In the phase I trial, the MGCD0103 is orally given three times weekly for patients with solid tumor acute myelogenous leukemia (AML) or myelodysplastic syndrome in optimum dose 60 mg/m2/d and higher for AML and 45 mg/m2/d for solid tumor [98, 100]. While in the phase II study, MGCD0103 was used for chronic lymphocytic leukemia (LLC). It was orally administered and given three times/week with a dose starting at 110 mg/day [99]. MGCD0103 is well-tolerated and demonstrated favorable pharmacokinetic and pharmacodynamic properties better than other HDACs [16]. Preclinical studies showed that MGCD0103 has significant antitumor activity against a broad spectrum of human cancer cells both in-vitro and in vivo due to the ability of MGCO0103 to increase induction of histone acetylation in tumors resulting in inducing apoptosis and cell cycle arrest in a variety of human cancer cells [13, 26]. It can target and kill tumor cells without cytotoxic effects on normal non-cancer cells [90]. In addition, recent studies have shown potential MGCD0103 in the induction of autophagy in different cancer cells [101], and it also affects the expression of the number of immunomodulation factors which can act as immune enhancers by increasing the expression PDL-1 mRNA, MHC-class I related (MIC-A) and MIC-B (Briere *et al*., 2018). MGCD0103 is unlike SAHA and MS-275 in inhibitory activity, which has activity inhibitory more potent than SAHA and MS-275 [13]. The HDAC inhibitory activity of MGCD0103 was more 7-fold stronger than SAHA in pancreatic cancer cells and 6-fold stronger than SAHA in HCT116 colon cancer [96], because MGCD0103 targets a specific HDAC compared with the pan HDAC such as SAHA and MS-275 that target multi HDACs enzymes in the inhibition of cell proliferation in many cancer cells [13].

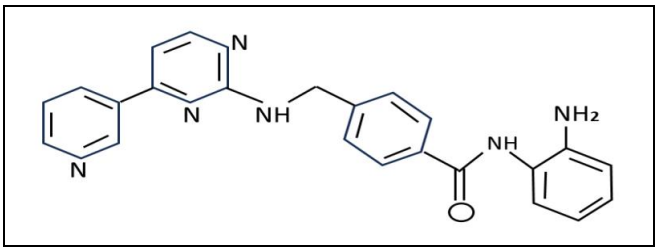

Figure 2. Chemical structure of MGCD0103.

6.2 Role of MGCD0103 in the induction of apoptosis in human cancer cells

MGCD0103 is a type-specific amino pheylenzamide that can suppress class I HDAC enzyme-induced apoptosis [13]. Generally, MGCD0103 can induce apoptosis and cell cycle arrest in many cancer cells through increased expression of the p21 protein and activates the intrinsic caspase pathway induced to apoptosis [15]. Studies have shown that mocetinostat significantly suppresses the growth of colon cancer-initiating cells (CCIC) and non-CCIC CRC cells by upregulating the non-canonical WNT signaling, and Dickkopf-1(DKK-1) involved in inhibition proliferation and clonogenicity [103]. MGCD0103 has a potent anticancer agent in Hodgkin lymphoma (HL) cell lines. The inhibition effects of MGD0103 on lymphoma are associated with an increase in the expression of TNFα and activates the NF-kB transcription factor [15]. El-Khoury *et al*. (2010) observed that MGCD0103 has more toxicity in neoplastic B-cells in comparison with normal cells. MGCD0103 can decrease the expression of MCL-1 and induce pro-apoptotic protein BAX mediated in reducing cytochrome C and activation of caspase C induced to apoptosis [101]. While another study found that MGCD0103 contributed to the treatment of Hodgkin's lymphoma (CHL) by decreasing Bcl2 level and increasing NFkB and PD-L1 expression in two cell lines (L1236 and L428) [104].

In liver cancer, MGCD0103 has a vital role in the suppression of cell proliferation and induction of cell cycle arrest in two liver cancer cell lines HepG2 and Huh7. Results showed that MGCD0103 could induce G2/M arrest via upregulating the proteins level of p21, p27, p-Cdc25C, and p-Cdc2. Also, MGCD0103 triggered apoptosis in liver cancer cells through downregulating antiapoptotic proteins Bcl2, Bcl-xl and upregulating proapoptotic proteins Bim, Bax, cytochrome C, and cleavage caspase 3,7,3 and PARP-1 in a dose -depend on manner. Moreover, the study reported the role of MGCD0103 in induction of autophagy in the liver in which MGCD0103 could significantly promote autophagy via increasing expression of RAGE Beclin -1, Pbkc3, and LC3II and decreasing expression of P62 3-MA.

Hence, MGCD0103 can induce autophagy and cell death in liver cancer cells [18]. The inhibitory efficacy of mocetinostat in killing prostate cancer also was studied by Zang and colleagues, who showed that proapoptotic miR-31 expression was significantly upregulated by mocetinostat, and downregulated its target antiapoptotic protein E2F6 both in vitro and in vivo in prostate cancer cells, this mechanism largely contributed to induce apoptosis in prostate cancer cells also Mocetinostat triggered the intrinsic pathway of apoptosis through increase expression of a pro-apoptotic protein (Bad) in turn activating (cleaved) caspase-9,3 and PARP [31]. The effects of Mocetinostat on human pancreatic cancer has been investigated when treated with different concentrations of MGCD0103 (0-10μM) on growth of pancreatic cancer tumor cells. The finding suggested that 1.0 μM MGCD0103 inhibits approximately 90% of pancreatic tumor cell colony formation in a semi-solid medium and causes cell cycle arrest through upregulating P21 and p15 expression, these results refer to that MGCD0103 might be an effective therapy for pancreatic cancer patient [105]. Gray *et al*. examined effect MGCD0103 on cell viability in small cell lung cancer (SCLC). The results suggested that MGCD0103 decreased cell viability by at least 60 % after 24h from treatment, but a combination of MGCD0103 with topoisomerase inhibitors, either amrubicin and epirubicin led to increase enhance apoptosis in four cell lines of small cell lung cancer (DMS114, NCL-H69, NCL-H82, and NCL-H526) through measuring caspase-3 activation that results in a2.7- to 4 -fold in combination compared to mgcd0103 alone that results in 2.4- to 3.7-fold [106]. The studies found that a combination of MGCD0103 caused enhanced the cytotoxic effect of MGCD0103 in killing many human cancer cells. For example, a synergism of MGCD0103 with gemcitabine significantly increase the toxic effect of mocetinostat in patients with pancreatic [107]. Some studies investigated MGCD0103 anti-angiogenesis activity. MGCD0103 has a potent inhibitory effect in tubule growth of cultured human endothelial cells in a dose-dependent manner in vitro through inducing transcription of anti-angiogenesis factor Thrombospondian1 (TSP-1) in the AML patient. While TSP-1 significantly increased its expression when the cell was treated with a combination of Vidaza and MGCD0103 compared with MGCD0103 alone [108].

7. Conclusions

Histone deacetylase HDAC has a crucial role in controlling epigenetic regulation and main major in the development of glioblastoma by removing the Acetyl group and condensing chromatin that leads to transcription regression. HDAC inhibitor is a novel drug in the treatment of different types of cancer disease by inhibiting the action of this HDAC enzyme and allowing transcription genes.MGCDO0103, a selective Class I HDAC inhibitor, is safe and efficacy as an HDAC inhibitor that has potent specific anticancer in the suppression of wide broad HDAC Class I. MGCD0103 has an important role in induction apoptosis in various types of cancer cells through modulating different mechanisms that cause inhibition of proliferation and suppression of cancer cells. The current and prospective studies of MGCD0103 will provide suitable therapy in cancer treatment.

Conflict of interest

The author declares no conflict of interest.

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