The Class I Histone deacetylase inhibitor a potent Therapeutic target for treating glioblastoma, MGCD0103 is a novel inhibitor in the induction death of cancer cells

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Abstract

Epigenetic abnormality is one of the hallmark glioblastoma cancer cells. Histone deacetylase modification has an important role in chromatin condensation, which results in the initiation and progression of glioblastoma cancer cells. Selective-isotype HDAC inhibitors are promising anti-cancer agents that target specific HDAC enzymes and inhibition of 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. 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 and inhibit cell migration, invasion, and angiogenesis in cancer cells while the normal cells showed more resistance to HDAC class I inhibitors. MGCD0103, a benzamide histone deacetylase, has a potent anti-cancer therapy that is used in the treatment of many cancers cell lines, and it has been approved by FAD in the treatment of Hodgkin lymphoma (HL) cell lines. MGCD0103 has vigorous inhibitory activity against HDAC1 but also targets action HDCA2, HDAC3and HDAC11. Therefore, MGCD0103 has expected to be a promising anti-cancer drug for treating a different variety of human cancer cells.

Introduction:

Histone deacetylase enzymes are a large family of enzymes that remove acetyl groups from lysine residues of histone and non-histone protein, causing transcription repression. In the human there are 18 HDAC divided into four classes on basis of similarity to yeast proteins: Class I 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 andSIRT7); and class VI proteins (HDAC11) (Seto& Yoshida,2014). In addition to histone substrate, HADC enzymes may bind to non-histone proteins substrate involved in the growth and development of cancer cells. The inhibition action of these enzymes largely contributes to the accumulation of the acetyl group in lysine residue in histone and non-histone proteins. consequently, these inhibitors will induce apoptosis, differentiation, cell cycle arrest, autophagic cell death, and reactive oxygen species (ROS)-induce death of cells (Xu et al,2007). Also, HDAC inhibitors prevent repair damage of DNA double-strand break (DSB) when combined with other cancer therapy such as radiation leading to enhance tumor cell death in glioblastoma (Shabason et al,2011). Histone deacetylase inhibitors (HDACi)is a promising cancer drug that has construction similarity to HDAC acetyl- lysine substrate (Bieliauskas& Pflum, 2008) There are two types of HDAC inhibitors enzyme: selective and non-selective inhibitors. Non-Selective-HDAC inhibitors also called (pan-inhibitor) are represent the majority of HDAC inhibitors that affect the activities of all HDAC enzymes, for example, SAHA and TSA are the canonical pan-inhibitors inducing the activity of HDAC1–9 with roughly equivalent potency (Khan et al,2015). While 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 & Pflum,2008). Selective HDACi has therapeutic effectiveness more than non-selective HDAC inhibitors in the killing of cancer cells because of the high similarity in the structure between them and the active site of the HDAC enzyme family (Min et al,2008). However, in glioblastoma cells, the overexpression of Class I histone deacetylase (HDAC) has been found linked to many biological processes such as cell cycle progression, cell survival, and differentiation. Inhibition of class I HDAC enzymes might be useful for the treatment of glioblastoma cancer cells (Was et al,2019). MGCD0103 is a novel class I iso-selective histone deacetylase inhibitor, that has a broad spectrum in suppressing the growth of cancer cells in both in vitro and in vivo (Fournel et al,2008). MGCD0103 inhibits a specific class I HADC enzyme for induction of dead cells and autophagy in tumor cells (Wei,2010). Recent studies have found that MGCD0103 has good tolerance and favorable pharmacokinetic and pharmacodynamic profile in clinical trials in patients with Hodgkin's lymphoma, also the drug show safe and less toxicity in treatment cancer cells (Bomber, et al,2011; Stanton et al,2018; Liao et al,2020). All these traits of MGCD0103 make them promise anti-cancer drugs to

1- The Role of the class I HDAC in glioblastoma

Epigenetic alteration is altering in gene expression without change of the DNA sequences, through modulation of specific signaling cascades within the tumor. Histone deacetylases (HDACs) play critical roles in epigenetic alteration in the human body (Allen et al,2015). The class I HDACs are part of the HDACs superfamily that have an important role in several biological activities (Haberland et al,2009). Class I HDAC enzymes consist of HDAC1,2,3 and 8 with a homology similarity to the reduced potassium dependency3(Rpd3) that is a transcriptional regulator present in yeast protein (Wang et al,2009). These enzymes are proteins ubiquitously expression, mainly found exclusively in the nucleus for most of the cells except HDAC3 HDAC8 present in the nucleus and cytoplasm(Yang et al,2002), they show a high enzyme activity on histone substrate and attach with transcriptional repressor and cofactor (Haberland et al,2009; Johnstone & Licht,2003). Recent studies have started investigating the expression types of HDACs in GBM. GBM cells and primary GBM tissues showed increased HDAC1, 3 expression levels compared to non-neoplastic brain tissues at both the RNA and protein levels(Staberg et al,2016). The structure of class I HDAC contains a conserved single deacetylase domain at the N terminus with short amino and carboxy-terminal extensions (Haberland et al,2009). Class I HDAC are classical HDAC family that needs zinc ion (ZN^{+2}) on the active side for enzyme activity (Imai et al,2000). Abnormal HDAC enzyme increases their expression in cancer cells and acts as an oncogene causing many types of malignancies in the human body such as glioblastoma (Li et al,2015) resulting in high dedifferentiation and cell proliferation tumor (Weichert,2009). The expression of different families of class I HDAC enzymes is implicated largely in cancer formation in glioblastoma through several mechanisms (Yelton and Ray,2018; Was et al,2019). A recent study found that role class I HDAC increased in high-grade gliomas by different mechanisms (Was et al,2019)(Table 1). There are proofs indicating to increase in HDAC1 expression in glioblastoma, a recent study observed that overexpression of HDAC1 was correlated with induction cell proliferation in glioma cells through a decrease in the expression BIM, BAX, caspase 3, and E-cadherin, and increase expression of TWIST, Snail, MMP in T98G glioma cell line(Wang et al,2017). Other studies suggested that HDAC1 is largely attributed to phosphor-special AT-rich Sequence-bind protein 1(SATB1) consider essential in the proliferation and invasion of glioblastoma cells. Phospho-SATB1 interacts 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 consider key in the regulation of glioma cells (Han et al,2013) HDAC2 is a member of the class I family, and has also a high expression in glioblastoma. The study had been investigated expression class I HDAC (1,2,3, and 8) in several cells line of glioblastoma U87, A172, U251, and LN229 cells compared with their expressions in normal cells, the finding found that HDAC2 was upregulated compared with other types of HDAC Class I and it is involved of cell proliferation, migration, and invasion in glioblastoma via increased mRNA and proteins expression of MRP1

(Zang et al,2016). While Was et al found that both HDAC 1 and HDAC2 were overexpression 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 (Was et al,2019). HDAC3 plays also an important role in developing brain function and is associated with the pathological grade of glioma (Norwood et al,2014). And it upregulates expression in children's glioma (Zhu et al,2013). Overexpression of HDAC3 is observed in glioblastoma and it is evaluated in both nuclear and cytoplasmic human astrocytic glioma tumors (Libý et al,2006). Norwood et al observed that HDAC 3 has an important role in regulating the development of the adult brain, in which HDAC3 can regulate glial cells growth and deleted of HDAC3 from neural progenitor cells leading to an increase in astrocytes through an Increased expression of GFAP in cortex and cerebellum of cKO MICE (Norwood et al,2015). While Geo et al 2019 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 (Geo et al,2019). HDAC3 also induces the proliferation and dedifferentiation of GSCs by Inhibition of TGF-β pathway induced SMAD7, SOX2 activation(Liang et al,2020).

HDAC8 is similar in sequence to HDAC1,2 and belongs to class I HDAC, and it is different from other class I HDAC in the location where located on the X chromosome at position q13. The expression of HDAC8 is wide in the body tissues, especially in the brain and prostate, and kidney (Van den-Wyngaert et al,2000). Overexpression of HDAC8 decreases apoptosis and increases cell proliferation in glioblastoma so it acts as an oncogene in the induction of tumor (Qi et al,2015). It is found that HDAC8 can interact with P53 and inactivate p53 resulting in cell proliferation in neuroblastoma (Oehme et al,2009). Besides, HDAC8 causes resistance glioblastoma cell line to 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 receptor ADRM1 that lead to promoting cell viability (Santos-Barriopedro et al,2019). Other studies showed also that levels of HDAC2, and HDAC8 dramatically increased in the glioblastoma and caused 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) (Zhang et al,2016).

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 ↑

Table(1) show the role of class I HDAC on the regulation of proteins involved in different biological activities in glioblastoma cancer cells

2- **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 (Eckschlager et al,2017; Chuech et al,2015) (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, immune system, inhibiting oncogenes, and downregulation oncogene (Lee et al,2015).The main function of HDAC class I inhibitor in the inhibition action of HDAC enzymes is happened by binding to the zinc ion in the active site of the HDAC leading to accumulating histone acetylation, thereby promoting transcription of gene expression for histone and non-histone proteins (Lawlor &yang,2019). These inhibitors are classified into 4 types depending on the structure of HDAC: hydroxamic acid, Benzamide, short fatty acid, and cyclic peptide (Bezecy 2014). HADC class I inhibitors can act against specific types of HDACs (selective- inhibitors) or all types of HDACs(pan-inhibitors) (Ceccacci & Minucci,2016). Recently some of the class I HDAC inhibitors is approved by Food and Drug American (FDA) for treating many types of human cancer cells such as vorinostat, Depsipeptide, and Belinstat in the treatment of T-cell lymphoma (Kim &Bae,2011; Eckschlager et al,2017), and the mechanisms of action of HDAC inhibitors in cancer cells depend on type and doses of cancer cells (Eckschlager et al,2017).These are many 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(Was et al,2019).The main purpose of HDAC inhibitors in glioblastoma is to create a balance between two enzymes HAT involved in the transcription of gene expression and HADC-induced gene silence to kill cancer (Sturm et al,2014).In addition, these inhibitors increase

cell cycle arrest at the G2/M or G0/G1 phase and induced DNA fragmentation that leads to apoptosis by increasing the expression of p21 and cleaved caspase 3 and PARP-1 in glioblastoma (Was et al,2019). These inhibitors have a high ability to cross the blood-brain barrier (BBB) with low toxicity on normal cells (Chateauieux et al,2010; Sturm et al,2014; Bialer &yagen,2007). Valproic acid (VPA) pans HDAC inhibitors (Venkataramani et al,2010), as well as it can effectively cross the BBB with a low cytotoxic profile (Peterson& Naunton, 2005). Valproic acid has also been studied on the glioblastoma cancer cell and found that VPA effectively inhibits cells proliferation of cancer cell 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,cdc2, and Bcl-XL in U87 and GBM8410 glioblastoma cells line (Tseng et al,2017). Entinostat selectively inhibited class I HDAC enzyme, examined its efficacy as anticancer therapy on the growth of glioblastoma, and revealed a potent therapy in the treatment of glioblastoma through direct inhibition of HDAC enzyme thereby, it can reduce cell proliferation and induce apoptosis, cell cycle arrest in the G0/G1 in U89MG, C6, F98 and SMA-560 (Eyüpoglu et al,2006). Was et al, found that compound 106 which specifically acts on inhibition HDAC3 can be caused an increase in the level of acetyl-H4 and significantly induce p21 and γ-h2ax proteins in U-87 MG cells (Was et al,2019). Histone deacetylase (HDAC8) also had been inhibited by HDAC8-specific inhibitor PCI3405 when the drug was treated with glioblastoma. PCI3405 decrease MGMT level and increase in phosphorylate H2Ax level that represents a DNA damage marker also PCI3405 decrease the expression of HDAC8 required for cell proliferation of T98Gglioblastoma(Santo-Barriopedio et al,2019). Influence phenylbutyrate (PBA) which is considered one of the pan histone deacetylase inhibitor class I HDAC has been studied to know the effect on glioblastoma.PBA was found to induce cell cycle arrest and apoptosis by upregulating the expression of P21 and downregulating antiapoptotic BCL2/Bcl-XL without affecting the expression of proapoptotic Bax and Bim in N-229 glioblastoma cells line (Kusaczuk et al,2016). The capability of class I HDAC inhibitor LAQ824 examined in effect on growth glioblastoma. LAQ824 helps promote apoptosis in glioblastoma through downregulation of the DNA double-strand break repair protein RADS (Chinnaiyan et al,2004).Panobinostat (LBH-589) is a pan HDAC inhibitor and it is in phase II trials for the treatment of glioblastoma (Yao et al,2017). LBH-589 is used against diffuse intrinsic potent glioma (DiPG). The researchers observed that LBH-589 is contributed to the increasing accumulation of H3 acetylation and H3K27 trimethylation subsequently it can stop the growth of brain tumors (Bacchi et al,2015). Romidepsin is one of the cyclic peptide compounds that have a potent inhibition of the growth of glioblastoma cells. Romidepsin has been trialed in phases I and II for the treatment of glioblastoma (Iwamoto et al,2011). Romidepsin (FK228) decreased tumor growth and induced apoptosis in the glioblastoma model through downregulating of antiapoptotic proteins Bcl1-XL and increasing expression of the cyclin-dependent kinase inhibitor p21 (Sawa et al,2004). Class I HDAC inhibitor DWP0016 effectively suppressed the growth and induced cell cycle arrest in U251 glioblastoma cells. The molecular

mechanism demonstrated the ability of DWP0016 in the induction of transcription and acetylation of p53 with p300, CBP, and PCAF. p53 activation involved BAX and PUMA expression to induce the mitochondrial death pathway (Jin et al,2013). Class, I HDAC inhibitor has been tested not only as a single agent but also in combination with other cancer therapy for the treatment of glioblastoma (Tan et al,2010). SAHA also plays a unique role as an HDAC inhibitor either alone or combined with 4HPR to inhibit the growth of two cells line C6 and t98g glioblastoma through activating mitochondrial extrinsic and intrinsic pathway-induced apoptosis (Khathayer et al,2020). 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 largely 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 to apoptosis and decreases in expression of Beclin-1 and LC3II induced to autophagy(Taylor et al,2019). VPA and radiotherapy (X-ray) significantly decrease the expression of Bcl2 and increase the expression of BAX protein compared with drugs alone in the treatment of C6 glioblastoma (Zhou et al,2014).

3- Role Class I HDAC in migration, invasion, and angiogenesis in glioblastoma

During the epithelial-to-mesenchymal transition (EMT) process start cells migration to other organs of the body by a blood vessel, the most extracellular metalloprotease in the degradation of extracellular matrix(ECM) are MMP1, and MMP9 that act as oncogene mediates degradation of the extracellular matrix that lead to cell migration and invasion of glioblastoma cell (Rao et al,2003). One of the upstream pathways controlling MMP expression is the PI3K/AKT pathway (Crespo et al, 2016; Wang et al, 2014) Histone modification has a high ability in regulating EMT (Sun& Fang,2016; Li et al,2015). Class, I HDAC enzymes play an important role in induction the of cell migration and invasion in human cancer cells and the regulation of gene expression of an extracellular matrix-related gene (ECM) (Whestine et al,2005) by reducing histone acetyl group from histone protein H3 that may lead to increase expression of MMP9, PEG1 (Li et al, 2015). 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 belong to HDAC class I significantly increase its expression during tumor progression in glioma cell compared with normal cells caused cell invasion in glioma cells by increasing expression of phosphorylated PI3K/AKT and MEK/ERK signaling pathway in vitro and in vivo (Li et al,2018) involved in secretion of MMP2,9 expression (Chen et al,2009). 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) (Wang et al,2017). Zhang et al investigated expression class I HDAC enzymes (1,2,3 and 8) and found that HDAC2 expression was significantly higher expression in the glioblastoma than the other class I HDAC and it is responsible for the progression of tumor glioma cells (Zhang et al,2016). Little studies are

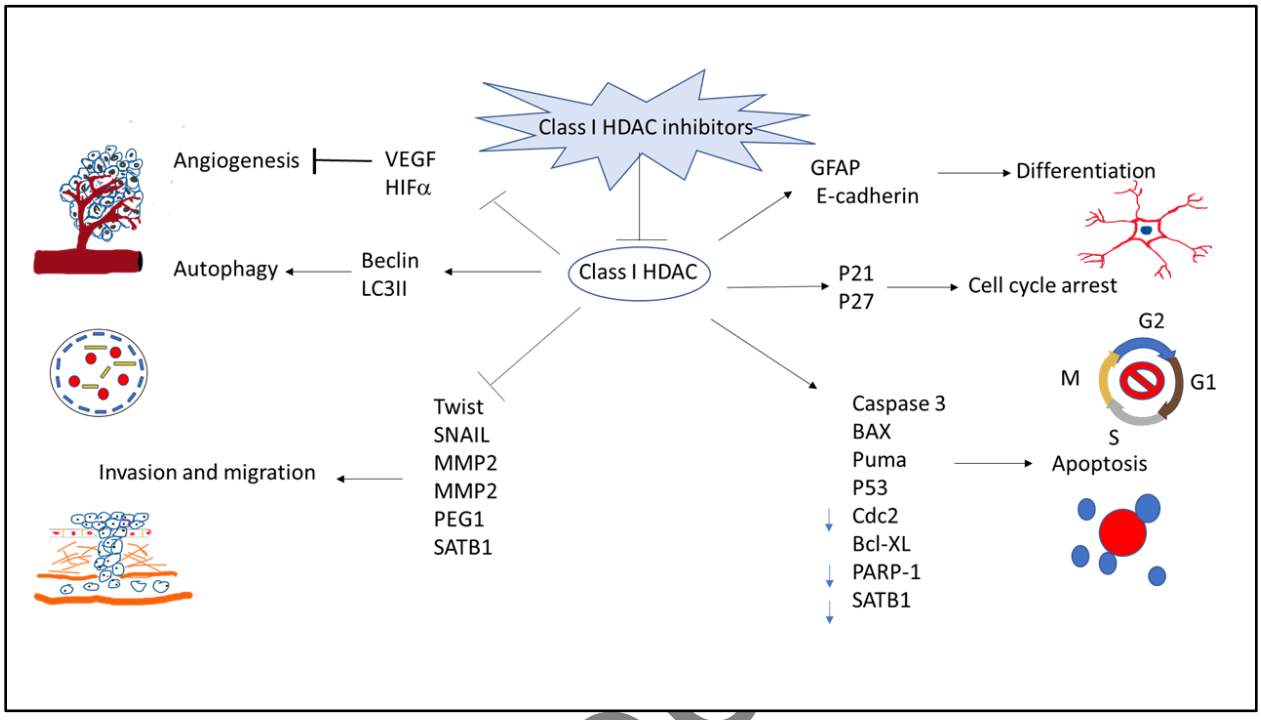
showing the role of the inhibitor in the suppression of migration and invasion of glioblastoma. Class I HDAC inhibitors induce inhibition invasion of glioma through decreasing expression of MMP in the glioma cell line (Wang et al, 2014). For example, Entinostat that class I HDAC selectively inhibited HDAC 1,3 has a cytotoxic effect in suppression migration of glioblastoma cells, the study suggested that entinostat was the most effective HDACi compared with trichostatin A (TSA), and MC1568 in decreasing cell migration and invasion of U87 glioblastoma cell line that reached to 44% as compared to the control that reaches to 100 % without a clear mechanism (Pastorino et al,2019). Urdiciain et al, 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 led to decrease migration in the LN405 glioblastoma cell line through increased expression of N-cadherin that represents mesenchymal marker and increase the level of E-cadherin protein (Urdiciain et al,2018). 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 NFKB and p38 involved in activation MMP9 and MMP2 responsible for invasion cells in both cell line C6 and T98G glioblastoma cells line (Khathayer et al,2020). Also, the studies observed that sodium butyrate inhibits migration and invasion of C6 glioblastoma cells (Herbert et al,2001) while Nakagawa et al found that sodium butyrate suppresses cell invasion in human GB A172 cells by increasing the phosphorylation of Focal Adhesion Kinase (FAK) that is a key regulator of adhesion and motility in cancer and normal cells (Nakagawa et al,2018).

Further, Glioblastoma multiforme (GBM) progression can express a transcription factor called hypoxia to induce factor-1 (HIFα-1) and (HIFα-2) that has a large role in GBM development and progression regulates angiogenesis (Wang et al,2017). HIFα-1 stimulates several genes including Vascular endothelium growth factor (VEGF) mediates angiogenesis in glioblastoma (Ho&Kuo,2007). The epigenetic therapy that targets the epigenetic alternation by multiple mechanisms cause also inhibition of angiogenesis (Kouraklis & Theocharis ,2006). HDAC enzymes that can remove acetyl groups from histone significantly increase the expression of HIFα-1 (Wellmann et al,2008). 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 (Chen et al,2020). 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 induce of HIFα-1 of histone(Scroggins et al,2007). Yao et al examined 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 (Yao et al,2017). Other groups of HDAC inhibitors including SAHA, TSA, and FK228, have also been reported as anti-angiogenic activity in glioblastoma cells line (Khathayer et al,2020; Sawa et al,2004).

4- Role class I HDAC inhibitors in Differentiation

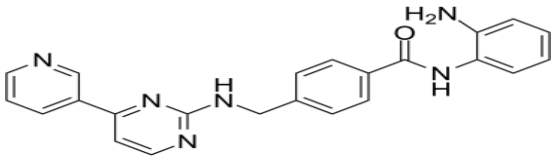
Neural differentiation of human pluripotent stem cells (hPSCs) inducing human embryonic stem cells (hESC) and human induced pluripotent stem cells (hPSCs) leads to differentiation into cell types of three germ layers (Thomson et al,1998). Neural progenitor cells (NPCs) generate from hPSC and convert finally NPC into neuronal or glial cells (Sikorsk et al,2008). Astrocytes are the most numerous types of glial cells and play an important role in the function and development brain (Doyle et al,2008). Astrocytes have subtypes of glial fibrillary acidic protein (GFAP-positive cell) in the human brain while there are two subtypes in rodents (Oberheim et al,2006). Epigenetic alteration of DNA and histone plays an important role in regulating gene transcription of neural cells (Sikorska et al,2008) HDAC deacetylase (HDAC) is the main agent to regulate 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 of cell growth, differentiation, and apoptosis (Di marcotullio et al,2011). Overexpression of class I HDAC involved in dedifferentiated tumor (Weichert ,2009). Class, I HDAC inhibitors are a group of small diverse molecules in structure and function known as an anticancer therapy in the induction of differentiation (Svechinkova et al,2008). HDAC inhibitors cause the accumulation of acetyl on both the histone and nonhistone proteins resulting in differentiation, apoptosis, and cell cycle arrest (Glozak & Seto,2007). SAHA potent promote the differentiation of glioblastoma stem cells and developed an astrocytic morphology through upregulating of glial fibrillary acidic protein (GFAP) and TUBB3 that represent differentiation marker 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. 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 mark (GFAP) and decrease the expression of vimentin and nestin involved in the dedifferentiation of glioblastoma (Svechnikova et al,2008).



Figure(1): scheme demonstrates the role of class I HDAC inhibitor on a variety of biological activites in glioblastoma.

5- Mocetinostat: Structure, Function:

The chemical name of MGD0103 is [N-(2-aminophenyl)-4-[[(4-pyridrin-3-3ylpyrimidin-2-yl)2amino] methyl] benzamide.MGC0103 was developed by a Methyl Gene company in Canada (Buglio et al,2010). The molecular weight is 558.279 mol (Zhou et al,2008). It is small molecular, chemically synthesized, and orally active in many cancer cells (Buglio et al,2010). The MGCD0103 is a non-hydroxamate HDAC inhibitor that is composed of a benzamide group instead of the hydroxamate group present in SAHA, Lbh589. MGCD0103 has various mechanisms in the inhibition 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 (Fournel et al,2008) (Figure



2).

Mocetinostat drugs may be useful for the treatment of health problems for patients such as cancer, cardiovascular disorders, and brain disorders.MGC0103 showed a high ability to increase induction 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 the heart-caused heart dysfunction (Schuetze et al,2017). Furthermore, MGC0103 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 MGC0103 may be a useful therapy in the treatment hypertension and renal pathophysiological condition (Kumar et al,2014). MGCD0103 significantly regulate glucose level in the blood, MGCD0103 showed a high ability to protect the pancreas from streptozotocin (STZ) mediate in induction type I diabetes and hyperglycemia through increasing expression antioxidation enzymes (SOD1,2,3) and increase in the histone acetylation level of an SP1 transcription factor on the promoters of the gene encode SOD. Thus, MGC0103 can protect pancreatic B-cell from STZ-induced oxidative stress (ROS) and β cell death in the pancreas that leads to type I Diabetes (Lee et al,2018). In people that have weak in memory and difficulty in learning, Mocetinostat also significantly showed neuroprotective effects and contribute 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, also it can increase the numbers of noradrenergic neurons and the expression of synaptophysin protein (Mei hsieh et al,2018). Mocetinostat (MGC0103) is an isotype-selective class I Histone deacetylase inhibitor (HDACi) that binds and inhibits class I HDAC 1,2,3 and 11 (Bonfils et al,2008), and they do not have any effect the class II HDACs (Buglio et al,2010). Mocetinostat has a potent effect to inhibit HDAC 1 with little inhibition against HDAC 2,3 and 11 (Ververis et al,2013). It is tested in phases I, and II for patients with acute leukemia (Blum et al,2009: Garcia-Manero et al,2008). In the phase I trial, the MGC0103 is orally given 3 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 (Garcia-Manero et al,2008; Siu et al,2007). While in phase II study MGCD0103 treated with chronic lymphocytic leukemia (LLC) is orally available and also given 3 times/week with a dose starting at a dose of 110 mg/day (Blum et al,2009). MGCD0103 is a good tolerated and demonstrated favorable pharmacokinetic and pharmacodynamic properties better than other HDACs (Boumber et al,2011). Preclinical studies

Figure(2) Chemical Structure of MGCD0103

showed that MGCD0103 have significant antitumor activity against a broad spectrum of human cancer cells both in-vitro and in vivo due to the ability of MGCO0103 in increased induction of histone acetylation in tumor resulting in inducing apoptosis and cell cycle arrest in a variety of human cancer cells(Fournel et al,2008; Li et al,2004). They can target and kill tumor cells without cytotoxic effects on normal non-cancer cells (Chiao et al,2013).In addition, recent studies have shown potential MGCD0103 in the induction of autophagy in different cancer cells (EL-Khoury et al,2010), and it affects the expression of the number of immunomodulation factors in which can act as immune enhancers by increasing the expression PDL-1 mRNA expression and MHC-class I related (MIC-A) and MIC-B (Briere et al,2018). MGCD0103 is unlike SAHA and MS-275 in the inhibitory activity which has activity inhibitory more potent than SAHA and MS-275(Fournelet al,2008). The HDAC inhibitory activity of MGCD0103 was more 7 – fold potent than SAHA in pancreatic cancer cells and more 6 fold stronger than SAHA in HCT116 colon cancer(Bonfils et al,2008), because of targeting MGCD0103 to 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 (Fournel et al,2008).

6- Role MGCD0103 in the induction of apoptosis in human cancer cells

MGCD0103 are type-specific amino pheylenzamide that can inhibit class I HDAC enzyme-induced apoptosis (Fournel et al,2008). Generally, MGCD0103 can induce apoptosis and cell cycle arrest in many cancer cells through increase expression of p21 protein and activates the intrinsic caspase pathway induced to apoptosis (Buglio et al,2011). 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 (Sikandar et al,2010). 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 NF-kB transcription factor (Buglio et al,2010). El-Khoury et al observed that MGC0103 has toxicity more in neoplastic B-cell compared with normal cells, MGCD0103 can decrease the expression of MCL-1 and induce pro-apoptotic protein BAX mediated in reducing cytochrome C and activation Caspase C induced to apoptosis (El-Khoury et al,2010) while another the study found that MGC0103 contributed in treatment of Hodgkin's lymphoma (CHL) by decreasing Bcl2 level and increase NFkB and PD-L1 expression in two cells line L1236 and L428. (Huang et al,2018). In liver cancer, MGCD0103 has an important role in the inhibition of cells proliferation and induction of cells cycle arrest in two cells line HepG2 and Huh7 liver cancer cells, the result found that MGCD0103 can induce G2/M arrest via upregulating the proteins level of p21,p27,p-cdc25c and pcdc2 also MGCD0103 triggered apoptosis in liver cancer cells through downregulating 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, further the study reported

role MGCD0103 in induction autophagy in the liver in which MGCD0103 can significantly promote autophagy via increase expression RAGE of Beclin -1 , Pbkc3 and LC3II and decrease expression of P62 3-MA. Hence, MGCD0103 is able to induce autophagy cell death in liver cancer cells (Liao et al,2020). The inhibitory efficacy of mocetinostat in killing prostate cancer was also studied by Zang and colleagues who have shown that proapoptotic miR-31 expression was significantly upregulated by mocetinostat and downregulated its target the 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 pro-apoptotic protein Bad which in turn activated (cleaved) caspase 9,3 and PARP(Zhang et al,2016). Mocetinostat on human pancreatic cancer was investigated when treated with different concentrations of MGC0103(0-10μM) on growth pancreatic cancer tumor cells. The finding suggested that 1.0 μM MGC0103 approximately inhibits 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 (Sung et al,2011). Gray et al examined effect MGCD0103 effect on cell viability of small cell lung cancer (SCLC), the result 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 increasing enhance apoptosis in four small cells lung cancer cell line 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 (Gray et al,2012). The studies found that a combination of MGCD0103 led to enhance the cytotoxic effect of MGCD0103 in killing many human cancer cells, for example, a combination of MGCD0103 with gemcitabine induce significantly increase the toxic effect of mocetinostat in patients with pancreatic (Chan et al,2018). There are some studies were investigated MGCD0103 anti-angiogenesis activity. MGC0103 has a potent effect inhibiting 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 increases its expression when the cell was treated with a combination of Vidaza and MGCD0103 compared with MGCD0103 alone(Liu et al,2008).

Conflict of interest: no conflict of interest.

Data availability

The data used to support the finding of this study are available within the article and no addition data available .

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