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Review Article

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Histone Deacetylase Inhibitor Valproic Acid and Cancer

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ABSTRACT

Histone modifications play major regulatory roles in many genetic events such as transcriptional activation and elongation, silencing and epigenetic cellular memory, level of histone acetylation is determined by the combined activities of two enzyme families including the histone acetyltransferases (HATs) and deacetylases (HDACs). Deacetylation of histone contributes to the development of malignancies. A number of HDACs inhibitors have been identified that induce cancer cells in culture to undergo growth inhibition, differentiation, and apoptosis in a wide variety of transformed cells including melanom, leukemia, prostate, lung, ovarian, breast and colon cancers. HDAC inhibitor valproic acid (VPA) is a short chain fatty acid with a long history of clinical use as an anticonvulsant drug which inhibits HDAC and induces apoptosis in selected solid and hematologic neoplasia. This review critically analyzes the available literature on the therapeutic role of VPA on different types of cancer.

Keywords: Valproic acid; Apoptosis; Cancer

INTRODUCTION

Nucleosomes, the basic structural units of chromatin, are comprised of the core histone octamer (H2A, H2B, H3 and H4) and the associated DNA that wraps around them [1]. It should be noted that the precise organization of chromatin is critical for many cellular processes, including transcription, repair, recombination, replication and chromosome segregation. Besides any change in chromatin structure is influenced by post-translational modifications of the amino-terminal tails of the histones [2,3]. Specific amino acids within these histone tails are targets for a number of post-translational modifications such as acetylation, phosphorylation, methylation and ubiquitination [4-6]. The amino-terminal portion of the core histones contains a basic tail region, the target of several types of post-translational modifications.

Histone modifications play major regulatory roles in many genetic events such as transcriptional activation and elongation, silencing and epigenetic cellular memory [7-9]. Level of histone acetylation is determined by the combined activities of two enzyme families, the histone acetyltransferases (HATs) and deacetylases (HDACs). These enzymes are responsible for setting patterns of acetylation across the genome [10,11]. It has been reported that acetylation of core histones, which is catalyzed by the histone acetyltransferases (HATs) and removed by the histone deacetylases (HDACs), is causally linked to transcriptional activation [12,13]. These enzymes are known as HDACs because histones were considered the most important target of HDACs and catalyse the transfer of an acetyl group from acetyl-CoA molecules to the lysine "-amino groups on the N-terminal tails of histones [14]. Deacetylation is one of the epigenetic processes linked to pathogenesis [15]. Recent studies indicate that deacetylation contributes to the development of malignancies [16,17]. During the past years, a number of HDACs inhibitors have been identified that induce cancer cells in culture and in tumor-bearing animals to undergo growth inhibition, differentiation, and apoptosis. It has been reported that HDAC inhibitors induce growth arrest, differentiation, and apoptosis in a wide variety of transformed cells in culture, including melanoma, leukemia, prostate, lung, ovarian, breast and colon cancers [18]. Histone deacetylase inhibitor compounds contain several chemical structural classes.

Valproic acid (VPA) is a short chain fatty acid with a long history of clinical use as an anticonvulsant drug. It has been shown that VPA inhibits HDAC and induces apoptosis in selected solid and hematologic neoplasias. The aim of this review was to define the effects of VPA on different cancers.

Histone Deacetylase Inhibitors

Histone deacetylase (HDAC) inhibitor compounds have been shown to be potent inducers of growth arrest, differentiation and apoptosis *in vitro* and *in vivo*. They contain several chemical structural classes including:

1) Short-chain fatty acids (e.g., butyrates and valproic acid) [19,20];
2) Cyclic tetrapeptides containing a 2-amino-8-oxo-9,10-epoxy-decanoyl (AOE) moiety (e.g., trapoxin A) [21];
3) Hydroxamic acids [e.g., trichostatin A (TSA) [22,23], suberoylanilide hydroxamic acid (SAHA) [24], and oxamflatin [25];
4) Benzamides (e.g., MS-27-275) [26] and
5) Cyclic peptides not containing the AOE moiety (e.g., FR901228 and apicidin) [27,28].

Valproic acid (VPA) is a short chain fatty acid with a long history of clinical use as an anticonvulsant drug. VPA has been shown to function as an HDAC inhibitor, leading to the acetylation of histone tails [29,30] which results in attenuation of the electrostatic charge interactions between histones and DNA and has been associated with chromatin decondensation [31-33]. It has been shown that VPA inhibits HDAC and induces apoptosis in selected solid and hematologic neoplasias [34-36].

Valproic Acid and Breast Cancer

Recent study has indicated that valproic acid induces chromatin decondensation in breast MCF-7 cancer cells by repression of SMC 1 to 5 and SMC associated proteins, DNMT-1, and HP1. This decondensation is associated with an increased sensitivity of DNA to nucleases and increased the association of DNA with intercalating agents. Besides, VPA potentiates DNA damage and apoptosis induced by cytotoxic agents that require access to the DNA for activity. Furthermore, VPA induces histone hyperacetylation *in vivo* and *in vitro* [37]. Other study has reported that VPA inhibits proliferation in four different human breast cancer cell lines: ER-positive and HER2-negative MCF7 cells, ER-negative and HER2-negative MDA-MB-231 cells, ER-negative and HER2-overexpressing SKBR3 cells, and ER-positive and HER2-negative BT474 cells. These results suggest that anti-proliferative mechanism of breast cancer cells by VPA is related to their HER2-expression status and also VPA induces cell cycle arrest with upregulation of p21 at 1 mM [38].

Valproic Acid and Ovarian Cancer

It has shown that VPA can significantly inhibit the growth of the ovarian cancer SKOV3 cells *in vitro* and *in vivo* which relate to the induction of cell cycle arrest and apoptosis. VPA inhibits proliferation in this cell line by decreasing of S-phase cells and increasing of G1-phase cells, but the changes of the G2-phase and M-phase are not significant. Diminished proliferation of ovarian SKOV3 cancer cells is the result of a reduction in the S-phase due to cell cycle blocks at the G1 checkpoint. According to this report VPA decreases VEGF and MMP-9 and increases the expression of E-cadherin and also can interrupt tumor angiogenesis and metastasis by down regulation of the VEGF protein and up-regulation of the E-cadherin protein and MMP-9 protein [39]. It has been demonstrated that VPA is highly effective in suppressing the growth of nine human ovarian carcinoma cell lines (SK-OV-3, OVCAR-3, TOV-21G, OV-90, TOV-112D, OVCA420, OVCA429, OVCA432, and OVCA433) [40]. VPA inhibits ovarian cancer cells proliferation by expression of p21WAF1 and p27KIP1, two proteins that play important roles in blocking the cell cycle in the G1 phase and the down-regulation of several antiapoptotic and cell cycle–related proteins, such as Bcl-2, cyclin D1, and cyclin D2 [41]. Furthermore, VPA can inhibit the growth of human SK-OV-3 ovarian cancer in the mice during 5 weeks of therapy and also can suppresse the growth of xenograft tumors of the ovarian cancer cell line SKOV3, with significant p21 up-regulation in tumor tissues [40].

Valproic Acid and Uterus Cancer

In vitro study has been reported that VPA inhibits clonal proliferation of six endometrial cancer cell lines (Ishikawa, Hec-1B, Hec59, RL95–2, KLE, and AN3CA) with a dose-dependent manner [34]. Therefore, it is highly possible that VPA affects these endometrial cell lines by upregulation of p21WAF1 and p27KIP1 [41] and increasing level of the Protein levels of both p21WAF1 and p27KIP1 [42]. Furthermore, it has been reported that the enhanced expression of p21WAF1 was accompanied by an accumulation of acetylated histones H3 and H4 associated with the p21WAF1 gene and also [43,44] have shown that VPA decreases levels of cyclin D1 and D2, and this appears to occur at the transcription level. Therefore, VPA decreases expression of D cyclins and increases expression of

p21WAF1, which probably combine to modulate the activity of the downstream pRb/E2F axis triggering cell cycle arrest [45]. *In vivo* study has demonstrated that VPA (20 mg/kg and 40 mg/kg) inhibit histone deacetylase activity [46]. Previous study has reported that VPA suppresses cell growth and upregulates the expression of Notch 1 and SSTR2, acting also as an activator of Notch and SST signalling in cervical cancer HeLa cells [47]. VPA inhibits the activities of cytosol and nuclear HDACs in HeLa cells [48] and inhibits growth of HeLa cells in dose- and time-dependent manners. This compound induces a G2/M phase arrest of the cell cycle at a concentration of 10 mM VPA in HeLa cells at 24 h. However, low concentration of VPA induces a G1 phase arrest in HeLa cells [49]. It should be noted that VPA increases the number of sub-G1 cells and induces apoptosis, which is accompanied by caspase-3, -8 and -9 activations [50]. It is demonstrated that VPA triggeres the loss of MMP ($\Delta\Psi m$) in HeLa cells in a dose-dependent manner. Furthermore, caspase inhibitors significantly prevent HeLa cell death caused by VPA which suggests that the mitochondrial pathway as well as the cell death receptor pathway is all together necessary for the induction of apoptosis in VPA-treated HeLa cells [51-53]. It has been reported that TNF-α synergistically enhances cell death in VPA-treated HeLa cells and VPA induces LDH release which indicates that HeLa cell death caused by VPA dont not result from the necrotic pathway. Therefore, the main cause of HeLa cell death induced by VPA is mediated by apoptosis rather than necrotic cell death [54].

Valproic Acid and Prostate Cancer

VPA induces apoptosis in ERG-positive prostate cancer cells by up regulation of p21/Waf1/CIP1 expression, repression of TMPRSS2-ERG expression, and affect acetylation status of p53 in in this cell line [55]. Several studies have demonstrated that ERG expression in prostate cancer contributes to the oncogenic properties of cell proliferation, metastasis, invasion, and cell motility [56-58] and the higher expression of this gene correlates with unfavorable prognosis of prostate cancer [59]. *In vitro* study has reported that VPA induces changes in the nuclear structure and change in chromatin remodeling in prostate cancer cells [60] and also reported that VPA increases histone H3 acetylation, CK18, and p21 and p27 expression and decreases androgen receptor, cyclin D1,and Ki-67 expression in prostate cancer cells *in vitro* and *in vivo* [61,62]. Furthermore, VPA at a low concentration increases apoptosis and decreases angiogenesis in prostate cancer xenografts [61]. It has been shown that VPA promotes neuroendocrine-like differentiation of androgen-dependent LNCaP prostate cancer cells which is associated with an increase in the secretion of neuron-specific enolase and down-regulation of androgen receptor protein, suggesting a role of VPA in the mechanism of androgen responsiveness of prostate cancer [63]. Other studies have reported that VPA causes reexpression of ERh in LNCaP cells [64] and also reported that the ERh promoter region shows a typical CpG island [65]. VPA reduces histone deacetylase activity at a concentration of 1 and 5 mmol/L in LNCaP cells significantly and induces apoptosis in LNCaP cell line by a strong caspase-3 activity and DNA fragmentation [66,67]. Valproic acid is able to check cell proliferation, upregulates the androgen receptor levels and E-cadherin expression in human prostate cancer cells [68] and able to induces the neuro-endocrine transdifferentiation (NET) in androgen independent PC3 cells at the both *in vitro* and *in vivo* level [69]. It should be noted that prostate glands contain a small population of neuroendocrine (NE) cells in the epithelial compartment [70]. In the advanced prostate cancer, the cells showing NE phenotypes with NE markers are increased [71]. Besides, VPA can modulate the expression of different androgen metabolism genes and may enhance dihydrotestosterone (DHT) catabolism [72]. Experimental study shows that a low concentration of VPA has an antiproliferative effect on prostate cancer cells which is related to the differentiation status and also inhibits cell growth in more differentiated LNCaP cells [73].

Valproic Acid and Gastric Cancer

VPA has an antiproliferative effect on gastric cancer cell line (OCUM-2MD3) *in vitro* and *in vivo* and increases the acetylation of histone H3, resulting in a significant reduction of tumor growth through induction of both p21WAF1 and apoptosis [74]. Besides, it induces acetylation of histone H3 with upregulation of p21WAF1 expression, supporting the suggestion that VPA induces differentiation of cancer cells [48]. Furthermore, VPA can induce alterations in the expression of p27 and cyclin D1. Since p21WAF1 and p27 are cyclin-dependent kinase inhibitors and bind to cyclin-dependent kinase complexes and decrease kinase activity, they may act as key regulators of G0/G1 accumulation [41]. It has been demonstrate that VPA inhibits both class I and II HDACs,10 and affects gastric cancer growth by inducing p21WAF1 [75,76]. Some studies have shown that VPA enhances the acetylation of nonhistone proteins in relation with apoptosis [77-79]. Other *in vitro* study shows that VPA can inhibit gastric carcinoma BGC- 823, HGC- 27, and SGC- 7901 cells growth in G1 phase significantly by activation of caspase 3, caspase 8, and caspase 9. The mechanism of G1 phase cell cycle arrest is due to the upregulation of P21and Mad1 expression and downregulation of Cyclin A and c-Myc expression [49].

Valproic Acid and Hepatocellular Carcinoma

VPA as a histone deacetylase inhibitor displayed anti-tumor activitie in many different types of cancers [80-82]. In hepatocellular carcinoma HTB-52 cells, VPA acts as a HDAC inhibitor to suppress HDAC4 and induce acetylation of histone H4 by which induces cell growth inhibition, cell cycle arrest and cell apoptosis [83]. Similar effect has been reported other HCC cells [84-86]. It should be noted that Notch signaling is a diagnostic marker in HCC and activation of this pathway is frequently seen in human HCCs. There is a high Notch1 [87-89], Notch3 and Notch4 signature in most HCC tissues [90]. There is similar report about the high frequency of Notch1 and Notch3 in HCC tissues [91]. Furthermore, HBV X protein (HBx), that is a critical factor in HCC carcinogenesis, is also found to up-regulate Notch signaling [92,93]. Accumulating evidence shows that Notch signaling is critical for HCC development and activation of Notch signaling in HCC cells plays an oncogenic role [92,94-96]. VPA acts as a Notch signaling inhibitor to suppress the expression of Notch1 and the Notch target gene HES1 and can reverse cell growth stimulated by Notch1 activation. Thus, VPA can suppress HCC cell growth via acting as a Notch signaling inhibitor [83]. Furthermore, it has reported that VPA is a HDACI, as HDAC activity and the HDAC1 gene expression in hepatocellular carcinoma BEL-7402, SMMC-7721 and HepG2 cell lines [97]. The expression of cyclins A, D1, and E increase in tumor tissues significantly [9,98]. Genetic transcription and protein expression of these cyclins can be blocked by P21. Abnormal expression of cyclin proteins is associated with the genesis and prognosis of certain tumors [99-104]. The expression of cyclins D1, A and E significantly increases in tumor tissue compared with normal tissue [105,106]. Genetic transcription and protein expression of these cyclins can be blocked by P21 [101]. VPA induces cell cycle arrest at the G0/G1 phase and downregulates the mRNA and protein expression of cyclin A and D1 in HepG2 cells and also VPA may upregulate P21Waf/cip1 mRNA and protein expression, which binds to CDKs competitively with cyclins and inhibits various cyclin-CDK compounds in Hep G 2 cell line. On the other hand VPA can upregulates protein expression of caspases 9 and 3 resulting apoptosis in HepG 2 cell line [96]. Previously, we indicated that VPA can inhibit proliferation and induce apoptosis in hepatocellular carcinoma HepG 2 cell line [102].

Valproic Acid and Cholangiocarcinoma

VPA has potent antitumor activity in a variety of tumor types *in vitro* and *in vivo* [103], including breast [104], colon [105,106], prostate [107,108], and hepatoma. It modulates the behavior of various tumors by affecting multiple pathways including cell cycle arrest, apoptosis, metastasis, angiogenesis, and differentiation [80]. It has been shown that VPA inhibits Cholangiocarcinoma (CCA) TFK-1, QBC939, and CCLP1 cells growth both *in vitro* and *in vivo*. VPA induces terminal differentiation of TFK-1 cells resulting cell division and cell proliferation ceases. Experimental Data shows that the antitumor effect of VPA on TFK-1 andQBC939 cells is associated predominantly with cell cycle arrest. It inhibits proliferation of TFK-1 cells at the G2/M phase [109]. Similar studies have reported that cells arrest at the G2/M phase after VPA treatment [110,111]. Finally, it has been demonstrated that VPA increases the inhibitory effect of 5- fluorouracil (5-FU) on chlongiocarcinoma (HuCCT1) cell line [112]. We reported apoptotic and inhibitory effect of VPA on HT 29 colon cancer previously [113].

Valproic Acid and Pancreatic Cancer

Several studies have shown that VPA modulates the biology of different cancer types by suppressing growth, metastasis and angiogenesis, and by inducing differentiation and apoptosis. Recent study has been shown that VPA inhibitory effect on pancreatic stellate cells (PSC) prolifration [114]. It has been reported that VPA potently diminishes the proliferation and adhesion capacity of pancreatic tumor cell line by shifting the integrin ß1 subunit balance from a 'pathological' towards a 'physiological' expression pattern, leading to reduced tumor growth and invasion [115]. VPA is reported to exert anti-tumor effects by upregulating the expression of NKG2DLs, such as MICA/B and UL16-binding proteins (ULBPs), in a number of tumors including hepatocellular carcinoma, myeloma, and myeloid leukemia [116-119]. These effects of VPA are linked to the activation of different signaling pathways in different cancers [120]. Other study reveals that the low expression of MICA and MICB is correlated with worse tumor differentiation, later TNM stage, and more lymphatic invasion [121]. VPA can inhibit pancreatic cancer cell (SUIT2) and increase the inhibitory effect of 5- fluorouracil (5-FU) on pancreatic cancer cell [112].

CONCLUSION

The studies summarized in this review indicate that VPA is a potent inhibitor of HDAC *in vitro* and *in vivo* and induce apoptosis and also inhibits prolifration in different cancer cells. We suggest that inhibition of HDAC activity leads to remodeling of chromatin associated with a specific set of programmed genes.

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