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Anti-Convulsant Drug Valproic Acid in Cancers and in Combination Anti-Cancer Therapeutics

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Abstract

The traditional anti-convulsant drug Valproic Acid (VPA) has been found to be involved in suppressing cancer progression while modulating various cancer-associated signaling pathways. In particular, VPA acts as either a Histone Deacetylase (HDAC) inhibitor or a Notch signaling activator in suppressing tumor growth. VPA is less toxic, and by itself, has limited anti-tumor effects. Thus, VPA has been used as an adjuvant in combination with a variety of other anti-cancer agents for many types of cancers. These combination strategies display potential applications in cancer treatments. In particular, VPA could up-regulate certain G Protein-Coupled Receptors (GPCRs) in some cancer cells. Some of these GPCRs are highly expressed naturally in many cancer cells and these characteristics have been applied towards novel enhanced combination therapeutics with VPA and specific receptor-targeted cytotoxic peptide-drug conjugates.

Keywords: Valproic acid (VPA); Combination therapeutics; Receptor-targeted; Peptide-drug conjugate

Introduction

Valproic Acid (VPA) is a branched short-chain chemical molecule ($C_8H_{16}O_2$) (Figure 1) and has been used as an anti-convulsant drug for several decades [1,2]. In recent years, VPA has been investigated further for its potential application in cancer treatments [3-6] since its initial use in treatment of pediatric malignant gliomas [2]. Due to its less potent anti-cancer efficacy alone, VPA is more frequently used as an adjuvant in combination with other anti-cancer therapeutic agents [3,4,7,8]. The combination therapy displays more synergistic anti-cancer effects than each individual agent alone. In particular, VPA has been found to enhance the expression of certain G Protein-Coupled Receptors (GPCRs) in certain cancers [9,10]. These characteristics could be applied in a combination treatment using VPA with receptor-specific cytotoxic conjugates. In this combination therapy, VPA plays a critical dual role via acting as a direct tumor suppressor and an indirect tumor-suppressing enhancer of receptor-specific cytotoxic conjugates.

VPA in anti-cancer treatment

VPA has been widely investigated for its anti-cancer efficacy in many cancers, including cervical cancer, prostate cancer, neuroblastoma, Medullary Thyroid Cancer (MTC), myeloma, colon cancer, glioma, leukemia, breast cancer, lung cancer, bladder cancer, melanoma, leukemia, glioblastoma, Renal Cell Cancer (RCC), esophageal squamous cell cancer, endometrial stromal sarcoma, osteosarcoma, Hepatocellular Cancer (HCC), gastrointestinal carcinoid, pheochromocytoma, mesothelioma, pancreatic cancer, head/neck squamous cell cancer, ovarian cancer, myeloma and cholangiocarcinoma [7,8,11-13]. VPA displays its effects in multiple cancer cell functions such as DNA damage, cell cycle arrest, cell apoptosis, differentiation, proliferation, and senescence as seen in serial *in vitro* studies. VPA is also involved with various associated signaling pathways [2,11,14]. Using serial *in vivo* studies, VPA is also found to suppress tumor growth, tumor angiogenesis and tumor metastasis [2,15,16]. VPA alone is currently under clinical evaluation in many cancers [7,8] but VPA has very limited effect due to its weak anti-cancer efficacy. Conversely, VPA has less toxic side effects and is more frequently used as an ideal adjuvant agent in combination with many other anti-cancer cytotoxic therapeutic agents. These combined therapeutics display synergistic anti-cancer effects discussed below.

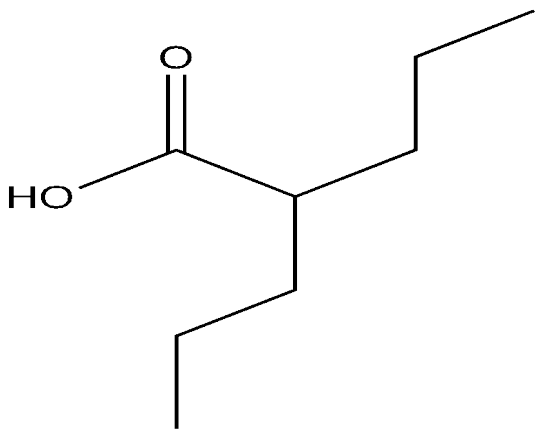

Figure 1: The schematic structure of valproic acid ($C_8H_{16}O2$, MW: 144).

VPA-mediated anti-cancer molecular signaling

VPA's anti-cancer effect is involved in multiple signaling pathways such as the Wnt signaling pathway, PI3K/AKT pathway, p21WAF1/CDKN1A pathway and MAPK/ERK [2,7,11,12,17-19]. VPA is believed most likely to act as a Histone Deacetylase (HDAC) inhibitor in mediating histone deacetylation and subsequent tumor suppression, along with its involvement in other signaling pathways [2,20]. Another critical signaling pathway, Notch signaling, is also believed to be involved in VPA-mediated tumor suppression [21-24]. It is not clear whether or how these two signaling pathways correlate or interact with each other in VPA-treated cancer cells. VPA could affect histone acetylation/deacetylation in many cases. VPA could also simultaneously modulate both signaling pathways in others. For instance, VPA up-regulates Notch1 and enhances acetylation of histone H3 in cervical cancer cells [9,25] and in Neuroblastoma (NB) cells [26]. However,

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VPA was found to suppress cell growth directly via the involvement of Notch signaling in others such as follicular thyroid cancer cells and pancreatic carcinoid cells [21,27]. We also observed that VPA up-regulates Notch1 expression and cell growth arrest in carcinoid cells, without the involvement of HDAC3 and HDAC4 (data not shown).

VPA acts as a histone deacetylase (HDAC) inhibitor

HDACs deacetylate histones via removing acetyl groups from lysine residues of histones. Histone deacetylation could block gene transcription, initiate cancer progression and lead to drug resistance [28,29]. VPA could induce HDAC inhibition, histone acetylation and hyperacetylation accumulation, and reverse HDAC-mediated transcriptional repression and subsequently mediate various cell functions such as cell differentiation and cell apoptosis [28,30-32]. In 2001, Klein and co-workers identified that VPA acted as a HDAC inhibitor [19] via targeting HDACs including HDAC 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 in the four major HDAC classes with 18 different HDAC members [28,32,33]. In most cases, VPA was reported mainly to induce the acetylation of histones H3 and H4. VPA has been identified in mediating histone acetylation/deacetylation and resulting in tumor suppression in many different cancer cells such as colon cancer cells, glioblastoma cells, neuroblastoma cells, cervical cancer cells, glioma cells, leukemia cells, teratocarcinoma cells, prostate cancer cells, bladder cancers cells and endometrial stromal sarcoma cells [7,8,30]. Besides its use in anti-convulsant treatments, the characterictics of VPA in decreasing deacetylation and increasing acetylation could be used as a strategy for treatment of cancers. In some cases, however, VPA does not always act as a HDAC inhibitor and instead acts as a HDAC activator to upregulate HDAC activity in glioma C6 cells [10] and also to reduce histone H3 expression but not to affect H3 acetylation in renal cell cancer Caki-1 cells [34].

VPA acts as a Notch signaling regulator

Notch signaling plays a critical role in determining cell fates and is involved in cancer progression. Notch signaling can play different roles in different cancers, acting as a tumor suppressor in certain cancers and an oncogene in some others. VPA is involved in regulation of the Notch signaling pathway and the subsequent tumor progression [22,23,26,35,36], playing different roles in regulating Notch signaling in a cancer type-dependent manner. Notch signaling acts as a tumor suppressor in certain NET tumors such as Medullary Thyroid Cancer (MTC) [21,22,37] and certain non-NET tumors such as cervical cancer [23,38-40]. In these cancers, VPA was found to act as a positive Notch1 signaling regulator to subsequently induce tumor suppression. For instance, in NET tumors, VPA could activate Notch1 signaling, regulate the neuroendocrine phenotype with down-regulation of neuroendocrine markers CgA and ASCL1, and further induce cell growth arrest and cell differentiation in phenochromocytoma cells, MTC cells, SCLC cells and carcinoid cells [21,22,35,36]. In pancreatic carcinoid BON cells, VPA could induce cell growth arrest via modulating Notch1 activation and the subsequent increase in p21 and decrease in ACSL [21]. In non-NET tumors such as thyroid cancer, cervical cancer, and osteosarcoma, Notch1 signaling also plays a tumor-suppressive role [9,23,25,27]. VPA mediates Notch1 upregulation and enhances histone H3 acetylation in cervical cancer Hela cells, with an increase of tumor suppressor p21 in a p53-independent manner [9,25]. In follicular thyroid cancer cells, Notch1 knockdown blocks VPA-induced anti-cell proliferation and reverses VPA-mediated expression of p21 and cyclin D1, indicating VPA induces cell cycle arrest via activating Notch1 signaling [27]. VPA could also act as a negative Notch regulator in certain cancers. Notch signaling is found to play an oncogenic role in Hepatocelluler Cancer (HCC) HEP3B cells [41]. In the HCC HuH7 cell line, VPA induced Notch1 down-regulation and caspase-3 up-regulation, with suppression of cell proliferation and tumor growth [24].

VPA in combination with cytotoxic agents

As described above, due to its limited anti-cancer efficacy alone and less toxic side effects, VPA has been more frequently used as an adjuvant agent in combination with other anti-cancer cytotoxic agents. VPA has been used in combination therapeutics with various other compounds, some of which are FDA-approved market drugs [7,8]. These combination treatments display more anti-cancer effects compared to each alone [9,42,43], with some under clinical investigations [7,8,42]. For instance, VPA was used in combination with the topoisomerase I inhibitors Camptothecin (CPT), its new analog irinotecan (CPT-11) or CPT conjugates for treating many cancers such as breast cancer, hepatocellular cancer, cervical cancer, lymphoma, thyroid cancer, pancreatic carcinoid, osteosarcoma and ovarian cancer, displaying synergistic *in vitro* anti-proliferative and *in vivo* anti-tumor effects [7,9,44]. In particular, the VPA/CPT combination is under phase III clinical evaluation for treating patients with cisplatin-resistant ovarian cancers and recurrent/metastatic cervical cancers [8]. The combinatin of VPA and All-Trans Retinoic Acid (ATRA, the carboxylic acid form of vitamin A, used to treat acute leukemia) was used to treat certain cancers such as cervical cancer, head/neck squamous cell cancer and leukemia and displayed synergistic anti-cancer effects [7,14,45,46]. VPA was also used to treat leukemia and lymphoma in combination with the anti-metabolite clofarabine, cytarabine, AZA, Aza-dC (5-aza-2'-deoxycytidine or decitabine), enzastaurin, rituximab, IFN-alpha, AY4 and CPT conjugates [7-9,47,48]. The combination therapeutics of VPA/ATRA, VPA/AZA and VPA/Aza-dC are under clinical evaluation for treating leukemia [7]. Moreover, VPA in combination was used to treat many more cancers such as neuroblastoma with the COX2-selective inhibitor celecoxib, glioblastoma with the mitotic inhibitor paclitaxel, prostate cancer with rapamycin (mTOR) inhibitor RAD001, cholangiocarcinoma with gemcitabine, glioma with temozolomide, renal cell cancer with AEE788, colorectal cancer with rexinoid IIF, lung cancer with the Ras inhibitor FTS, melanoma with dacarbazine, mesothelioma with lovastatin and doxorubicin, glioblastoma with sorafenib and bortezomib, thyroid cancer with doxorubicin, breast cancer with CPT and tamoxifen as well as neuroblastoma with ellipticine and celecoxib [3,4,7,8,13,34,44,45,49,50]. Many of these combination treatments show synergistic functions and enhanced anti-cancer effects while reducing the toxic side effects in some organs that result from a single specific high-dose drug, or the multi-drug resistance of cancer cells resulting from long-term treatments. VPA, in combination with multiple anti-cancer agents, is currently under clinical investigations for treating various types of cancers [8,51].

VPA in combination with receptor-targeted cytotoxic peptide-drug conjugates

While displaying tumor suppression, VPA was also found to enhance the expression of certain GPCRs in cancer cells. Thus, these unique dual functions displayed by VPA could result in a novel combination therapy of VPA with a receptor-specific cytotoxic conjugate and this combination could enhance the anti-tumor efficacy of the conjugate via increasing its quick internalization. This may display unique and significant advantages compared to the conventional combination therapeutics of VPA and the other agents described above.

VPA acts as a G protein-coupled receptor (GPCR) regulator

GPCRs belong to a large family with nearly 1000 members and

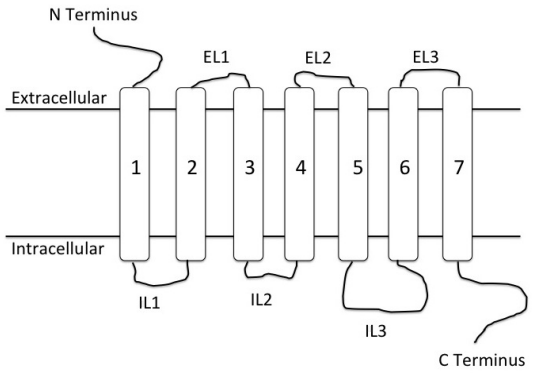

Figure 2: The schematic structure of the G Protein-Coupled Receptors (GPCRs). GPCRs belong to a large gene family with nearly 1000 members. They consist of seven trans-membrane domains, three extracellular loops and three intracellular loops with an N-terminus at outside and a C-terminus at inside.

consist of seven trans-membrane domains, with three extracellular loops and a N-terminus outside the cell membranes and with three intracellular loops and a C-terminus inside (Figure 2). These receptors are involved in various physiological and pathological processes and their associated signaling pathways. They are the critical drug targets associated with 30-50% of global market drugs. VPA could regulate the expression of certain GPCRs in some cancer cells and their receptor-associated downstream signaling pathways. For instance, VPA was found to induce an increase of melatonin MT1 and MT2 receptors in glioma C6 cells [10,52] and breast cancer MCF-7 cells [53]. VPA was also found to increase the expression of CXCR4 in RCC Caki-1 cells. In prostate cancer cells, VPA could decrease intracellular CXCR4 and increase CXCR4 accumulation on the cell surface [54]. However, in AML cells, VPA exerts different effects on CXCR4 depending on cell maturation status [55]. VPA decreased CXCR4 in more differentiated CD34-negative AML cells, and increased CXCR4 in highly CD34-positive, immature AML cells [55]. VPA also decreased the expression of beta-adrenergic receptor (β-AR) and β-AR-stimulated cAMP production and modulated the expression of Protein Kinase C (PKC) [56] while it conversely increased serotonin-2A(5-HT2A) receptors in rat glioma C6 cells [57]. VPA-induced increase of SSTR2 was also observed in some cancer cells such as pancreatic carcinoid BON cells, pulmonary carcinoid H727, HCC HTB-52 cells and MTC TT cells. VPA could also up-regulate the expression of GRPR [9] in many other cancer cells such as HCC HTB-52 cells, cervical cancer Hela cells [9], SCLC DMS53 cells, pancreatic carcinoid BON cells, pulmonary carcinoid H727 cells and mid-gut carcinoid CNDT2 cells. VPA was found to affect Vasoactive Intestinal Peptide (VIP) receptors PAC1, VPAC1 and VPAC2 in cancer cells. VPA could increase PAC1 in cervical cancer Hela cells and SCLC DMS53 cells, VPAC2 in carcinoid BON cells and MTC TT cells, and decrease VPAC2 in Hela cells. Many of these cell surface receptors such as somatostatin receptors, Vasoactive Intestinal Peptide (VIP) receptors, melatonin receptors and bombesin receptors [7,52,55,56] have their specific ligands, agonists/antagonists and even specific antibodies. These peptides and antibodies could be used as drug delivery vehicles when coupled with anti-cancer drugs and thus form new receptor-targeted peptide- or antibody-drug conjugates. Especially, certain of these receptors such as SSTR2 and GRPR are highly expressed in many tumor cells or tumor blood vessels [58-60] and have been used for receptor-targeted therapeutics. Put together, these findings could provide a novel strategy of receptor-targeted therapy by combining VPA with these receptor-targeted anti-cancer chemotherapeutics such as peptide-drug conjugates and antibody-drug conjugates.

Receptor-targeted peptide-drug conjugates

Modified long-acting peptide analogs have already been used as drug delivery vehicles by being coupled with various small molecule anti-cancer agents to form cytotoxic peptide-drug conjugates (Figure 3). These new peptide-drug conjugates could target the specific GPCRs on cancer cell surfaces and quickly internalize drugs of interest inside cells [60]. Moreover, these conjugates have been demonstrated capable of improving the non-specific small molecule agent's anti-cancer efficacy while reducing severe toxic side effects and multiple drug resistance [61,62]. For instance, cytotoxic peptide-drug conjugates such as SSTR2-specific cytotoxic conjugates DOX-SST, COL-SST and CPT-SST, and the GRPR-specific cytotoxic conjugates CPT-BN and DOX-BN [61,63] display more effective anti-tumor activity in various tumors [61,62]. The increase of the specific receptor density will accelarate the internalization of these peptide-drug conjugates and further improve the anti-cancer efficacy of drugs.

VPA in combination with cytotoxic peptide-drug conjugates

As described above, VPA could function as a tumor suppressor and a receptor activator in the same cancer cells. VPA-induced increase of receptor density could more quickly promote cell internalization of these receptor-targeting conjugates and further enhance their anti-tumor ability. Thus, the combination application of peptide-drug conjugates and VPA may provide great opportunities to improve the anti-tumor efficacy compared to each alone. Indeed, it has been demonstrated that VPA-induced receptor up-regulation could dramatically enhance the anti-cancer efficacy of these receptor-targeted therapeutic agents [9].

Currently, investigators concentrate more interest on peptide-drug conjugates that target GPCRs, like SSTR2 and GRPR, due to these receptors having been identified as highly expressed in many cancer cells. VPA was found to enhance the expression of abundant SSTR2 and GRPR in natual cancer cells such as cervical cancer cells, carcinoid cells, SCLC cells and hepatocellular cancer cells as described above. Thus, a combination therapy with VPA and SSTR2-targeted cytotoxic SST-drug conjugates (such as CPT-SST, DOX-SST, COL-SST), or VPA and GRPR-targeted cytotoxic BN-drug conjugates (such as CPT-BN, DOX-BN, COL-BN) may possibly be applied in treating these cancers. It has been observed that the combination of VPA and the GRPR-targeted CPT-BN conjugate additively suppress *in vitro* cell proliferation in leukemia MOLT-4, Jurkat cells, osteosarcoma U2OS cells, carcinoid BON cells and CNDT2 cells. We also have observed that the combination of VPA and another SSTR2-targeted CPT-SST conjugate could enhance the cell proliferative suppression in various cancer cells,

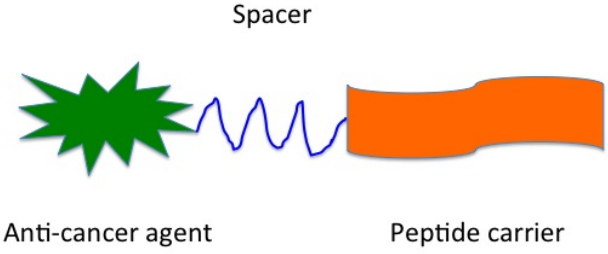

Figure 3: The schematic structure of a peptide-drug conjugate consisting of a peptide carrier, a small anti-cancer molecule of interest and a spacer.

including cervical cancer Hela cells, carcinoid BON cells, SCLC DMS53 cells, HCC HTB-52, HB8064 cells, pancreatic cancer CFPAC-1 cells, colon cancer HT-29 cells, ovarian cancer OVCAR8 cells, SKOV3 cells, MTC TT cells, prostate cancer DU-145 cells and PC-3 cells, leukemia MOLT-4 and Jurkat cells [unpublished data]. The *in vivo* studies further confirm their synergitic suppressive effects on tumor growth [9,43]. For instance, VPA could act as a tumor suppressor and up-regulate the SSTR2 that is highly expressed in cervical cancer Hela cells. Based on this, VPA and the SSTR2-targeted conjugate COL-SST, used at much lower doses, display a much more synergitic effect on cervical cancer Hela tumor growth than did each single one given at higher doses [7,43]. Similar results were also observed with the treatment of VPA and another conjugate CPT-SST in Hela tumors in xenografts [9]. The synergitic effects of VPA and COL-SST, or VPA and CPT-SST were also observed in treating pancreatic carcinoid BON tumors and ovarian cancer OVCAR8 tumors [unpublished data]. These findings suggest that VPA-mediated receptor up-regulation could increase the uptake and anti-tumor efficacy of receptor-targeting conjugates.

Conclusion

VPA has less toxic side effects on patients and also has broad but limited anti-cancer effects on many cancers. Thus, VPA is a potential anti-cancer adjuvant in combination with other anti-cancer agents. In particular, with the characteristics of receptor-expressing enhancement, VPA in combination with receptor-targeted cytotoxic peptide-drug conjugates could be a potential anti-cancer approach.

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