



Review

HDAC Inhibitors and RECK Modulate Endoplasmic Reticulum Stress in Tumor Cells

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Abstract: In the tumor microenvironment hypoxia and nutrient deprived states can induce endoplasmic reticulum (ER) stress. If ER stress is not relieved, the tumor cells may become apoptotic. Therefore, targeting ER homeostasis is a potential strategy for cancer treatment. Various chemotherapeutic agents including histone deacetylase (HDAC) inhibitors can induce ER stress to cause cell death in cancers. Some HDAC inhibitors can prevent HDAC from binding to the specificity protein 1-binding site of the promoter of reversion-inducing cysteine-rich protein with Kazal motifs (*RECK*) and up-regulate *RECK* expression. Up-regulation of *RECK* expression by HDAC inhibitors has been observed in various cancer types. *RECK* is a tumor and metastasis suppressor gene and is critical for regulating tumor cell invasiveness and metastasis. *RECK* also modulates ER stress via binding to and sequestering glucose-regulated protein 78 protein, so that the transmembrane sensors, such as protein kinase RNA-like ER kinase are released to activate eukaryotic translational initiation factor 2 α phosphorylation and enhance ER stress. Therefore, HDAC inhibitors may directly induce ER stress or indirectly induce this stress by up-regulating *RECK* in cancer cells.

Keywords: histone deacetylase inhibitors; reversion-inducing cysteine-rich protein with Kazal motifs; endoplasmic reticulum stress; cancers

1. Endoplasmic Reticulum Stress in Cancers

The endoplasmic reticulum (ER) is an important cellular compartment involved in protein synthesis and maturation. Protein maturation requires the coordinated activity of many chaperones and folding enzymes [1,2]. When the number of unfolded proteins exceeds the capacity of the ER, cellular protein homeostasis is disrupted and ER stress occurs, leading to the accumulation of unfolded or misfolded proteins [1–3]. To reduce the excessive protein load, cells activate the unfolded protein response (UPR), which causes transient attenuation of protein translation, degradation of misfolded proteins, and induction of molecular chaperones and folding enzymes to augment the ER capacity for protein folding and degradation [2]. The UPR is controlled by glucose-regulated protein 78 (GRP78) and three different ER transmembrane sensor proteins: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor-6 [1,3–5]. GRP78 acts on newly-synthesized proteins by chaperoning them through folding, assembly, and translocation across the ER membrane [6]. In normal and non-stressed cells, GRP78 binds to ER transmembrane sensor proteins and maintains them in an inactive form [1,4,5]. During ER stress, an increase in unfolded substrates leads to the sequestration of GRP78, releasing the sensors to initiate

UPR signals [1]. If this ER stress is not relieved, the injured cells may become apoptotic [2]. ER stress can be induced by various insults, such as hypoxia, reactive oxygen species, nutrient deprivation, disruption of calcium homeostasis, inhibition of protein glycosylation or disulfide bond formation, and viral or bacterial infection [2,3].

ER stress also plays an important role in tumor cell survival, tumor progression, angiogenesis, metastasis, and drug resistance; common conditions in the tumor microenvironment such as hypoxia, reactive oxygen species, and nutrient deprivation can trigger the UPR [2–4,6,7]. Tumor cells often produce more mutant proteins than the normal ER capacity can handle because of rapid biosynthesis in cancers, and eventually the nutrient requirements exceed the capacity of the vascular supply, making the tumors hypoxic and causing tumor cell apoptosis [1,5,6]. During ER stress, GRP78 increases so that tumor cells can adapt to the chronic ER stress [2,4]. Increased GRP78 expression has been observed in various cancer cell lines and human cancer specimens, such as bladder, breast, lung, and stomach cancers, glioma, melanoma, and epidermoid carcinoma, [5,6,8–12]. ER stress may not induce cell death because the downstream pathways of ER stress vary between cells in cancers depending on the chronicity of ER stress and on the relative expression of key factors [1]. The cell death induced by ER stress can reduce the tumor mass and decrease nutrient and oxygen requirements [1]. In addition, activation of the UPR may increase autophagy, which has a cytoprotective function during stress by liberating amino acids from long-lived proteins and removing damaged organelles [1,13]. PERK mediates upregulation of the autophagy factors LC3 and autophagy-related gene 5 via ATF4 and CCAAT/enhancer-binding protein-homologous protein (CHOP) and promotes phagophore formation [1,13]. The IRE1 arm of the UPR is also important for the survival of hypoxic tumor cells [14]. During hypoxia-induced ER stress, IRE1-driven X-box-binding protein 1 splicing increases tumor cell tolerance to hypoxia, whereas loss of this protein impairs hypoxic tumor growth [14]. Further, generation of reactive oxygen species (ROS) during ER stress, while potentially toxic, may help limit tumor growth to match the nutrient supply by initiating DNA damage checkpoints [1]. Excess toxicity from ROS is limited by ATF4-mediated antioxidant pathways [1].

2. Histone Deacetylase (HDAC) Inhibitors Induce ER Stress and Cause Cell Death in Cancer Cells

Since ER stress plays an important role in tumor cell survival, targeting ER homeostasis is considered a potential strategy for the management of cancers [7,15]. Various chemotherapeutic agents induce ER stress in cancer cells [16,17]. In addition, chemotherapy may cause drug resistance in cancer cells, and the underlying mechanisms were found to be related to the induction of ER stress tolerance, GRP78-dependent Akt activation, and suppressed activation of caspase-4 and caspase-7 [9,10,18]. In contrast, suppression of GRP78 using inhibitors or siRNA can enhance the chemotherapy-induced tumor cell apoptosis and drug sensitivity of endothelial cells in tumors [4–6,8,18].

In recent years, histone deacetylase (HDAC) has been a target of cancer therapy because it catalyzes the reversible acetylation of histones and nonhistone substrates to control the epigenetic and transcriptomic landscape of normal and tumor cells [19]. Some HDAC inhibitors have been developed for the treatment of cancers, such as apicidin, Gd-metallofullerenol nanomaterial, MS-275, M344, *N*-hydroxy-7-(2-naphthylthio) heptanamide (HNHA), panobinostat, *trans*-3,4,5-trihydroxystilbene (resveratrol), romidepsin, *S*-7-oxo-7-(4-phenylthiazol-2-ylamino)-heptyl 2-methylpropanethioate (PTACH), sodium butyrate, suberoylanilide hydroxamic acid (SAHA), TMP269, trichostatin A (TSA), valproic acid (VPA), and WJ25591, among others (Table 1) [7,15,17,18,20–28]. HDAC inhibitors can suppress cellular proliferation, induce apoptosis, and exert anti-metastatic and anti-angiogenic effects in cancers [29–31]. They also induce ER stress, cause hyperacetylation of chaperones including GRP78 and affect their function in protein homeostasis, and induce protein misfolding and proteotoxic stress [7,16,18,19,27]. Several class I HDAC inhibitors including MS-275, apicidin, and romidepsin were shown to potently cause ROS-dependent ER stress-induced apoptosis of nasopharyngeal carcinoma cells [23]. In p53-deficient human colon cells, HDAC inhibitors including sodium butyrate, MS-275, M344, TSA, SAHA, and VPA activated ER stress sensor PERK and eukaryotic translational

initiation factor 2 α (eIF-2 α) phosphorylation, as well as induced the ATF4/ATF3/CHOP pathway [26]. HNHA increases Ca²⁺ release from the ER to the cytoplasm and induces ER-stress-dependent apoptosis in papillary and anaplastic thyroid cancer cells [25]. PTACH and SAHA also enhance ER stress, induce cellular apoptosis, and exert antitumor effects in non-small cell lung cancer (NSCLC) cells [7,17]. SAHA up-regulates ER stress-regulated proteins including ATF4, GRP78, and CCAAT/enhancer-binding protein homologous protein in NSCLC [22]. SAHA treatment rapidly induces sustained eIF2 α phosphorylation and enhances cisplatin-induced ER stress-mediated apoptosis in oral squamous cell carcinoma cells; inhibition of ER stress by salubrinal, an inhibitor of eIF2 α dephosphorylation, ameliorates this cytotoxicity [28]. In addition, SAHA exerts therapeutic effects on breast cancer cells and shows synergistic therapeutic effects with ionizing radiation (IR) compared with either SAHA or IR treatment alone in MCF-7 and MDA-MB-231 human breast cancer cells, or in 4T1 mouse breast cancer cells [21]. The synergistic effects of combined treatment are thought to occur through autophagy, ER stress, and inhibition of DNA repair proteins [21].

Table 1. List of histone deacetylase inhibitors.

| Histone Deacetylase Inhibitors |
|---|
| Apicidin |
| Gd-metallofullerenol nanomaterial |
| MS-275 |
| M344 |
| N-hydroxy-7-(2-naphthylthio) heptanamide (HNHA) |
| Panobinostat |
| Romidepsin |
| S-7-oxo-7-(4-phenylthiazol-2-ylamino)-heptyl 2-methylpropanethioate (PTACH) |
| Sodium butyrate |
| Suberoylanilide hydroxamic acid (SAHA) |
| TMP269 |
| <i>trans</i> -3,4,5-trihydroxystilbene (resveratrol) |
| Trichostatin A (TSA) |
| Valproic acid (VPA) |
| WJ25591 |

The HDAC inhibitor panobinostat also induces apoptosis and ER stress and inhibits the growth of Caki-1, ACHN, and 769-P renal cancer cells [15]. Panobinostat kills renal cancer cells by inhibiting the degradation of unfolded proteins, causing ubiquitinated proteins to accumulate and inducing ER stress [15]. It also increases the levels of phosphorylated eIF-2 α , ATF4, and CHOP and causes GRP78 acetylation, which dissociates GRP78 from PERK, and is associated with the activation of a lethal UPR in human breast cancer cells [27]. In addition, GRP78 knockdown sensitizes MCF-7 breast cancer cells to panobinostat-induced UPR and cell death [27]. Similarly, treatment with TSA causes more apoptosis in MDA-MB-435 breast cancer cells and HCT116 colon cancer cells with GRP78 knockdown by siRNA than in wild-type tumor cells [18]. In multiple myeloma cell lines, the selective class IIa HDAC inhibitor TMP269 enhances cytotoxicity, up-regulates ATF4 and CHOP, and induces apoptosis; however, the enhanced cytotoxicity is abrogated by ATF4 knockdown [24]. WJ25591, a hydroxysuberamide derivative, inhibits HDAC1 and cell proliferation in human PC-3 and DU-145 hormone-refractory prostate cancer cells [20]. In addition, the proteasome inhibitor MG-132 dramatically sensitizes WJ2559-induced apoptosis of prostate cancer cells and ER stress contributes to the synergistic effect [20]. Apicidin can induce histone H3 hyperacetylation and reduction of HDAD2 mRNA expression [22]. It causes apoptotic cell death and activates caspase-3, caspase-9, and caspase-12 [22]. In addition, it increases the expression of ER stress-associated proteins, including CCAAT/CHOP, cleavage of activating transcription factor-6 α , and phosphorylation of eIF2 α in cancer cells [22]. Inhibition of ER stress by CHOP knockdown or using the ER stress inhibitors salubrinal and 4-phenylbutyric acid reduces apicidin-induced cell death [22]. Apicidin also causes cellular apoptosis

by ER stress and mitochondrial dysfunction via phospholipase C γ 1 activation, Ca²⁺ release, and ROS accumulation in Neuro-2a neuroblastoma cells [22]. All of these data suggest HDAC inhibitors induce ER stress to cause cancer cell death.

3. Reversion-Inducing Cysteine-Rich Protein with Kazal Motifs (RECK) and Regulation of RECK Expression

The reversion-inducing cysteine-rich protein with Kazal motifs (*RECK*) gene encodes a glycosylphosphatidylinositol-anchored glycoprotein of approximately 110 kDa which contains multiple serine protease inhibitor-like motifs [32–34]. *RECK* is expressed ubiquitously in normal tissues and has various functions in tissue development, morphogenesis, remodeling, tissue architecture, cell migration, cell-cell interaction, chondrogenesis, myogenesis, and angiogenesis [29,33]. It regulates the function of the extracellular matrix and suppresses the activity of matrix metalloproteinases (MMPs), including MMP-2, MMP-9, and membrane type-1, through direct inhibition of its protease activity, regulation of cellular release, and sequestration at the cell surface [34,35]. In addition, the expressions of *RECK* and MMPs are inversely correlated [36]. Low *RECK* expression is strongly associated with high expression of MMP-2 and MMP-9 in different types of cancers [29,34,37]. *RECK* is considered to be a tumor and metastasis suppressor gene [32–34]. *RECK* expression is reduced in various cancer types including breast, colorectal, lung, pancreatic, prostate, and stomach cancer and cholangiocarcinoma, ameloblastic tumor, middle ear squamous cell cancer, and osteosarcoma [29]. In addition, *RECK* expression is positively correlated with the survival of cancer patients; down-regulation of *RECK* often predicts poor prognosis in cancer patients [29]. Restoration of *RECK* expression in tumor cells suppresses the angiogenesis, invasion, and metastasis of tumors [34,35].

RECK expression is affected by multiple factors. The specificity protein 1 (SP1)-binding site of the *RECK* promoter gene is a common negative target for oncogenic signals [38]. *RECK* expression is decreased upon cell transformation by human epidermal growth factor receptor 2 (HER-2/neu) and rat sarcoma (RAS) oncoproteins [39–42]. HER-2/neu induces the binding of SP proteins and HDAC1 to the *RECK* promoter to repress *RECK* and activates the extracellular signal-regulated kinase signaling pathway [41]. RAS suppresses *RECK* through inhibition of the SP1 promoter site of the *RECK* gene and via histone deacetylation and promoter methylation mechanisms [39,40]. Further, retinoblastoma binding protein-7, the Ha-RAS (val12)-upregulated gene, forms a complex with HDAC1 and Sp1, which binds to the Sp1 binding site of the *RECK* promoter to suppress *RECK* expression in 7–4 cells (derived from mouse fibroblast NIH3T3 cells) [43]. Therefore, the SP1 site of the *RECK* promoter is important for the function of *RECK*.

Histone acetylation/deacetylation plays a key role in the epigenetic regulation of multiple genes [44]. *RECK* expression is frequently silenced in aggressive tumor cells by HDAC, and suppressed by HER-2/neu and RAS also through a histone deacetylation mechanism [39–41,44,45]. The amount or activity of extracellular matrix-degrading enzymes such as MMPs can be modulated by regulating *RECK* or at the transcriptional and translational levels using HDAC inhibitors [46]. In contrast, *RECK* expression can be restored by suppressing HDAC with HDAC inhibitors or siRNA [31,39,44–46]. Hypoxia-induced down-regulation of *RECK* is also abolished by knockdown of HDAC1 with siRNA [42]. Further, HDAC inhibitors such as TSA can up-regulate *RECK* via transcriptional activation in CL-1 human lung cancer cells, as well as rescue hypoxia-suppressed *RECK* expression in the H-Ras-transformed human breast MCF10A and HT1080 human fibrosarcoma cell lines [31,45]. TSA antagonizes the inhibitory action of Ras on *RECK* and reverses angiotensin-II-induced *RECK* suppression by inhibiting Sp1 binding to the *RECK* promoter [39,44]. Apicidin, which is also a HDAC inhibitor, markedly decreases HDAC4 expression, blocks cell migration and invasion of human ovarian cancer SKOV-3 cells, and suppresses the growth of SKOV-3 xenografts [47]. Apicidin inhibits cell migration through down-regulation of MMP-2 and up-regulation of *RECK* in HDAC4-blocked SKOV-3 cells [47]. Further, apicidin significantly suppresses the binding of HDAC4 to Sp1 binding elements of the *RECK* promoter by repressing HDAC4 [47]. Valproic acid induces cytotoxicity and apoptosis and

suppresses the invasiveness of T98G glioma cells by up-regulating RECK expression and inhibiting MMP-2 and MMP-9 activity [30]. Gd-metallofullerenol nanomaterial can suppress pancreatic cancer metastasis through down-regulation of metastasis-associated protein 1, HDAC1, hypoxia-inducible factor 1 α , and MMP-2/9, and up-regulation of RECK [48]. These data suggest that HDAC inhibitors regulate RECK expression and activity via the SP1 binding site of the promoter and affect cancer cell survival.

4. HDAC Inhibitors, RECK, and ER Stress

As described above, HDAC inhibitors can induce ER stress, exert antitumor effects, and induce RECK expression in tumor cells; however, the role of RECK in HDAC inhibitor-induced ER stress is unclear. In H460 NSCLC cells, overexpression of microRNA-200c (miR-200c) can suppress cell growth by targeting RECK, followed by activation of the c-jun-N-terminal kinase signaling pathway and ER stress with increased GRP78 and CHOP [49]. Resveratrol, a natural polyphenolic extracted from red wine, is also an HDAC inhibitor and can induce ER stress in miR-200c-transfected H460 NSCLC cells [49]. In addition, resveratrol enhances RECK, GRP78, CHOP, JNK, c-jun, caspase-3, and caspase-9 expression in miR-200c-transfected cells but not in untransfected cells [49]. These findings suggest that miR-200c overexpression can induce ER stress and sensitize H460 cells to resveratrol, which is thought to occur because of increased RECK expression [49]. RECK and GRP78 were shown to colocalize in the cytoplasm and perinuclear area in neuroblastoma cells, indicating that RECK and GRP78 are colocalized in the ER because the glycosylphosphatidylinositol-anchored RECK is transported from the ER to the plasma membrane through the Golgi apparatus [16,34]. Further, RECK overexpression can induce ER stress, as demonstrated by the increased level of phosphorylated PERK and eIF-2 α , and exert a cytotoxic effect in neuroblastoma cells [16]. In contrast, GRP78 overexpression inhibits the RECK-induced expression of phosphorylated PERK and eIF-2 α in neuroblastoma cells [16]. These findings suggest that RECK binds to and sequesters the GRP78 protein, and transmembrane sensors, such as PERK are released to activate eIF-2 α phosphorylation and enhance ER stress in neuroblastoma cells [16]. Collectively, HDAC inhibitors may act on the SP1 binding site of the *RECK* promoter to increase RECK expression. Due to the colocalization and interaction of RECK and GRP78, the increased RECK binds to and sequesters GRP78, eventually activating ER stress.

5. Conclusions

In cancers, microenvironmental conditions, like hypoxia, reactive oxygen species, and nutrient deprivation, may lead to the accumulation of unfolded or misfolded proteins and induce ER stress [2-4,6,7]. If the ER stress is not relieved, the tumor cells may become apoptotic. Therefore, targeting ER homeostasis is a potential strategy for cancer treatment. HDAC inhibitors can induce ER stress to cause cell death in cancers [7,16,18,27]. In addition, HDAC inhibitors have been found to up-regulate RECK expression by preventing HDAC binding to the SP1 site of the *RECK* promoter [39-41,44,45,47]. RECK was found to colocalize with GRP78 to modulate ER stress by binding to and sequestering GRP78. This causes transmembrane sensors, such as PERK, to be released to activate eIF-2 α phosphorylation and enhance ER stress [16]. These findings suggest HDAC inhibitors act on the SP1 binding site of the *RECK* promoter to increase RECK expression; the increased RECK sequesters GRP78 and eventually activates ER stress and causes cellular apoptosis (Figure 1) [16,39,44,47]. Collectively, HDAC inhibitors may directly induce ER stress or indirectly induce stress by up-regulating RECK in cancer cells. However, additional studies are necessary to confirm this hypothesis.

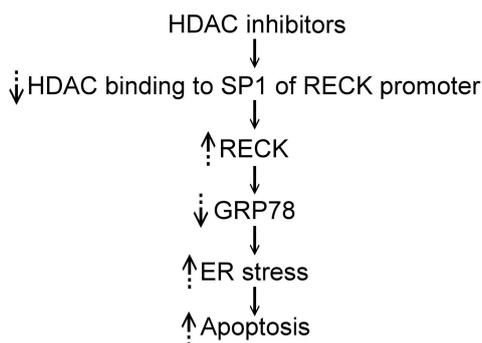


Figure 1. The pathway of the influence of HDAC inhibitors on the ER stress in the tumor cells is speculated as: HDAC inhibitors prevent the binding of HDAC to the SP1 site of the RECK promoter and then increase RECK expression; the increased RECK sequesters GRP78 and eventually activates ER stress and causes cellular apoptosis. ↓ indicates pathway. ↑ indicates increased. ↓ indicates decreased.

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References

- Clarke, H.J.; Chambers, J.E.; Liniker, E.; Marciniak, S.J. Endoplasmic reticulum stress in malignancy. *Cancer Cell* **2014**, *25*, 563–573. [[CrossRef](#)] [[PubMed](#)]
- Ni, M.; Zhang, Y.; Lee, A.S. Beyond the endoplasmic reticulum: Atypical GRP78 in cell viability, signaling and therapeutic targeting. *Biochem. J.* **2011**, *434*, 181–188. [[CrossRef](#)] [[PubMed](#)]
- Penaranda Fajardo, N.M.; Meijer, C.; Kruyt, F.A. The endoplasmic reticulum stress/unfolded protein response in gliomatosis, tumor progression and as a therapeutic target in glioblastoma. *Biochem. Pharmacol.* **2016**, *118*, 1–8. [[CrossRef](#)] [[PubMed](#)]
- Lee, A.S. GRP78 induction in cancer: Therapeutic and prognostic implications. *Cancer Res.* **2007**, *67*, 3496–3499. [[CrossRef](#)] [[PubMed](#)]
- Zhang, L.H.; Zhang, X. Roles of GRP78 in physiology and cancer. *J. Cell Biochem.* **2010**, *110*, 1299–1305. [[CrossRef](#)] [[PubMed](#)]
- Li, J.; Lee, A.S. Stress induction of GRP78/BiP and its role in cancer. *Curr. Mol. Med.* **2006**, *6*, 45–54. [[CrossRef](#)] [[PubMed](#)]
- Zismanov, V.; Drucker, L.; Gottfried, M. ER homeostasis and motility of NSCLC cell lines can be therapeutically targeted with combined Hsp90 and HDAC inhibitors. *Pulm. Pharmacol. Ther.* **2013**, *26*, 388–394. [[CrossRef](#)] [[PubMed](#)]
- Dong, D.; Ko, B.; Baumeister, P.; Swenson, S.; Costa, F.; Markland, F.; Stiles, C.; Patterson, J.B.; Bates, S.E.; Lee, A.S. Vascular targeting and antiangiogenesis agents induce drug resistance effector GRP78 within the tumor microenvironment. *Cancer Res.* **2005**, *65*, 5785–5791. [[CrossRef](#)] [[PubMed](#)]
- Jiang, C.C.; Mao, Z.G.; Avery-Kiejda, K.A.; Wade, M.; Hersey, P.; Zhang, X.D. Glucose-regulated protein 78 antagonizes cisplatin and adriamycin in human melanoma cells. *Carcinogenesis* **2009**, *30*, 197–204. [[CrossRef](#)] [[PubMed](#)]
- Lin, W.; Lin, Y.; Li, J.; Harding, H.P.; Ron, D.; Jamison, S. A deregulated integrated stress response promotes interferon- γ -induced medulloblastoma. *J. Neurosci. Res.* **2011**, *89*, 1586–1595. [[CrossRef](#)] [[PubMed](#)]
- Ma, Y.; Hendershot, L.M. The role of unfolded protein response in tumor development: Friend or foe? *Nat. Rev. Cancer* **2004**, *4*, 966–977. [[CrossRef](#)] [[PubMed](#)]
- Ranganathan, A.C.; Zhang, L.; Adam, A.P.; Aguirre-Ghiso, J.A. Functional coupling of p38-induced upregulation of BiP and activation of RNA-dependent protein kinase-like endoplasmic reticulum kinase to drug resistance of dormant carcinoma cells. *Cancer Res.* **2006**, *66*, 1702–1711. [[CrossRef](#)] [[PubMed](#)]

13. Rouschop, K.M.; van den Beucken, T.; Dubois, L.; Niessen, H.; Bussink, J.; Savelkoul, K.; Keulers, T.; Mujcic, H.; Landuyt, W.; Voncken, J.W.; et al. The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5. *J. Clin. Investig.* **2010**, *120*, 127–141. [[CrossRef](#)] [[PubMed](#)]
14. Romero-Ramirez, L.; Cao, H.; Nelson, D.; Hammond, E.; Lee, A.H.; Yoshida, H.; Mori, K.; Glimcher, L.H.; Denko, N.C.; Giaccia, A.J.; et al. XBP1 is essential for survival under hypoxic conditions and is required for tumor growth. *Cancer Res.* **2004**, *64*, 5943–5947. [[CrossRef](#)] [[PubMed](#)]
15. Sato, A.; Asano, T.; Isono, M.; Ito, K.; Asano, T. Panobinostat synergizes with bortezomib to induce endoplasmic reticulum stress and ubiquitinated protein accumulation in renal cancer cells. *BMC Urol.* **2014**, *14*, 71. [[CrossRef](#)] [[PubMed](#)]
16. Chen, Y.; Tsai, Y.H.; Tseng, S.H. RECK regulated endoplasmic reticulum stress response and enhanced cisplatin-induced cell death in neuroblastoma cells. *Surgery* **2013**, *154*, 968–979. [[CrossRef](#)] [[PubMed](#)]
17. Hanke, N.T.; Garland, L.L.; Baker, A.F. Carfilzomib combined with suberanilohydroxamic acid (SAHA) synergistically promotes endoplasmic reticulum stress in non-small cell lung cancer cell lines. *J. Cancer Res. Clin. Oncol.* **2016**, *142*, 549–560. [[CrossRef](#)] [[PubMed](#)]
18. Baumeister, P.; Dong, D.; Fu, Y.; Lee, A.S. Transcriptional induction of GRP78/BiP by histone deacetylase inhibitors and resistance to histone deacetylase inhibitor-induced apoptosis. *Mol. Cancer Ther.* **2009**, *8*, 1086–1094. [[CrossRef](#)] [[PubMed](#)]
19. Rao, R.; Fiskus, W.; Ganguly, S.; Kambhampati, S.; Bhalla, K.N. HDAC inhibitors and chaperone function. *Adv. Cancer Res.* **2012**, *116*, 239–262. [[PubMed](#)]
20. Chen, Y.C.; Huang, W.J.; Hsu, J.L.; Yu, C.C.; Wang, W.T.; Guh, J.H. A novel hydroxysubamide derivative potentiates MG132-mediated anticancer activity against human hormone refractory prostate cancers—The role of histone deacetylase and endoplasmic reticulum stress. *Prostate* **2013**, *73*, 1270–1280. [[CrossRef](#)] [[PubMed](#)]
21. Chiu, H.W.; Yeh, Y.L.; Wang, Y.C.; Huang, W.J.; Chen, Y.A.; Chiou, Y.S.; Ho, S.Y.; Lin, P.; Wang, Y.J. Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, enhances radiosensitivity and suppresses lung metastasis in breast cancer in vitro and in vivo. *PLoS ONE* **2013**, *8*, e76340. [[CrossRef](#)] [[PubMed](#)]
22. Choi, J.H.; Lee, J.Y.; Choi, A.Y.; Hwang, K.Y.; Choe, W.; Yoon, K.S.; Ha, J.; Yeo, E.J.; Kang, I. Apicidin induces endoplasmic reticulum stress- and mitochondrial dysfunction-associated apoptosis via phospholipase C γ 1- and Ca²⁺-dependent pathway in mouse Neuro-2a neuroblastoma cells. *Apoptosis* **2012**, *17*, 1340–1358. [[CrossRef](#)] [[PubMed](#)]
23. Hui, K.F.; Chiang, A.K. Combination of proteasome and class I HDAC inhibitors induces apoptosis of NPC cells through an HDAC6-independent ER stress-induced mechanism. *Int. J. Cancer* **2014**, *135*, 2950–2961. [[CrossRef](#)] [[PubMed](#)]
24. Kikuchi, S.; Suzuki, R.; Ohguchi, H.; Yoshida, Y.; Lu, D.; Cottini, F.; Jakubikova, J.; Bianchi, G.; Harada, T.; Gorgun, G.; et al. Class IIa HDAC inhibition enhances ER stress-mediated cell death in multiple myeloma. *Leukemia* **2015**, *29*, 1918–1927. [[CrossRef](#)] [[PubMed](#)]
25. Kim, S.M.; Park, K.C.; Jeon, J.Y.; Kim, B.W.; Kim, H.K.; Chang, H.J.; Choi, S.H.; Park, C.S.; Chang, H.S. Potential anti-cancer effect of N-hydroxy-7-(2-naphthylthio) heptanamide (HNHA), a novel histone deacetylase inhibitor, for the treatment of thyroid cancer. *BMC Cancer* **2015**, *15*, 1003. [[CrossRef](#)] [[PubMed](#)]
26. Liu, J.; Edagawa, M.; Goshima, H.; Inoue, M.; Yagita, H.; Liu, Z.; Kitajima, S. Role of ATF3 in synergistic cancer cell killing by a combination of HDAC inhibitors and agonistic anti-DR5 antibody through ER stress in human colon cancer cells. *Biochem. Biophys. Res. Commun.* **2014**, *445*, 320–326. [[CrossRef](#)] [[PubMed](#)]
27. Rao, R.; Nalluri, S.; Kolhe, R.; Yang, Y.; Fiskus, W.; Chen, J.; Ha, K.; Buckley, K.M.; Balusu, R.; Coothankandaswamy, V.; et al. Treatment with panobinostat induces glucose-regulated protein 78 acetylation and endoplasmic reticulum stress in breast cancer cells. *Mol. Cancer Ther.* **2010**, *9*, 942–952. [[CrossRef](#)] [[PubMed](#)]
28. Suzuki, M.; Endo, M.; Shinohara, F.; Echigo, S.; Rikiishi, H. Enhancement of cisplatin cytotoxicity by SAHA involves endoplasmic reticulum stress-mediated apoptosis in oral squamous cell carcinoma cells. *Cancer Chemother. Pharmacol.* **2009**, *64*, 1115–1122. [[CrossRef](#)] [[PubMed](#)]
29. Chen, Y.; Tseng, S.H. The potential of RECK inducers as antitumor agents for glioma. *Anticancer Res.* **2012**, *32*, 2991–2998. [[PubMed](#)]

30. Chen, Y.; Tsai, Y.H.; Tseng, S.H. Valproic acid affected the survival and invasiveness of human glioma cells through diverse mechanisms. *J. Neurooncol.* **2012**, *109*, 23–33. [[CrossRef](#)] [[PubMed](#)]
31. Liu, L.T.; Chang, H.C.; Chiang, L.C.; Hung, W.C. Histone deacetylase inhibitor up-regulates RECK to inhibit MMP-2 activation and cancer cell invasion. *Cancer Res.* **2003**, *63*, 3069–3072. [[PubMed](#)]
32. Clark, J.C.; Thomas, D.M.; Choong, P.F.; Dass, C.R. RECK—A newly discovered inhibitor of metastasis with prognostic significance in multiple forms of cancer. *Cancer Metastasis Rev.* **2007**, *26*, 675–683. [[CrossRef](#)] [[PubMed](#)]
33. Meng, N.; Li, Y.; Zhang, H.; Sun, X.F. RECK, a novel matrix metalloproteinase regulator. *Histol. Histopathol.* **2008**, *23*, 1003–1010.
34. Noda, M.; Takahashi, C. Recklessness as a hallmark of aggressive cancer. *Cancer Sci.* **2007**, *98*, 1659–1665. [[CrossRef](#)] [[PubMed](#)]
35. Silveira Correa, T.C.; Massaro, R.R.; Brohem, C.A.; Taboga, S.R.; Lamers, M.L.; Santos, M.F.; Maria-Engler, S.S. RECK-mediated inhibition of glioma migration and invasion. *J. Cell Biochem.* **2010**, *110*, 52–61. [[CrossRef](#)] [[PubMed](#)]
36. Silveira Correa, T.C.; Brohem, C.A.; Winnischofer, S.M.B.; da Silva Cardeal, L.B.; Sasahara, R.M.; Taboga, S.R.; Sogayar, M.C.; Maria-Engler, S.S. Down-regulation of the RECK-tumor- and metastasis-suppressor gene in glioma invasiveness. *J. Cell Biochem.* **2006**, *99*, 156–167.
37. Namwat, N.; Puetkasichonpasutha, J.; Loilome, W.; Yongvanit, P.; Techasen, A.; Puapairoj, A.; Sripa, B.; Tassaneeyakul, W.; Khuntikeo, N.; Wongkham, S. Downregulation of reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) is associated with enhanced expression of matrix metalloproteinases and cholangiocarcinoma metastases. *J. Gastroenterol.* **2011**, *46*, 664–675. [[CrossRef](#)] [[PubMed](#)]
38. Nagini, S. RECKing MMP: Relevance of reversion-inducing cysteine-rich protein with Kazal motifs as a prognostic marker and therapeutic target for cancer (a review). *Anticancer Agents Med. Chem.* **2012**, *12*, 718–725. [[CrossRef](#)] [[PubMed](#)]
39. Chang, H.C.; Liu, L.T.; Hung, W.C. Involvement of histone deacetylase in RAS-induced down-regulation of the metastasis suppressor RECK. *Cell Signal* **2004**, *16*, 675–679. [[CrossRef](#)] [[PubMed](#)]
40. Chang, H.C.; Cho, C.Y.; Hung, W.C. Silencing of the metastasis suppressor RECK by RAS oncogene is mediated by DNA methyltransferase 3b-induced promoter methylation. *Cancer Res.* **2006**, *66*, 8413–8420. [[CrossRef](#)] [[PubMed](#)]
41. Hsu, M.C.; Chang, H.C.; Hung, W.C. HER-2/neu represses the metastasis suppressor RECK via ERK and Sp transcription factors to promote cell invasion. *J. Biol. Chem.* **2006**, *281*, 4718–4725. [[CrossRef](#)] [[PubMed](#)]
42. Lee, K.J.; Lee, K.Y.; Lee, Y.M. Downregulation of a tumor suppressor RECK by hypoxia through recruitment of HDAC1 and HIF-1 α to reverse HRE site in the promoter. *Biochim. Biophys. Acta* **2010**, *1803*, 608–616. [[CrossRef](#)] [[PubMed](#)]
43. Yeh, H.H.; Tseng, Y.F.; Hsu, Y.C.; Lan, S.H.; Wu, S.Y.; Raghavaraju, G.; Cheng, D.E.; Lee, Y.R.; Chang, T.Y.; Chow, N.H.; et al. Ras induces experimental lung metastasis through up-regulation of RbAp46 to suppress RECK promoter activity. *BMC Cancer* **2015**, *15*, 172. [[CrossRef](#)] [[PubMed](#)]
44. Somanna, N.K.; Valente, A.J.; Krenz, M.; McDonald, K.S.; Higashi, Y.; Noda, M.; Chandrasekar, B. Histone deacetyltransferase inhibitors Trichostatin A and Mocetinostat differentially regulate MMP9, IL-18 and RECK expression, and attenuate Angiotensin II-induced cardiac fibroblast migration and proliferation. *Hypertens. Res.* **2016**, *39*, 709–716. [[CrossRef](#)] [[PubMed](#)]
45. Jeon, H.W.; Lee, Y.M. Inhibition of histone deacetylase attenuates hypoxia-induced migration and invasion of cancer cells via the restoration of RECK expression. *Mol. Cancer Ther.* **2010**, *9*, 1361–1370. [[CrossRef](#)] [[PubMed](#)]
46. Berezin, V.; Walmod, P.S.; Filippov, M.; Dityatev, A. Targeting of ECM molecules and their metabolizing enzymes and receptors for the treatment of CNS diseases. *Prog. Brain Res.* **2014**, *214*, 353–388. [[PubMed](#)]
47. Ahn, M.Y.; Kang, D.O.; Na, Y.J.; Yoon, S.; Choi, W.S.; Kang, K.W.; Chung, H.Y.; Jung, J.H.; Kim, H.S. Histone deacetylase inhibitor, apicidin, inhibits human ovarian cancer cell migration via class II histone deacetylase 4 silencing. *Cancer Lett.* **2012**, *325*, 189–199. [[CrossRef](#)] [[PubMed](#)]

48. Pan, Y.; Wang, L.; Kang, S.G.; Lu, Y.; Yang, Z.; Huynh, T.; Chen, C.; Zhou, R.; Guo, M.; Zhao, Y. Gd-metallofullerenol nanomaterial suppresses pancreatic cancer metastasis by inhibiting the interaction of histone deacetylase 1 and metastasis-associated protein 1. *ACS Nano* **2015**, *9*, 6826–6836. [[CrossRef](#)] [[PubMed](#)]
49. Bai, T.; Dong, D.S.; Pei, L. Synergistic antitumor activity of resveratrol and miR-200c in human lung cancer. *Oncol. Rep.* **2014**, *31*, 2293–2297. [[CrossRef](#)] [[PubMed](#)]



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