HDAC11, an emerging therapeutic target for metabolic disorders

Huizhen Chen1,2, Chunguang Xie1, Qiu Chen1 and Shougang Zhuang2,3*

1Department of Endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China, 2Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China, 3Department of Medicine, Rhode Island Hospital and Alpert Medical School, Brown University, Providence, RI, United States

Histone deacetylase 11 (HDAC11) is the only member of the class IV HDAC, and the latest member identified. It is highly expressed in brain, heart, kidney and some other organs, and located in mitochondria, cytoplasm and nuclei, depending on the tissue and cell types. Although studies in HDAC11 total knockout mice suggest its dispensable features for tissue development and life, it participates in diverse pathophysiological processes, such as DNA replication, tumor growth, immune regulation, oxidant stress injury and neurological function of cocaine. Recent studies have shown that HDAC11 is also critically involved in the pathogenesis of some metabolic diseases, including obesity, diabetes and complications of diabetes. In this review, we summarize the recent progress on the role and mechanism of HDAC11 in the regulation of metabolic disorders, with the focus on its regulation on adipogenesis, lipid metabolism, metabolic inflammation, glucose tolerance, immune responses and energy consumption. We also discuss the property and selectivity of HDAC11 inhibitors and their applications in a variety of in vitro and in vivo models of metabolic disorders. Given that pharmacological and genetic inhibition of HDAC11 exerts a beneficial effect on various metabolic disorders, HDAC11 may be a potential therapeutic target to treat chronic metabolic diseases.

KEYWORDS
HDAC11, metabolic disorders, obesity, diabetic complications, diabetes

Abbreviations: HDAC11, Histone deacetylase 11; HDACs, Histone deacetylases; NAD+, nicotinamide adenine dinucleotide; SIRT, sirtuins; AMD, age-related macular degeneration; MS, multiple sclerosis; PPAR, peroxisome proliferator-activated receptor; β-ARs, β-adrenergic receptors; WAT, white adipose tissue; BAT, brown adipose tissue; UCP1, uncoupling protein 1; WT, wild type; KO, knockout; AMPK, AMP-activated protein kinase; HFD, high fat diet; DN, Diabetic nephropathy; PAI-1, Plasminogen agonist inhibitor type 1; AP-2α, activator protein 2α; KLF15, Kruppel-like factor 15; LPL, Lipoprotein lipase; TG, triglyceride; HUVECs, human umbilical vein endothelial cells; AS, atherosclerosis; APCs, antigen-presenting cells; TSA, trichostatin A; TpxA, trapoxin A; SAHA, Suberoylanilide hydroxamic acid; i.p., intraperitoneal; IC50, half maximal inhibitory concentration; PFS, progression-free survival; AZA, 5-azacytidine; PTCL, Peripheral T-cell lymphomas; PFS, progression-free survival.
Introduction

The removal of acetyl groups from e-lysine residues in proteins (1) connected to condensed chromatin structures that inhibit gene transcription (2) is catalyzed by a class of enzymes called histone deacetylases (HDACs). Mammals currently contain 18 HDACs that are classified into two families: the Zn2+-dependent or classical HDACs, and the nicotinamide adenine dinucleotide (NAD+-dependent HDACs or sirtuins (SIRT)). According to the homology of their catalytic domains, classical HDACs are further split into three classes: class I, class II, and class IV HDACs. Class I HDACs include HDAC1, HDAC2, HDAC3, and HDAC8, whereas class II HDACs include HDAC4, HDAC5, HDAC6, HDAC8, HDAC9, and HDAC10, and class IV HDACs include HDAC11 (1).

HDAC11, the solitary member of class IV HDAC, contains an open reading frame encoding a 347-residue protein and shares sequence homology with both class I and class II HDAC proteins in the catalytic core regions. HDAC11 is highly conserved, even in invertebrates and plants as the most recently identified (3–5) and combines with other HDACs to form functional complexes (6–8). Although HDAC11 structure has still not been discovered, it has been effectively modeled from HDAC8 structure (4, 9). HDAC11 can be degraded by the proteasome system and has an unstable half-life at around four hours (10). While most class I-III HDACs are involved in deacetylating their substrates (reviewed in (11)), HDAC11 has defattyacylase activity in addition to its deacetylase activity. In fact, as the only HDAC family member that has a clear predilection for the removal of long-acyl instead of acetyl groups (12, 13), HDAC11 has still not been discovered, it has been effectively modeled from HDAC8 structure (4, 9). HDAC11 can be degraded by the proteasome system and has an unstable half-life at around four hours (10). While most class I-III HDACs are involved in deacetylating their substrates (reviewed in (11)), HDAC11 has defattyacylase activity in addition to its deacetylase activity. In fact, as the only HDAC member that has a clear predilection for the removal of long-acyl instead of acetyl groups (12, 13), HDAC11 is the family’s most effective fatty deacylase (9). It has been reported that the efficiency of HDAC11 defattyacylase activity is greater than 10,000 times its deacetylase activity (13). The activation of HDAC11 can be triggered by physiologic levels of free fatty acids and their metabolites (9).

HDAC11 is expressed in multiple organs and distributed in diverse organelles. It is primarily expressed in heart, kidney, smooth muscle (3), skeletal muscle (14–16), brain (3, 15, 17–20), testis (14, 21) and gall bladder (22). At cellular level, HDAC11 is expressed in the rat brain, and pancreatic β cells (27).

Emerging evidence has indicated that HDAC11 is critically involved in physiological and pathological processes. HDAC11 has a variety of physiological functions, including immunomodulation (24, 28–36), genomic stability (21, 37–39), cell cycle progression (21, 40, 41), and nervous system development (42). Pathologically, HDAC11 plays a role in epithelial barrier dysfunction (43–45) and ischemic injury (46–48) and required for the growth of several tumors (49–56), such as hepatic carcinoma (57–61), and lung cancer (62, 63). Moreover, it contributes to the development of some other diseases (56, 64), including hepatitis B (65–67) and age-related macular degeneration (68).

In the past two decades, HDACs have been revealed to be implicated in the regulation of multiple metabolic processes and pathogenesis of some metabolic disorders. For example, most class I HDAC members are associated with insulin resistance, energy metabolism and glucose homeostasis, and contribute to the pathogenesis of diabetes and its associated complications (69, 70), and obesity (71). Class II HDACs are required for regulating the transcription of genes associated with glucose homeostasis and hepatic gluconeogenesis (72). Moreover, HDACs are involved in the regulation of several events related to the pathogenesis of diabetes (i.e., oxidative stress, inflammation and fibrosis) and its associated complications (70, 73). Very recently, HDAC11 has been linked to the pathogenesis of obesity (74), diabetes, and diabetic complications (64, 75). Given that global deletion of HDAC11 in mice does not affect their development and health (24), pharmacological inhibition of HDAC11 could be a potential therapeutic approach for the treatment of metabolic disorders. In this review article, we summarize the role and possible mechanisms of HDAC11 in metabolic disorders, including obesity, metabolic inflammation, and diabetes and its complications, and provide detailed information about HDAC11 inhibitors developed so far.

HDAC11 in obesity

Obesity is an excessive fat gain due to unbalanced energy intake and consumption (76), and its prevalence rises yearly in children and adults (77). HDAC11 is related to obesity in multiple ways.

HDAC11 participates in the regulation of adipogenesis. The differentiation of adipocytes is strictly controlled. Mature adipocytes are differentiated from mesenchymal precursor cells. Several essential adipocyte transcription factors, such as peroxisome proliferator-activated receptor γ (PPARγ), CCAAT-enhancer-binding protein β, and steroid regulatory element-binding proteins regulate this process (78–80). It has also been reported that various HDACs, in particular, HDAC11 are critically involved in adipogenic differentiation (81–83). Silencing the HDAC11 gene by small interfering RNA results in reduced perilipin, adipon, and PPAR2 expression, and decreased formation of intracellular lipid droplets (84). By the use of HDAC11-KO mice and adipocytes from WT and HDAC11 KO mice exposed to FT895, it was also found that HDAC11 binds to a nearby gravin-α region and demyristoylates...
those spots. Gravin-α lysine myristoylation in brown and white adipocytes is necessary for the signal through β2- and β3-adrenergic receptors (β-ARs). Gravin-α lysine myristoylation induces the expression of protective thermogenic genes by directing β-ARs to lipid raft membrane microdomains and stimulating activation of PKA and its downstream signaling. These results establish reversible lysine myristoylation as a pattern of GPCR signaling regulation and emphasize the importance of HDAC11 in regulating adipocyte phenotypes (85).

HDAC11 is essential for regulating the balance of brown adipose tissue (BAT) and white adipose tissue (WAT) (86). The WAT is the body’s greatest energy storage tissue, and can secretes cytokines and adipokines as part of its endocrine function; BAT is imperative in maintaining body temperature in newborns’ nonshivering thermogenesis (87–90). A role for HDAC11 in regulating adipose tissue and thermogenic capability has been suggested by the fact that HDAC11 is more expressed in WAT than BAT and that deletion of HDAC11 in mice enhances the development of BAT and “browning” of WAT (26). These are essential changes as WAT contributes to obesity by storing extra energy as fat in the body, while BAT is capable of turning fat into energy (90). Meanwhile, in HDAC11-knockout (KO) mice, the histological study of BAT reveals a compacted tissue size with noticeably smaller lipid droplets (75). Mouse hepatic cell line AML12 with HDAC11 knockdown exhibits enhanced metabolic activity and oxygen consumption due to improved lipid oxidation capability (75), which is consistent with previous observations in skeletal muscle tissue (14).

Mechanistically, uncoupling protein 1 (UCP1), a mitochondrial long-chain fatty acid/H+ symporter, and PGC1-α, a primary regulator of mitochondrial biogenesis, are both downregulated by HDAC11 to inhibit the BAT transcriptional program (26). HDAC11 deletion increases metabolic pool clearance, thermogenic capability, UCP1 expression in BAT, and energy expenditure. Through its physical interaction with BRD2 (an enhancer regulating Ucp1 gene) (26), HDAC11 inhibits the thermogenic gene program. HDAC11 inhibition increases oxygen consumption and boosts adiponectin, a hormone that controls fatty acid oxidation, blood glucose levels, and stimulates lipid metabolism by activating the adiponectin-AdipoR-AMPK pathway (75).

Recent studies have also shown that HDAC11 is a critical regulator of the body’s overall metabolism. HDAC11 KO mice exhibit higher body temperatures than wild type (WT) controls both at room temperature (22°C) and during a 24-hour cold challenge (4°C), which is correlated with higher metabolic rate and oxygen consumption (26, 75). Importantly, HDAC11-deficient mice show alleviated hypercholesterolemia, hepatic steatosis and liver damage (26, 75).

Altogether, these results suggest that HDAC11 is a new metabolic regulator, lowering its levels might improve cells’ ability to adapt to an elevated energy requirement under stressful circumstances. Furthermore, as a result of the considerable rise in metabolic rate and oxygen consumption caused by HDAC11 inhibition, there is an increase in lipid oxidation and energy expenditure. Therefore, HDAC11 would be a prospective therapeutic target for obesity and the related metabolic effects.

**HDAC11 in diabetes**

**Diabetes**

Diabetes is a metabolic, chronic, multisystem disease and chronic exposure to hyperglycemia eventually leads to multiple complications, such as diabetic nephropathy, cardiovascular disease, retinopathy and neuropathy with considerable impact on the quality of life and overall life expectancy.

HDAC11 is essential for preserving insulin sensitivity and glucose homeostasis. In mice fed with high fat diet (HFD), HDAC11 deletion significantly decreases blood insulin levels, stabilizes blood glucose, and greatly reduces blood glucose levels after insulin challenge, thereby enhancing glucose tolerance and ameliorating diabetes (75). In addition, adiponectin significantly increases in HDAC11 KO mice (91). By using adiponectin-knockout mice fed on a HFD or either regular chow, it has been demonstrated that adiponectin-deficient mice fed on a HFD exhibit higher body temperatures than wild type (WT) controls and exhibit higher body temperatures than wild type (WT) controls, which is consistent with previous observations in skeletal muscle tissue (14).

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**Diabetic nephropathy**

Diabetic nephropathy (DN) is a serious complication of diabetes. It presents as localized kidney inflammation and fibrosis that lead to structural remodeling (92–94).

Although there is no report about the role of HDAC11 in DN so far, HDAC11 is vital in the response to renal inflammation and fibrosis. Plasminogen agonist inhibitor type 1, a physiological inhibitor of fibrinolysis (PAI-1), is elevated in DN (95). Excess PAI-1 lead to the accumulation of extracellular matrix proteins, whereas PAI-1 deficiency protected the kidney from injury-induced fibrosis (96). In a murine model of renal ischemia/reperfusion (I/R), increased testosterone can decrease the ability of HDAC11 to bind to PAI-1 promoter, leading to increased histone 3 acetylation and PAI-1 expression and accelerated I/R-induced renal injury (46, 47). Moreover, HDAC11 expression are increased in the kidneys in animal
models of renal fibrosis induced by unilateral ureteral obstruction and angiotensin II by suppressing Kruppel-like factor 15, an anti-fibrogenic factor (97). Since renal inflammation and fibrosis contribute to the pathogenesis of DN, it is speculated that HDAC11 would also play a role in the development of DN. Further studies are needed to address this issue.

**Diabetic cardiopathy**

Type 2 diabetes and cardiovascular diseases are predisposed to by obesity (98). Increased body weight can, in fact, cause metabolic changes in cardiomyocytes that switch them from processing fatty acids to sugar, which adds to lipid storage in the pericardium and, as a severe consequence of type 2 diabetes, causes myocardial infarction (99). Interestingly, inhibition of HDAC11 activity could prevent or ameliorate diabetic cardiomyopathy. In apoE mice fed with HFD, atherosclerosis and blood lipid levels have recently been shown to be alleviated by HDAC11-AS1. HDAC11-AS1 improves lipoprotein lipase (LPL), a crucial rate-limiting enzyme involved in triglyceride hydrolysis, via controlling adiponectin histone deacetylation both in vitro and in vivo (100). Another study shows that suppression of HDAC11 enhances the prevention of pyroptosis in human umbilical vein endothelial cells (HUVECs) triggered by TNF-α, indicating that vascular endothelial pyroptosis might be prevented through downregulation of HDAC11 related signaling pathways in atherosclerosis (AS) (101). In addition, a fructose injury-induced mouse model of diabetic heart failure that lacks HDAC11 had lower levels of apoptosis, dyslipidemia, inflammation, and oxidative stress (102). HDAC11 has also been suggested to be an essential regulator in heart failure (103). Therefore, HDAC11 contributes to the pathogenesis of diabetic Cardiopathy.

**HDAC11 in metabolic inflammation**

Metabolic disorders are closely associated with chronic mild inflammation (104–106). Most obese people develop inflammation in their adipose tissue, like chronically damaged tissue, along with immune cell remodeling and infiltration. During the early phases of adipose swelling and the progression of chronic obesity, inflammation is induced, and the immune system is irreversibly changed into a proinflammatory phenotype (107). Changes in adipose tissue function are related to obesity, and the loss of adipocytes also contributes to chronic mild inflammation (104). The regulating function of HDAC11 in metabolic inflammation is crucial.

HDAC11 regulates metabolic inflammation primarily through the control of the IL-10 released by antigen-presenting cells (APCs) (28). Inhibition of HDAC11 causes macrophages to express more IL-10, whereas overexpression of HDAC11 reduces IL-10 expression (108, 109). In addition, HDAC11 overexpression in APCs is efficient in reactivating tolerant T cell responses and CD4+ T cells specific for antigens. And APC had the reverse result when HDAC11 expression was absent (33). Conversely, suppression of HDAC11 resulted in impaired antigen-specific expression, increased IL-10 expression, downregulated IL-12 expression and immune cell expression (such as myeloid-derived suppressor cells, neutrophils, and T cells), leading to immune tolerance (110, 111). In addition, mutated HDAC11 transcripts boosted the synthesis of IL-17 and TNF in the supernatants of HL cells (112). Moreover, liver immune tolerance is regulated by HDAC11 through TNF-α, interferon-γ, IL-2, and IL-4 (80, 90, 113–120).

**HDAC11 inhibitors**

Most HDACi are pan-HDACi that target multiple HDACs with different nanomolar potency. Zinc-dependent catalytic processes are shared by Classes I, II, and IV HDACs. Many pan-HDACi have been synthesized, including Aes-135 (121), AR-42, belinostat (PXD101, PXI05684), fimepinostat (CUDC-907) (9), FT895 (122), M344(D237, MS344), Panobinostat (LBHS85, NVP-LBH859), pracinostat (SB939), dacinostat, quisinostat (NJ-2648185), trichostatin A (TSA), vorinostat (34) (SAHA, MK0683), mocetinostat (123)(MGCD0103), tucidinostat (Chimade, HBI-8000, CS055), trapoxin A (124) (TpxA, C34H42N4O6), garcinol (125), romidepsin (126). Recently, Compound 8, a newly designed novel HDAC6 selective inhibitor with 2-mercaptoquinazolinone as the Cap Moiety, has displayed stronger inhibition activity against HDAC11 than Belinostat (127). The toxicity caused by general inhibition of HDACs restricts their potential utility. Among the pan-HDAC inhibitors, garcinol shows more HDAC11 selectivity and efficiency than other HDACs (125). The deacetylase and demethylase activities of HDAC11 are also suggested to be effectively inhibited by Fimepinostat (9). At concentrations of 0.02, 0.2, and 2μM, respectively, Suberoylanilide hydroxamic acid (SAHA) could suppress 10, 50, and 90% of HDAC11 activity (34). Additionally, it has been noted that trichostatin A (TSA) and romidepsin have a nanomolar potency toward HDAC11 (126). However, pracinostat, dacinostat, mocetinostat, quisinostin, trapoxin A, and trichostatin A have been found not as efficient in inhibiting HDAC11 deacetylation activity as reported before (9). Unexpectedly, butyrate, valproate, SAHA, and TSA could trigger myeloid cells to express HDAC11 (128). And low doses of MS275 have been found to show agonistic actions (129).

Elevenostat (JB3-22) (21, 24), SIS7, SIS17 (130), and FT895 (122) are selective HDAC11 inhibitors. Nevertheless, the
inhibitory capacity of elevenostat (JB3-22) on myristoylated and acetylated peptidic derivatives is extremely poor (9). To date, the HDAC11 inhibitors that are considered to be the most potent and selective are SIS17 and FT895. SIS17 is better than FT895 and SIS7 in terms of its cell permeability and metabolic stability (60), while FT895, SIS17, and SIS7 can all inhibit HDAC11’s demyristoylase activity (130).

Though several HDAC11 inhibitors have been developed, only FT895 (85, 122), romidepsin (131), and quisinostat (97, 131, 132) have been reported to be utilized in animal studies. To explore the pharmacokinetic properties of FT895, it was injected to male Balb/c nude mice via i.v. at 1 mg/kg or i.p. at 5 mg/kg. After i.v. dosing, with a t1/2 of 9.4 hours, FT895 exhibits a high volume of distribution and a moderate clearance (42 mL/min/kg). In comparison, FT895 dosed intravenously has enhanced exposure, a similar half-life (10.2 h), a bioavailability of 81%, and sustains free drug levels above the cellular half-maximal inhibitory concentration (IC50) for up to 4 hours (122). Quisinostat (10 mg/kg Monday, Wednesday, and Friday) and romidepsin (0.3 mg/kg, 1 mg/kg, or 3 mg/kg Monday, Friday) were administered intraperitoneally (i.p.) for one week to tumor-bearing athymic NOD.Cg-Prkdscid Il2rgtm1Wjl/SzJ (NSG) mice. Romidepsin has unacceptable toxicity at 3 mg/kg; anemia and aspartate aminotransferase elevations are a result of 1 mg/kg dosing; without causing considerable weight loss (>20%) or neurotoxicity, both 0.3 mg/kg and 1 mg/kg are tolerated. Treatment with quisinostat (10 mg/kg Monday, Wednesday, Friday) shows no systemic toxicity (131). Similarly, in BALB/c nude mice and NOD/SCID mice, quisinostat (3 and 10 mg/kg/day, i.p) has been used to treat tongue and esophageal squamous cell carcinoma (132, 133) and malaria (134). Romidepsin is also used in C57BL/6 (0.03 mg/kg twice a week) (135, 136) and BALB/C (1 mg/kg/2 days) (137) mice for cancer treatment. Therefore, FT895, quisinostat and romidepsin are tolerable and safe in vivo.

In addition, quisinostat and romidepsin have been tested in clinical trials. The maximum tolerable dose of quisinostat for the treatment of cancer in patients is 10 mg administered orally three times per week along with bortezomib and dexamethasone, with median progression-free survival (PFS) 8.2 months and median duration of response 9.4 months (138). Combined with 5-azacytidine (AZA), romidepsin (14 mg/m², day 8, 15,22, per 35 days, IV) is used to treat peripheral T-cell lymphomas (PTCL) with the overall survival not met (at a median follow-up of 13.5 months), and the median progression-free survival (PFS) 8.0 months, duration of response 20.3 months (139). Romidepsin has also been reported to treat HIV-1-infected patients with a 5 mg/m² dosage as a 4 hour infusion (140).

Thus, taking effectiveness, selectivity, toxicity, half-life, tolerance and survivability in vivo into consideration, FT895 exhibits pharmacokinetic properties that are reasonable in vivo research, and the most significant potential to advance into clinical trials.

Conclusion and perspectives

The incidence of metabolic disorders is increasing worldwide, ranging from obesity to type 2 diabetes, leading to complications in the heart, kidney, retina, bone, skin and foot.
HDAC11 participates in many aspects of metabolic diseases. HDAC11 mediates obesity and metabolic syndrome by regulating adipogenesis, increasing energy consumption and promoting lipid metabolism. It also contributes to adipose tissue inflammation by regulating immune responses and insulin resistance. HDAC11 was shown to have inhibitory roles in the development of diabetic cardiovascular disease. (Figure 1) In addition, a recent study shows that HDAC11 contributes to osteoporosis susceptibility and reduced peak bone mass through a mechanism of 11β-HSD2’s low-functional programming. This is triggered by corticosterone through GR/HDAC11 signaling, which amplifies the effect of corticosterone on inhibiting the function of BMSCs in osteogenesis (141, 142). However, studies on diabetic osteoporosis, lipoid nephrosis, fatty liver disease and obesity cardiomyopathy are still lacking. As such, further research on the effect of HDAC11 on metabolic diseases is required.

Studies listed in Table 1 have shown the well-tolerated HDAC11 global deletion in mice, suggesting that its inhibition or depletion is without apparent side effects. Currently, toxicity and safe doses of HDAC11 inhibitors are far from clear and none of the inhibitors have been used in patients with metabolic disorders. Thus, more studies on the safe dosage and toxicity of HDAC11 inhibitors in animal models are needed before advancing them to human clinical trials. In addition, development of more effective HDAC11 inhibitors with enhanced selectivity is worth investigating.

### Author contributions

HC drafted the article. The manuscript was edited by SZ, CX, and QC. After reviewing the manuscript, all authors gave their approval for publication.

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### Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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et al. Histone deactylase gene expression profiles in kidney ischemia- and reperfusion-induced pae-1 expression and injury. Am J Physiol Renal Physiol (2010) 400(3):284–94. doi: 10.1152/jphysiol.00531.2009

Baugi TK, Sharma SS, Ma L, Pledger WJ. Proliferative status regulates Hdac11 mrna abundance in nontransformed fibroblasts. Cell Cycle (Georgetown) (2013) 12(21):3443–41. doi:10.4161/cc.26433

Byun SK, An TH, Son MJ, Lee DS, Kang HS, Lee EW, et al. Hdac11 inhibits myoblast differentiation through repression of myod-dependent transcription. Molecules (Cell) (2017) 40(9):667–76. doi: 10.14348/molecules.2017.0116

Blix NC, Fauldster BK, Astfeld K, Leihch R, Scherring J, Spencer E, et al. Class ii and iv hdacs function as inhibitors of osteoclast differentiation. PLoS One (2017) 12(9):e0185441. doi:10.1371/journal.pone.0185441

Yue L, Sharma V, Horvat NP, Akuffo AA, Beatty MS, Murdun C, et al. Hdac11 deficiency disrupts oncoprotein-induced hematopoiesis in myeoproliferative neoplasms. Blood (2020) 135(3):191–207. doi:10.1182/blood.2019095326

Zhang R, Ge J. Proteinase-activated receptor-2 modulates ve-cadherin expression to affect human vascular endothelial barrier function. J Cell Biochem (2017) 118(12):4857–93. doi:10.1002/jcb.26213

Zhou B, Zeng S, Li N, Yu L, Yang G, Yang Y, et al. Angiogenic factor with G patch and fha domains 1 is a novel regulator of vascular injury. Arteriosclerosis Thrombosis Vasc Biol (2017) 37(4):675–84. doi:10.1161/arterba.117.308992

Liu FH, Li SS, Li XX, Wang S, Li MG, Guan L, et al. Vitamin D3 induces vitamin d receptor and Hdac11 binding to relieve the promoter of the tight junction function. Oncotarget (2017) 8(55):58781–9. doi:10.18632/oncotarget.17692

Mrgu M, Sanders PW. Beware the low Hdac11. Males at risk for ischemic kidney injury. Am J Physiol Renal Physiol (2013) 305(7):F973–4. doi:10.1152/ajprenal.00015.2013

Kim II, Jung KJ, Jang HS, Park KM. Gender-specific role of Hdac11 in kidney ischemia and expression induced pae-1 expression and injury. Am J Physiol Renal Physiol (2013) 305(1):F61–70. doi:10.1152/ajprenal.00015.2013

Sillesen M, Bambakides T, Dekker SE, Fabricius R, Svenningsen P, Bruhn PJ, et al. Histone deacetylase gene expression profiles are associated with outcomes in blunt trauma patients. J Trauma Acute Care Surg (2016) 80(1):26–32. doi:10.1097/TA.0000000000000896

Klieser E, Urbs A, Stätter S, Primavesi F, Joger T, Dinnewitzer A, et al. Comprehensive immunohistochemical analysis of histone deacetylases in pancreatic neuroendocrine tumors: Hdac5 as a predictor of poor clinical outcome. Hum Pathol (2017) 65:41–52. doi:10.1016/j.humpath.2017.02.009

Shi Y, Fan S, Wu M, Zuo Z, Li X, Jang I, et al. Yhdfl1 links hypoxia adaptation and non-small cell lung cancer progression. Nat Commun (2019) 10(1):4992. doi:10.1038/s41467-018-12801-6

Leslie PL, Chao YL, Tsai YH, Ghosh SK, Porrello R, Van Swearingen AE, et al. Histone deacetylase 11 inhibition promotes breast cancer metastasis from lymph nodes. Nat Commun (2019) 10(1):4192. doi:10.1038/s41467-019-12225-2

Denker C, Leslack C, Tutt A, von Minckwitz G. Molecular alterations in triple-negative breast cancer: the road to new treatment strategies. Lancet (London Engl) (2017) 389(10078):2430–42. doi:10.1016/S0140-6736(16)32454-0

van Schaijik B, Davis PF, Wickremesekera AC, Tan ST, Itinteang T. Subcellular localisation of the stem cell markers Oct4, Sox2, nanog, Klf4 and c-myc in cancer: A review. J Clin Pathol (2018) 71(8):88–91. doi:10.1136/jclinpath-2017-204815

Bora-Singhal N, Mohankumar D, Saha B, Collin CM, Lee JY, Martin MW, et al. Novel Hdap11 inhibitors suppress lung adenocarcinoma stem cell self-renewal and overcome drug resistance by suppressing Sox2. Sci Rep (2020) 10(1):4722. doi:10.1038/s41598-020-61995-6

Dallavalle S, Musso L, Cincinelli R, Darwiche N, Gervasoni S, Vitali G, et al. Antitumor activity of novel Pola1-Hdac11 dual inhibitors. Eur J Med Chem (2022) 228:113971. doi:10.1016/j.ejmech.2021.113971

Liu SS, Wu F, Jin YM, Chang WX, Xu TM. Hdap11: A rising star in epigenetics. Biomolecules pharmaocore (2020) 131:110607. doi:10.1016/j.biomolph.2020.110607

Freese K, Seitz T, Dietrich P, Lee SML, Thaler WE, Beschorner A, et al. Histone deacetylase expressions in hepatocellular carcinoma and functional effects of histone deacetylase inhibitors on liver cancer cells in vitro. Cancers (2019) 11(10):1587. doi:10.3390/cancers11101587

Gong D, Zeng Z, Yi F, Wu J. Inhibition of histone deacetylase 11 promotes human liver cancer cell apoptosis. Am J Trans Ret (2019) 20112:983–90.
83. Zhou Y, Peng J, Jiang S. Role of histone acetyltransferases and histone deacetylases in adipocyte differentiation and adipogenesis. Eur J Cell Biol (2014) 93 (4):170–7. doi: 10.1016/j.ejcb.2014.03.001

84. Yang H, Chen L, Sun Q, Yao F, Muhammad S, Sun C. The role of Hdac1 in obesity-related metabolic disorders: A critical review. J Cell Physiol (2021) 236 (8):5582–91. doi: 10.1002/jcp.30286

85. Bagchi RA, Robinson EL, Hu T, Cao J, Hong YJ, Tharp CA, et al. (2022). Reversible lysine fatty acylation of an anchoring protein mediates adipocyte adrenergic signaling, in: Proceedings of the National Academy of Sciences of the United States of America 119. doi: 10.1073/pnas.2109781119

86. Gesta S, Tseng YH, Kuhn CR. Developmental origin of fat: Tracking obesity to its source. J Cell Physiol (2017) 232(12):9209–13. doi: 10.1002/jcp.26880

87. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest (2017) 127(1):1–4. doi: 10.1172/jci92035

88. Georgopoulos K. From immunity to tolerance through hdc. Nat Immunol (2009) 10(1):13–4. doi: 10.1038/ni0913

89. Wang X, Wu Y, Jiao J, Huang Q. Mycobacterium tuberculosis infection induces il-10 gene expression by disturbing histone deacetylase 6 and histone deacetylase 11 equilibrium in macrophages. Tuberculosis (Edinburgh Scotland) (2018) 108:118–23. doi: 10.1016/j.tube.2017.11.008

90. Wang L, Tao R, Hancock WW. Using histone deacetylase inhibitors to enhance Foxp3 (+) regulatory T-cell function and induce allograft tolerance. Immunol Cell Biol (2009) 87(3):195–202. doi: 10.1073/iscb.2008.10.9

91. Tao R, de Zeeen EF, Okazaki E, Chen W, Lang P, Purmort FM, et al. Deacetylase inhibition promotes the generation and function of regulatory T cells. Nat Med (2013) 19(1):129–307. doi: 10.1038/nm1652

92. Bugilo D, Khaskhey NM, Voo KS, Martinez-Valdez H, Liu Y, Younes A. Hdcα plays an essential role in regulating Oxl0 ligand expression in Hodgkin lymphoma. Blood (2011) 117(10):2686–92. doi: 10.1182/blood-2010-03-303781

93. Lian ZR, Xu YF, Wang XB, Geng JP, Liu ZJ. Suppression of histone deacetylase 11 promotes expression of il-10 in kuffer cells and induces tolerance following orthotopic liver transplantation in rats. J Surg Res (2012) 174(2):359–68. doi: 10.1016/j.jss.2012.03.035

94. Luo XQ, Shao JB, Xie RD, Zeng L, Li XQ, Qiu SQ, et al. Micro rna-19a interferes with il-10 expression in peripheral dendritic cells of patients with nasal polypsis. Oncotarget (2017) 8(30):48915–21. doi: 10.18632/oncotarget.16555

95. Ramos-Nino ME. The role of chronic inflammation in obesity-associated cancers. ISRN Oncol (2013) 2013:697521. doi: 10.1155/2013/697521

96. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell (2014) 156(1–2):20–44. doi: 10.1016/j.cell.2013.12.012

97. Santos CR, Schulze A. Lipid metabolism in cancer. FEBS J (2012) 279 (15):2610–23. doi: 10.1111/j.1742-4658.2012.08644.x

98. Scott I. Regulation of cellular homoeostasis by reversible lysine acetylation. Essays Biochem (2012) 52:13–22. doi: 10.1042/bse0520013

99. Selvi RB, Kondu TK. Reversible acetylation of chromatin: Implication in regulation of gene expression, disease and therapeutics. Biotechnol J (2009) 4 (3):375–90. doi: 10.1002/biot.200900302

100. Shalda Y, Vaisière T, Herceg Z. Histone acetylation and chromatin signature in stem cell identity and cancer. Mutat Res (2008) 637(1–2):1–15. doi: 10.1016/j.mrfmmm.2007.07.012

101. Shouksmith AE, Shah F, Grimard ML, Gavel [M, Rosaf YS, Geletu M, et al. Identification and characterization of aeo-135, a hydroxamic acid-based hdac inhibitor that prolongs survival in an orthotopic mouse model of pancreatic cancer. J medicinal Chem (2019) 62(25):6515–61. doi: 10.1021/acs.jmedchem.9b01957

102. Martin MW, Lee JY, Lancia DRJr., Ng PY, Han B, Thomason JR, et al. Discovery of novel n-Hydroxy-2-Arylisoindoline-4-Carboxamides as potent and selective inhibitors of histone deacetylase 6 selective inhibitors with 2-mercaptopquinazolinone as the cap moiety. ACS Chem Biol (2021) 16:2143–51. doi: 10.1021/acschembio.0c00719

103. Kutil Z, Mikesova I, Kopecka M, Meleshin M, Nova M, et al. Continuous activity assay for Hdac11 enabling reevaluation of hdac inhibitors. ACS Chem Biol (2022) 17:2024–35. doi: 10.1021/acschembio.2b00432

104. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and cancer mechanisms: Tumor microenvironment and inflammation. J Clin Oncol (2014) 32(35):4270–6. doi: 10.1200/jco.2014.67.4283
129. Tian Y, Lv W, Li X, Wang C, Wang D, Wang PG, et al. Stabilizing Hdac11 with saha to assay slow-binding benzamide inhibitors. *Bioorganic medicinal Chem Lett* (2017) 27(13):2943–5. doi:10.1016/bmcl.2017.05.004

130. Son SI, Cao J, Zhu CL, Miller SP, Lin H. Activity-guided design of Hdac11-specific inhibitors. *ACS Chem Biol* (2019) 14(7):1393–7. doi: 10.1021/acschembio.9b00292

131. Vitanna NA, Biery MC, Myers C, Ferguson E, Zheng Y, Giraud EL, et al. Optimal therapeutic targeting by hdac inhibition in biopsy-derived treatment-naive diffuse midline glioma models. *Neuro-oncology* (2021) 23(3):376–86. doi: 10.1093/neuonc/noaa249

132. Wang X, Liu K, Gong H, Li D, Chu W, Zhao D, et al. Death by histone deacetylase inhibitor quisinostat in tongue squamous cell carcinoma via apoptosis, pyroptosis, and ferroptosis. *Toxicol Appl Pharmacol* (2021) 410:115363. doi: 10.1016/j.taap.2020.115363

133. Zhong L, Zhou S, Tong R, Shi J, Bai L, Zhu Y, et al. Preclinical assessment of histone deacetylase inhibitor quisinostat as a therapeutic agent against esophageal squamous cell carcinoma. *Investigational New Drugs* (2019) 37(4):616–24. doi: 10.1007/s10637-018-0651-4

134. Li R, Ling D, Tang T, Huang Z, Wang M, Ding Y, et al. Discovery of novel plasmidum fallopium Hdad1 inhibitors with dual-stage antimalarial potency and improved safety based on the clinical anticancer drug candidate quisinostat. *J medicinal Chem* (2021) 64(4):2254–71. doi: 10.1021/acs.jmedchem.0c02104

135. Afaloniati H, Poutahidis T, Giakoustidis A, Gargavanis A, Giakoustidis D, Angelopoulou K. Romidepsin hepatocellular carcinoma suppression in mice is associated with deregulated gene expression of bone morphogenetic protein and notch signaling pathway components. *Cell Biol Rep* (2021) 48(1):551–70. doi: 10.1007/s10633-020-06089-9

136. Afaloniati H, Angelopoudou K, Giakoustidis A, Hardas A, Peftogas A, Makledou K, et al. Hdac1/2 inhibitor romidepsin suppresses den-induced hepatocellular carcinogenesis in mice. *Oncotar Ther* (2020) 13:5575–88. doi: 10.2147/ott.252023

137. Shi Y, Fu Y, Zhang X, Zhao G, Yao Y, Guo Y, et al. Romidepsin (Fk228) regulates the expression of the immune checkpoint ligand pd-L1 and suppresses cellular immune functions in colon cancer. *Cancer immunol immunother* (2021) 70(1):61–73. doi: 10.1007/s00262-020-02653-1

138. Moreau P, Facon T, Touzeau C, Benboubker L, Delain M, Badamo-Dotzis J, et al. Quisinostat, bortezomib, and dexamethasone combination therapy for relapsed multiple myeloma. *Leukemia lymphoma* (2016) 57(7):1546–59. doi: 10.1007/10428194.2015.111761

139. Falchi L, Ma H, Klein S, Lue JK, Montanari F, Marchi E, et al. Combined oral 5-azacytidine and romidepsin are highly effective in patients with ptd. A multicenter phase 2 study. *Blood* (2021) 137(16):2161–70. doi: 10.1182/blood.2020009004

140. Moltò J, Rosás-Umbert M, Miranda C, Manzardo C, Puertas MC, Ruiz-Riol M, et al. Pharmacokinetic/Pharmacodynamic analysis of romidepsin used as an hiv latency reversing agent. *J antimicrobial chemother* (2021) 76(4):1032–40. doi: 10.1093/jac/dkaa523

141. Xiao H, Wu Z, Li B, Shangguan Y, Stoltz JF, Magdalou J, et al. The low-expression programming of 11β-Hsd2 mediates osteoporosis susceptibility induced by prenatal caffeine exposure in Male offspring rats. *Br J Pharmacol* (2020) 177(20):4683–700. doi: 10.1111/bph.15225

142. Wu Z, Wen Y, Xiao H, Zhu J, Li B, Shangguan Y, et al. 11β-hydroxysteroid dehydrogenase 2: A key mediator of high susceptibility to osteoporosis in offspring after prenatal dexamethasone exposure. *Pharmacol Res* (2022) 175:105990. doi: 10.1016/j.phrs.2021.105990