Name of journal: World Journal of Stem Cells

ESPS Manuscript NO: 16367

Columns: Minireviews

**Histone deacetylases and** **cardiovascular cell lineage commitment**

Yang JY *et al.* HDACs and differentiation

Jun-Yao Yang, Qian Wang, Wen Wang, Ling-Fang Zeng

**Jun-Yao Yang, Ling-Fang Zeng,** Cardiovascular Division, King’s College London, SE5 9NU London, United Kingdom

**Jun-Yao Yang, Qian Wang,** Laboratory Medicine Centre, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong Province, China

**Jun-Yao Yang, Wen Wang,** School of Engineering and Materials Science, Queen Mary, University of London, E1 4NS London, United Kingdom

**Author contributions:** All authors contributed to this manuscript.

**Supported by** British Heart Foundation project, No. PG13-63-30419.

**Conflict-of-interest:** None of the authors have interest of conflicts.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to:** **Dr. Ling-Fang Zeng,** Cardiovascular Division, King’s College London, Strand, SE5 9NU London, United Kingdom. lingfang.zeng@kcl.ac.uk

**Telephone:** +44-20-78485286

**Fax:** +44-20-78485296

**Received:** January 13, 2015

**Peer-review started:** January 16, 2015

**First decision:** February 7, 2015

**Revised:** February 14, 2015

**Accepted:** April 1, 2015

**Article in press:**

**Published online:**

**Abstract**

Cardiovascular diseases (CVDs), which include all diseases of the heart and circulation system, are the leading cause of deaths on the globally. During the development of CVDs, choric inflammatory, lipid metabolism disorder and endothelial dysfunction are widely recognized risk factors. Recently, the new treatment for CVDs that designed to regenerate the damaged myocardium and injured vascular endothelium and improve recovery by the use of stem cells, attracts more and more public attention. Histone deacetylases (HDACs) are a family of enzymes that remove acetyl groups from lysine residues of histone proteins allowing the histones to wrap the DNA more tightly and commonly known as epigenetic regulators of gene transcription. HDACs play indispensable roles in nearly all biological processes, such as transcriptional regulation, cell cycle progression and developmental events, and have originally shown to be involved in cancer and neurological diseases. HDACs are also found to play crucial roles in cardiovascular diseases by modulating vascular cell homeostasis (e.g. proliferation, migration, and apoptosis of both ECs and SMCs). This review focuses on the roles of different members of HDACs and HDAC inhibitors (HDACi) on stem cell/ progenitor cell differentiation toward vascular cell lineages (endothelial cells, smooth muscle cells and Cardiomyocytes) and its potential therapeutics.

**Key words:** Histone deacetylases; Stem cell; Endothelial cell; Smooth muscle cell; Cardiovascular diseases

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Stem cell differentiation toward vascular cell lineages is an area of important active research at present. Histone deacetylases (HDACs) are found to play important roles in cardiovascular diseases. Through modulating the homeostasis of acetylation status in histone and non-histone proteins and regulating grow factor activities, HDACs participate in stem cell differentiation and vascular cell homeostasis. In this review we provide an update on the roles of HDACs and HDAC inhibitors (HDACi) on stem cell differentiation toward vascular cell lineages.

Yang JY, Wang Q, Wang W, Zeng LF. Histone deacetylases and cardiovascular cell lineage commitment. *World J Stem Cells* 2015; In press

**INTRODUCTION**

Cardiovascular diseases (CVDs) are the number one killer of human beings globally, which is a class of disorders of the heart and blood vessels. CVDs include all diseases of the heart and circulation system, including coronary heart disease, angina, heart attack, congenital heart disease and stroke. Coronary heart disease (angina and heart attack) and stroke may be caused by the same problem – atherosclerosis[[1](#_ENREF_1)].

Atherosclerosis is a chronic inflammation process marked with thickened artery wall as a result of invasion and accumulation of fatty material (called atheroma) inside arteries. During this process, the endothelium, as the major regulator of vascular homeostasis, shows a number of vasoprotective effects, such as vasodilation, suppression of smooth muscle cell growth, and inhibition of inflammatory responses[[2](#_ENREF_2)]. Accumulating evidence suggests that endothelial dysfunction is an early marker for atherosclerosis and can be detected and repaired prior to structural changes within the vessel wall[[3](#_ENREF_3)].

Normally the repairing treatments for injured vascular endothelium include physical exercise and drug treatments aimed at reducing cardiovascular risk factors, such as lowering cholesterol, antihypertensive therapy, smoking cessation and some regulator replacement strategies such as angiotensin-converting enzyme 2 inhibitor therapy, estrogen replacement therapy in postmenopausal women, supplementation with folic acid[[4](#_ENREF_4)]. Recently, a new therapeutic strategy, that designed to regenerate the damaged myocardium and injured vascular endothelium and improve recovery by the use of stem cells, attracts more and more public attention[[5](#_ENREF_5)]. Till now, there has not established a specific cell type to serve best the treatment of CVDs. Many stem cell types such as embryonic stem cells (ESCs), adult stem cells and induced pluripotent stem cells have the ability to differentiate into vascular cell lineages in vitro.

Stem cell therapy is based on the stem cell characters, the potential to differentiate into specific cell types under different stimulation and proliferate to replace damaged cells with healthy functional ones[[6](#_ENREF_6)]. Like any biological process, the differentiation of stem cell involves gene expression reprogramming via histone acetylation homeostasis mediated chromatin remodelling. Histone deacetylases (HDACs) are key components of the regulating system that controls histone acetylation homeostasis. HDACs play an essential role in multiple biology processes regulating cell survival, proliferation and apoptosis via histone and non-histone protein modification. Accumulating evidence showed that HDACs play an important role in vascular remodelling[[7](#_ENREF_7)].

**HDACS**

Histone acetylation is a reversible process characterized by histone and non-histone protein acetyl-transferase transferring the acetyl moiety from acetyl co-enzyme A to lysine residues. HDACs are a family of enzymes that remove acetyl groups from the N-acetylated lysine residues on histones[[8](#_ENREF_8)] and non-histone proteins. Histone acetylation/ deacetylation alters chromosome structure and affects transcription factors access to DNA[[9](#_ENREF_9)]. Accumulating evidence indicates that HDACs play a fundamental role in transcriptional regulation, cell cycle progression, and contribute to developmental events.

Mammalian genome encodes 18 HDACs, which can be grouped into four classes based on the homology with yeast histone deacetylases[[10](#_ENREF_10)]. All members share a highly conserved deacetylase domain but differ in structure, subcellular localization and expression pattern, which results in different cellular functions[[11](#_ENREF_11)]. Class I HDACs (homologous to yeast Rpd3) comprise of HDAC1, -2, -3 and -8, which are widely expressed in many human tissues and cell lines. Among them both HDAC3 and HDAC8 can shuttle between the cytosol and the nucleus, while HDAC1 and HDAC2 are exclusively located in nucleus[[12](#_ENREF_12),[13](#_ENREF_13)]. The deacetylation of histones to repress gene transcription is the main function of class I HDACs. Class I HDACs form large multi-subunit complex that associates with transcription factors and other chromatin modifiers, except HDAC8 whose function is not clearly clarified[[14](#_ENREF_14)]. In mammals, HDAC1 and -2 can bind to each other forming the catalytic core of three different complexes: Sin3, nucleosome remodelling deacetylase and corepressor of RE1-silencing transcription factor. HDAC3 can form two different multi-protein complexes, nuclear receptor corepressor and silencing mediator of retinoic acid and thyroid hormone receptors. Class I HDACs are mainly found in such nuclear complexes. Furthermore, the association with several different proteins show an essential role in regulating their activity, which is highly pronounced in developmental processes that requires a global modulation of transcriptional programmes. With the exception of HDAC8, knockout of class I HDACs in mice have indeed resulted in embryonic lethality[[15](#_ENREF_15)].

Class II HDACs can be divided into two sub-class groups. Class IIa members include HDAC4, -5, -7, -9, while class IIb comprises of HDAC6 and -10. Class II HDACs differ from Class I mainly for their tissue-specific expression pattern and the considerable lower deacetylase activity. Besides, their length (almost the double of Class I HDACs) and cellular localization are all different. Class II HDACs can shuttle between nucleus and cytoplasm. Class IIa HDACs have conserved binding sites for the transcription factor myocyte enhancer factor 2 and the chaperone protein 14-3-3, which help HDACs shuttle from the nucleus to the cytoplasm. The nuclear-cytoplasm shuttling and occurrence of post-translational modification such as phosphorylation, indicates their primary role as signal transducers in numerous tissues during development and disease[[16](#_ENREF_16)].

Class IIb family includes HDAC6 and HDAC10. HDAC10 presents a leucin-rich domain at the C-terminal. Recent reports showed HDAC10 might be upregulated on human myeloma cell lines[[17](#_ENREF_17)]. DAC6 is different from all other HDACs, as it harbours two deacetylase domains and a C-terminal zinc finger, being the important cytoplasmic deacetylase in mammalian cells[[18](#_ENREF_18)]. Cytoskeletal proteins such as α-tubulin and cortactin, transmembrane proteins such as the interferon -α receptor, and chaperones are all targets of HDAC6[[19](#_ENREF_19),[20](#_ENREF_20)].

Class III HDACs comprises a group of protein called Sirtuins (SIRT1-7). Although they possess a deacetylase domain, they diverge from classical HDACs as their enzymatic activity requires the cofactor NAD+. This feature suggests their involvement in metabolic functions[[21](#_ENREF_21)]. DAC11 is the last discovered and the only member of Class IV HDACs[[22](#_ENREF_22)]. This review will focus on the classical HDACs, class I and II HDACs. The protein length, cellular location and potential cellular functions of these HDACs can be referred to references[[11](#_ENREF_11),[23](#_ENREF_23)].

**HDACS AND ENDOTHELIAL CELL DIFFERENTIATION**

In response to vascular injury, endothelial cell (EC) migration and proliferation contribute to the repairing of the damaged EC or denuded endothelium. Recent reports show that circulating or local resident stem/progenitor cell differentiation is also involved in this process[[24](#_ENREF_24)]. Through modulating chromatin structures and non-histone transcription factors, HDACs are involved in the gene expression reprograming in multiple biological processes such as cell-cycle, cell differentiation and survival[[25](#_ENREF_25)]. Therefore, the involvement of HDACs in EC differentiation is expected.

The first evidence came from studies with HDAC inhibitors (HDACi). HDACi decreases endothelial lineage commitment of endothelial progenitor cells[[26](#_ENREF_26),[27](#_ENREF_27)]. Rössig *et al*[[27](#_ENREF_27)] found that the suppressive effect of HDACi on EC differentiation was mediated by the down-regulation of homeobox transcription factor HoxA9, which directs the transcription of EC markers such as eNOS, VEGFR2 and VE-cadherin, suggesting that the HDAC-dependent activation of Hox-A9 is essential for EC differentiation[[27](#_ENREF_27)].

There is no direct evidence that HDAC1, 2 and 8 are involved in EC differentiation, although indirect evidence indicates that HDAC1 may suppress EC differentiation. Rajasingh *et al*[28] showed that HDACs inhibitor, trichostatin A, improved AceH3K9 and reduced HDAC1 expression in bone marrow progenitor cells, leading to differentiation into myocytes and ECs, which suggests that HDAC1 plays a suppressive role in bone marrow progenitor cell differentiation toward EC lineage[[28](#_ENREF_28)]. Different from other members within class I HDACs, accumulating evidence suggests that HDAC3 possesses a pivotal function in stem cells differentiation into ECs, which is capable of repairing the damaged endothelium. VEGF is a well-known EC differentiation inducer. Xiao *et al*[29] reported that VEGF up-regulated HDAC3 in ESC-derived Sca1+ cells. Over-expression of HDAC3 via adenoviral gene transfer increased, while trichostatin A or HDAC3 siRNA abolished VEGF-induced EC marker expression in Sca1+ cells, suggesting HDAC3 may function downstream of VEGF signal pathway[[29](#_ENREF_29)]. Our study[[29](#_ENREF_29)] and reports from Illi B[[30](#_ENREF_30)] demonstrated that laminar flow enhanced ESC-derived progenitor cell differentiation into EC lineage in an HDAC dependent manner. We found that laminar flow stabilized and activated HDAC3 through the Flk-1-PI3K-Akt pathway in a ligand independent manner, which in turn deacetylated p53, leading to p21 activation, contributing to EC differentiation[[31](#_ENREF_31)]. Similar mechanism is involved in VEGF-induced EC differentiation, in which HDAC3 modulates differentiation process via regulating non-histone proteins. Our recent study found that unconventional splicing of HDAC3 might change HDAC3 function, inducing endothelial-to-mesenchymal transition[[32](#_ENREF_32)]. These reports suggest a critical role of HDAC3 in EC fate determination.

Class II HDACs seem not directly involved in EC differentiation. Several groups tried to link class II HDACs with EC differentiation, but no solid evidence has been obtained. In Spallotta *et al*[[33](#_ENREF_33),[34](#_ENREF_34)]’s reports, nitric oxide induced a cross-talk between class I HDACs (HDAC3) and class II HDACs (HDAC4 and 7), which might contribute to the neovascularization in ischemic tissue and skin repairing[[33](#_ENREF_33),[34](#_ENREF_34)]. However, the effect of nitric oxide on EC differentiation may be largely derived from HDACs-mediated global hypoacetylation on pluripotency maintaining genes like Oct4, Nanog, KLF4, *etc.* Considering class II HDACs have only weak deacetylase activity, the histone hypoacetylation might be mainly caused by HDAC3 in the complex. Reports from other groups indicate that HDAC7 may participate in EC proliferation and cell-to-cell contact but is not involved in EC differentiation[[35](#_ENREF_35),[36](#_ENREF_36)]. A recent report from Song *et al*[[37](#_ENREF_37)] showed that AMPK activation participated in endothelial colony forming cells differentiation. During this process, HDAC5 could be phosphorylated by AMPK. However, there is no direct evidence on the involvement of HDAC5.

**HDACS AND SMOOTH MUSCLE CELL DIFFERENTIATION**

Smooth muscle cells (SMCs) are the major cellular components within vessel wall, located in the tunica media controlling the calibre of the vessel. It is widely believed that in response to vascular injury SMCs in the tunica media undergo from contractile to synthetic phenotype change, followed by the migration into the intima and proliferation, contributing to the neointima formation. However, recent reports show that stem/progenitor cell-derived SMCs play an important role in neointima formation and atherosclerosis,but the origin of the progenitor cells is controversial. Reports from Shimizu *et al*[[38](#_ENREF_38)], Han *et al*[[39](#_ENREF_39)] and Li *et al*[[40](#_ENREF_40)] support the notion that the circulating bone-marrow-derived progenitor cells contribute to SMC differentiation and neointimation formation, but reports from Hu *et al*[[41](#_ENREF_41)] and Tang *et al*[[42](#_ENREF_42)] exclude the involvement of bone marrow-derived progenitor cells. They demonstrated that SMCs in the lesion area were mainly derived from local resident progenitor cells.

HDACs play diverse roles in SMC differentiation depending on the HDAC species, stem cell source and stimulus, exerting promoting or suppressive effects. Except HDAC1, all other three members of class I HDACs are reported to be involved in SMC differentiation. In response to oxidized lipids or PDGF, HDAC2 forms a complex with Class II HDACs (HDAC4/5) to deacetylate histone H4 in SMC marker gene promoter region, thereby suppressing SMC differentiation[[43](#_ENREF_43),[44](#_ENREF_44)]. Recently, Liu*et al*[45] reported that HDAC2 exerted suppressive effect on bone marrow mesenchymal stem cells to SMCs differentiation[[45](#_ENREF_45)]. In contrast, HDAC3 and 8 may play a positive role in SMC differentiation. Loss of HDAC3 in neural crest caused deficiency of aortic arch artery SMCs in midgestation during embryonic development via down-regulation of Notch signalling, suggesting a positive regulatory role of HDAC3 in the neural crest-derived smooth muscle lineage[[46](#_ENREF_46)]. Several reports demonstrate that HDAC8 is critical for SMC differentiation, therefore HDAC8 is even regarded as a novel SMC differentiation marker[[13](#_ENREF_13),[47](#_ENREF_47),[48](#_ENREF_48)]. The involvement of class II HDACs in SMC differentiation seems restricted to HDAC4, 5 and 7. Different from the suppressive role of HDAC4 and 5 from the reports by Yoshida *et al*[[43](#_ENREF_43),[44](#_ENREF_44)], studies from Glenisson *et al*[49] revealed that HDAC4 is necessary for SMC marker expression in TGFβ1-induced myofibroblast differentiation[[49](#_ENREF_49)]. Our group found that different isoforms of HDAC7 might play opposite function in SMC differentiation. During ESC differentiation toward SMC lineage, HDAC7 mRNA underwent further splicing, which was enhanced by PDGF. The full spliced HDAC7 increased SMC marker expression through modulating the SRF-myocardin complex while the partially spliced HDAC7 decreased SMC marker expression by degrading myocyte enhancer factor 2C[[50](#_ENREF_50)].

**HDACS AND CARDIOMYOCYTES DIFFERENTIATION**

Cardiomyocytes (CMs) build the [atria](http://en.wikipedia.org/wiki/Atrium_(heart)) and [ventricles](http://en.wikipedia.org/wiki/Ventricle_(heart)) of the heart, which are critical to the proper form during the beating of the heart. So the differentiation towards CMs is a prerequisite and an essential part of heart development[[51](#_ENREF_51)].

The effect of class I HDACs on CM differentiation seems a bit controversial, especially on HDAC1. Opposite effect of HDAC1 on CM differentiation has been reported by different groups. Dovey *et al*[[52](#_ENREF_52)] reported that HDAC1 deficiency in ESCs increases CM marker expression in the embryoid bodies, suggesting a suppressive role of HDAC1 in CM differentiation[[52](#_ENREF_52)]. Lu *et al*[[53](#_ENREF_53),[54](#_ENREF_54)] also reported that HDAC1 exerted negative effect on cardiac cell differentiation from mesenchymal stem cells under a myocardial microenvironment[[53](#_ENREF_53),[54](#_ENREF_54)]. The suppressive role of HDAC1 was further supported by Liu *et al*[[55](#_ENREF_55)] as down-regulation of HDAC1 promoted cardiac cell differentiation[[55](#_ENREF_55)]. However, Hoxha *et al*[[56](#_ENREF_56),[57](#_ENREF_57)] reported that HDAC1 knockdown decreased CMs marker expression in ES and induced pluripotent stem cells, suggesting a supportive role in CMs differentiation. HDAC1 favours stem cell differentiation via turning off pluripotency genes by modulating histone acetylation and DNA methylation[[56](#_ENREF_56),[57](#_ENREF_57)]. HDAC2 may play a positive role in CM differentiation, contributing to angiotensin II-induced cardiac hypertrophy[[58](#_ENREF_58)]. In contrast, HDAC3 suppresses CM differentiation through modulating transcription factor Tbx5, preventing the pre-maturation of cardiac progenitor cells[[59](#_ENREF_59)].

Current reports revealed that Class II HDACs mainly played a suppressive role in CMs differentiation. The inhibition of HDAC4 facilitates c-kit(+) cardiac stem cells to differentiate into cardiac lineage, leading to cardiogenesis and the restoration of cardiac function in myocardial infarction mouse model[[60](#_ENREF_60)]. Chang *et al*[[61](#_ENREF_61)] reported that retention of HDAC5 in nucleus suppressed cardiac foetal gene expression and CMs hypertrophy. Gene disruption studies from Chang *et al*[[62](#_ENREF_62)] revealed that HDAC5 or 9 deficiency induced cardiac hypertrophy in mice.

Depending on the stem cell source and stimulus, different HDACs may play different roles in stem cell differentiation toward different cell lineages. HDACs and their potential roles in cardiovascular lineage commitment are summarized in Table 1. Different HDACs (HDAC1, 2, 3, 4, 5, 7, 8) play different roles in stem cell differentiation toward different cell lineages, HDACs and their potential roles in cardiovascular lineage(ECs, SMCs, CSCs) commitment are summarized in Table 1.

**HDACS INHIBITORS**

The role of HDACs in injured vessel repairing and stem/progenitor cell differentiation derived originally from investigations on HDACi, which are a large number of natural and synthetic compounds. Generally, HDACi can be divided into 4 classes according to their chemical structure: hydroxamic acids, short chain fatty acids, cyclic tetra-peptides, and benzamides[[63](#_ENREF_63)]. These HDACi share the presence of an active group targeting a three-part structure consisting of a zinc-binding group of HDACs and inhibits their enzymatic activity. Some HDACi are able to discriminate HDACs among different classes and a few of them can even inhibit a single member[[64](#_ENREF_64),[65](#_ENREF_65)]. In addition to suppress the deacetylase activity of HDACs, HDACi may exert functions in HDAC-independent way, like through SP1[[66](#_ENREF_66)]. HDACi has been shown to regulate multiple cellular processes, including cell apoptosis and survival, proliferation and growth arrest, senescence, differentiation, immunogenicity, etc. Some kinds of HDACi are used in clinical trials as therapeutic drug against cancers. Detailed information on this aspect won’t be discussed in this review.

**SUMMARY AND PERSPECTIVES**

CVDs characterized by vascular injury are one of the greatest health challenges we have been facing for decades. During the development of CVDs, HDACs play a critical role in various signal pathways by modulating vascular cell homeostasis (*e.g.*, proliferation, migration, and apoptosis of both ECs and SMCs) and stem cell differentiation towards vascular cells. HDAC3 and HDAC7 have been proved to be capable of directing stem cell differentiation towards ECs and SMCs respectively. Through modulating the homeostasis of acetylation status in histone and non-histone proteins and regulating grow factor activities, HDACs participate in stem cell differentiation and vascular cell homeostasis. Targeting HDACs activities and their inhibitors’ effect on injured vessel and heart will undoubtedly provide new therapeutic strategies for the treatment of CVDs.

**REFERENCES**

1 **Sun L**, Ma C, Liu S, Zou L, Jia D. Mitral annular tissue velocity in the diagnosis of coronary artery disease. *Eur Rev Med Pharmacol Sci* 2014; **18**: 3754-3760 [PMID: 25555863]

2 **Kinlay S**, Libby P, Ganz P. Endothelial function and coronary artery disease. *Curr Opin Lipidol* 2001; **12**: 383-389 [PMID: 11507322]

3 **Davignon J**, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation* 2004; **109**: III27-III32 [PMID: 15198963 DOI: 10.1161/01.CIR.0000131515.03336.f8]

4 **Anderson TJ**. Nitric oxide, atherosclerosis and the clinical relevance of endothelial dysfunction. *Heart Fail Rev* 2003; **8**: 71-86 [PMID: 12652161]

5 **Malgieri A**, Kantzari E, Patrizi MP, Gambardella S. Bone marrow and umbilical cord blood human mesenchymal stem cells: state of the art. *Int J Clin Exp Med* 2010; **3**: 248-269 [PMID: 21072260]

6 **Beltrami AP**, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, Kasahara H, Rota M, Musso E, Urbanek K, Leri A, Kajstura J, Nadal-Ginard B, Anversa P. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell* 2003; **114**: 763-776 [PMID: 14505575]

7 **Findeisen HM**, Gizard F, Zhao Y, Qing H, Heywood EB, Jones KL, Cohn D, Bruemmer D. Epigenetic regulation of vascular smooth muscle cell proliferation and neointima formation by histone deacetylase inhibition. *Arterioscler Thromb Vasc Biol* 2011; **31**: 851-860 [PMID: 21233448 DOI: 10.1161/ATVBAHA.110.221952]

8 **Berndsen CE**, Denu JM. Catalysis and substrate selection by histone/protein lysine acetyltransferases. *Curr Opin Struct Biol* 2008; **18**: 682-689 [PMID: 19056256 DOI: 10.1016/j.sbi.2008.11.004]

9 **Lee JH**, Hart SR, Skalnik DG. Histone deacetylase activity is required for embryonic stem cell differentiation. *Genesis* 2004; **38**: 32-38 [PMID: 14755802 DOI: 10.1002/gene.10250]

10 **Thiagalingam S**, Cheng KH, Lee HJ, Mineva N, Thiagalingam A, Ponte JF. Histone deacetylases: unique players in shaping the epigenetic histone code. *Ann N Y Acad Sci* 2003; **983**: 84-100 [PMID: 12724214]

11 **Dario U**, Yi L, Zeng LF. Roles of histone deacetylases in angiogenic cellular processes. *Current Angiogenesis* 2013; **2**: 7 Available from: URL: http: //www.ingentaconnect.com/content/ben/cag/2013/00000002/00000001/art00008

12 **Longworth MS**, Laimins LA. Histone deacetylase 3 localizes to the plasma membrane and is a substrate of Src. *Oncogene* 2006; **25**: 4495-4500 [PMID: 16532030 DOI: 10.1038/sj.onc.1209473]

13 **Waltregny D**, De Leval L, Glénisson W, Ly Tran S, North BJ, Bellahcène A, Weidle U, Verdin E, Castronovo V. Expression of histone deacetylase 8, a class I histone deacetylase, is restricted to cells showing smooth muscle differentiation in normal human tissues. *Am J Pathol* 2004; **165**: 553-564 [PMID: 15277229 DOI: 10.1016/S0002-9440(10)63320-2]

14 **Yang XJ**, Seto E. The Rpd3/Hda1 family of lysine deacetylases: from bacteria and yeast to mice and men. *Nat Rev Mol Cell Biol* 2008; **9**: 206-218 [PMID: 18292778 DOI: 10.1038/nrm2346]

15 **Haberland M**, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. *Nat Rev Genet* 2009; **10**: 32-42 [PMID: 19065135 DOI: 10.1038/nrg2485]

16 **Yang XJ**, Grégoire S. Class II histone deacetylases: from sequence to function, regulation, and clinical implication. *Mol Cell Biol* 2005; **25**: 2873-2884 [PMID: 15798178 DOI: 10.1128/MCB.25.8.2873-2884.2005]

17 **Mithraprabhu S**, Kalff A, Chow A, Khong T, Spencer A. Dysregulated Class I histone deacetylases are indicators of poor prognosis in multiple myeloma. *Epigenetics* 2014; **9**: 1511-1520 [PMID: 25482492 DOI: 10.4161/15592294.2014.983367]

18 **Guardiola AR**, Yao TP. Molecular cloning and characterization of a novel histone deacetylase HDAC10. *J Biol Chem* 2002; **277**: 3350-3356 [PMID: 11726666 DOI: 10.1074/jbc.M109861200]

19 **Dregan A**, Charlton J, Wolfe CD, Gulliford MC, Markus HS. Is sodium valproate, an HDAC inhibitor, associated with reduced risk of stroke and myocardial infarction? A nested case-control study. *Pharmacoepidemiol Drug Saf* 2014; **23**: 759-767 [PMID: 24890032 DOI: 10.1002/pds.3651]

20 **Zhang X**, Yuan Z, Zhang Y, Yong S, Salas-Burgos A, Koomen J, Olashaw N, Parsons JT, Yang XJ, Dent SR, Yao TP, Lane WS, Seto E. HDAC6 modulates cell motility by altering the acetylation level of cortactin. *Mol Cell* 2007; **27**: 197-213 [PMID: 17643370 DOI: 10.1016/j.molcel.2007.05.033]

21 **Longo VD**, Kennedy BK. Sirtuins in aging and age-related disease. *Cell* 2006; **126**: 257-268 [PMID: 16873059 DOI: 10.1016/j.cell.2006.07.002]

22 **Gao L**, Cueto MA, Asselbergs F, Atadja P. Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. *J Biol Chem* 2002; **277**: 25748-25755 [PMID: 11948178 DOI: 10.1074/jbc.M111871200]

23 **Oellerich MF**, Potente M. FOXOs and sirtuins in vascular growth, maintenance, and aging. *Circ Res* 2012; **110**: 1238-1251 [PMID: 22539757 DOI: 10.1161/CIRCRESAHA.111.246488]

24 **Rinkevich Y**, Lindau P, Ueno H, Longaker MT, Weissman IL. Germ-layer and lineage-restricted stem/progenitors regenerate the mouse digit tip. *Nature* 2011; **476**: 409-413 [PMID: 21866153 DOI: 10.1038/nature10346]

25 **Sata M**, Saiura A, Kunisato A, Tojo A, Okada S, Tokuhisa T, Hirai H, Makuuchi M, Hirata Y, Nagai R. Hematopoietic stem cells differentiate into vascular cells that participate in the pathogenesis of atherosclerosis. *Nat Med* 2002; **8**: 403-409 [PMID: 11927948 DOI: 10.1038/nm0402-403]

26 **Iordache F**, Buzila C, Constantinescu A, Andrei E, Maniu H. Histone deacetylase (HDAC) inhibitors down-regulate endothelial lineage commitment of umbilical cord blood derived endothelial progenitor cells. *Int J Mol Sci* 2012; **13**: 15074-15085 [PMID: 23203112 DOI: 10.3390/ijms131115074]

27 **Rössig L**, Urbich C, Brühl T, Dernbach E, Heeschen C, Chavakis E, Sasaki K, Aicher D, Diehl F, Seeger F, Potente M, Aicher A, Zanetta L, Dejana E, Zeiher AM, Dimmeler S. Histone deacetylase activity is essential for the expression of HoxA9 and for endothelial commitment of progenitor cells. *J Exp Med* 2005; **201**: 1825-1835 [PMID: 15928198 DOI: 10.1084/jem.20042097]

28 **Rajasingh J**, Thangavel J, Siddiqui MR, Gomes I, Gao XP, Kishore R, Malik AB. Improvement of cardiac function in mouse myocardial infarction after transplantation of epigenetically-modified bone marrow progenitor cells. *PLoS One* 2011; **6**: e22550 [PMID: 21799893 DOI: 10.1371/journal.pone.0022550]

29 **Xiao Q**, Zeng L, Zhang Z, Margariti A, Ali ZA, Channon KM, Xu Q, Hu Y. Sca-1+ progenitors derived from embryonic stem cells differentiate into endothelial cells capable of vascular repair after arterial injury. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2244-2251 [PMID: 16902164 DOI: 10.1161/01.ATV.0000240251.50215.50]

30 **Kajstura J**, Rota M, Whang B, Cascapera S, Hosoda T, Bearzi C, Nurzynska D, Kasahara H, Zias E, Bonafé M, Nadal-Ginard B, Torella D, Nascimbene A, Quaini F, Urbanek K, Leri A, Anversa P. Bone marrow cells differentiate in cardiac cell lineages after infarction independently of cell fusion. *Circ Res* 2005; **96**: 127-137 [PMID: 15569828 DOI: 10.1161/01.RES.0000151843.79801.60]

31 **Zeng L**, Xiao Q, Margariti A, Zhang Z, Zampetaki A, Patel S, Capogrossi MC, Hu Y, Xu Q. HDAC3 is crucial in shear- and VEGF-induced stem cell differentiation toward endothelial cells. *J Cell Biol* 2006; **174**: 1059-1069 [PMID: 16982804 DOI: 10.1083/jcb.200605113]

32 **Zeng L**, Wang G, Ummarino D, Margariti A, Xu Q, Xiao Q, Wang W, Zhang Z, Yin X, Mayr M, Cockerill G, Li JY, Chien S, Hu Y, Xu Q. Histone deacetylase 3 unconventional splicing mediates endothelial-to-mesenchymal transition through transforming growth factor β2. *J Biol Chem* 2013; **288**: 31853-31866 [PMID: 24045946 DOI: 10.1074/jbc.M113.463745]

33 **Spallotta F**, Rosati J, Straino S, Nanni S, Grasselli A, Ambrosino V, Rotili D, Valente S, Farsetti A, Mai A, Capogrossi MC, Gaetano C, Illi B. Nitric oxide determines mesodermic differentiation of mouse embryonic stem cells by activating class IIa histone deacetylases: potential therapeutic implications in a mouse model of hindlimb ischemia. *Stem Cells* 2010; **28**: 431-442 [PMID: 20073046 DOI: 10.1002/stem.300]

34 **Spallotta F**, Cencioni C, Straino S, Nanni S, Rosati J, Artuso S, Manni I, Colussi C, Piaggio G, Martelli F, Valente S, Mai A, Capogrossi MC, Farsetti A, Gaetano C. A nitric oxide-dependent cross-talk between class I and III histone deacetylases accelerates skin repair. *J Biol Chem* 2013; **288**: 11004-11012 [PMID: 23463510]

35 **Chang S**, Young BD, Li S, Qi X, Richardson JA, Olson EN. Histone deacetylase 7 maintains vascular integrity by repressing matrix metalloproteinase 10. *Cell* 2006; **126**: 321-334 [PMID: 16873063 DOI: 10.1016/j.cell.2006.05.040]

36 **Margariti A**, Zampetaki A, Xiao Q, Zhou B, Karamariti E, Martin D, Yin X, Mayr M, Li H, Zhang Z, De Falco E, Hu Y, Cockerill G, Xu Q, Zeng L. Histone deacetylase 7 controls endothelial cell growth through modulation of beta-catenin. *Circ Res* 2010; **106**: 1202-1211 [PMID: 20224040 DOI: 10.1161/circresaha.109.213165]

37 **Song Y**, Li X, Wang D, Fu C, Zhu Z, Zou MH, Zhu Y. Transcription factor Krüppel-like factor 2 plays a vital role in endothelial colony forming cells differentiation. *Cardiovasc Res* 2013; **99**: 514-524 [PMID: 23667185 DOI: 10.1093/cvr/cvt113]

38 **Shimizu K**, Sugiyama S, Aikawa M, Fukumoto Y, Rabkin E, Libby P, Mitchell RN. Host bone-marrow cells are a source of donor intimal smooth- muscle-like cells in murine aortic transplant arteriopathy. *Nat Med* 2001; **7**: 738-741 [PMID: 11385513 DOI: 10.1038/89121]

39 **Han CI**, Campbell GR, Campbell JH. Circulating bone marrow cells can contribute to neointimal formation. *J Vasc Res* 2001; **38**: 113-119 [PMID: 11316947 DOI: 10.1159/000051038]

40 **Li J**, Han X, Jiang J, Zhong R, Williams GM, Pickering JG, Chow LH. Vascular smooth muscle cells of recipient origin mediate intimal expansion after aortic allotransplantation in mice. *Am J Pathol* 2001; **158**: 1943-1947 [PMID: 11395369 DOI: 10.1016/S0002-9440(10)64663-9]

41 **Hu Y**, Davison F, Ludewig B, Erdel M, Mayr M, Url M, Dietrich H, Xu Q. Smooth muscle cells in transplant atherosclerotic lesions are originated from recipients, but not bone marrow progenitor cells. *Circulation* 2002; **106**: 1834-1839 [PMID: 12356638 DOI: 10.1161/01.CIR.0000031333.86845.DD]

42 **Tang Z**, Wang A, Yuan F, Yan Z, Liu B, Chu JS, Helms JA, Li S. Differentiation of multipotent vascular stem cells contributes to vascular diseases. *Nat Commun* 2012; **3**: 875 [PMID: 22673902 DOI: 10.1038/ncomms1867]

43 **Yoshida T**, Gan Q, Owens GK. Kruppel-like factor 4, Elk-1, and histone deacetylases cooperatively suppress smooth muscle cell differentiation markers in response to oxidized phospholipids. *Am J Physiol Cell Physiol* 2008; **295**: C1175-C1182 [PMID: 18768922 DOI: 10.1152/ajpcell.00288.2008]

44 **Yoshida T**, Gan Q, Shang Y, Owens GK. Platelet-derived growth factor-BB represses smooth muscle cell marker genes via changes in binding of MKL factors and histone deacetylases to their promoters. *Am J Physiol Cell Physiol* 2007; **292**: C886-C895 [PMID: 16987998 DOI: 10.1152/ajpcell.00449.2006]

45 **Liu J**, Wang Y, Wu Y, Ni B, Liang Z. Sodium butyrate promotes the differentiation of rat bone marrow mesenchymal stem cells to smooth muscle cells through histone acetylation. *PLoS One* 2014; **9**: e116183 [PMID: 25548915 DOI: 10.1371/journal.pone.0116183]

46 **Singh N**, Trivedi CM, Lu M, Mullican SE, Lazar MA, Epstein JA. Histone deacetylase 3 regulates smooth muscle differentiation in neural crest cells and development of the cardiac outflow tract. *Circ Res* 2011; **109**: 1240-1249 [PMID: 21959220 DOI: 10.1161/CIRCRESAHA.111.255067]

47 **Waltregny D**, Glénisson W, Tran SL, North BJ, Verdin E, Colige A, Castronovo V. Histone deacetylase HDAC8 associates with smooth muscle alpha-actin and is essential for smooth muscle cell contractility. *FASEB J* 2005; **19**: 966-968 [PMID: 15772115]

48 **Li J**, Chen S, Cleary RA, Wang R, Gannon OJ, Seto E, Tang DD. Histone deacetylase 8 regulates cortactin deacetylation and contraction in smooth muscle tissues. *Am J Physiol Cell Physiol* 2014; **307**: C288-C295 [PMID: 24920679 DOI: 10.1152/ajpcell.00102.2014]

49 **Glenisson W**, Castronovo V, Waltregny D. Histone deacetylase 4 is required for TGFbeta1-induced myofibroblastic differentiation. *Biochim Biophys Acta* 2007; **1773**: 1572-1582 [PMID: 17610967 DOI: 10.1016/j.bbamcr.2007.05.016]

50 **Margariti A**, Xiao Q, Zampetaki A, Zhang Z, Li H, Martin D, Hu Y, Zeng L, Xu Q. Splicing of HDAC7 modulates the SRF-myocardin complex during stem-cell differentiation towards smooth muscle cells. *J Cell Sci* 2009; **122**: 460-470 [PMID: 19174469 DOI: 10.1242/jcs.034850]

51 **Gan L**, Schwengberg S, Denecke B. Transcriptome analysis in cardiomyocyte-specific differentiation of murine embryonic stem cells reveals transcriptional regulation network. *Gene Expr Patterns* 2014; **16**: 8-22 [PMID: 25058891 DOI: 10.1016/j.gep.2014.07.002]

52 **Dovey OM**, Foster CT, Cowley SM. Histone deacetylase 1 (HDAC1), but not HDAC2, controls embryonic stem cell differentiation. *Proc Natl Acad Sci U S A* 2010; **107**: 8242-8247 [PMID: 20404188 DOI: 10.1073/pnas.1000478107]

53 **Lu DF**, Yao Y, Su ZZ, Zeng ZH, Xing XW, He ZY, Zhang C. Downregulation of HDAC1 is involved in the cardiomyocyte differentiation from mesenchymal stem cells in a myocardial microenvironment. *PLoS One* 2014; **9**: e93222 [PMID: 24690943 DOI: 10.1371/journal.pone.0093222]

54 **Lu DF**, Wang Y, Su ZZ, Zeng ZH, Xing XW, He ZY, Zhang C. Knockdown of the HDAC1 promotes the directed differentiation of bone mesenchymal stem cells into cardiomyocytes. *PLoS One* 2014; **9**: e92179 [PMID: 24686813 DOI: 10.1371/journal.pone.0092179]

55 **Liu Z**, Li T, Liu Y, Jia Z, Li Y, Zhang C, Chen P, Ma K, Affara N, Zhou C. WNT signaling promotes Nkx2.5 expression and early cardiomyogenesis via downregulation of Hdac1. *Biochim Biophys Acta* 2009; **1793**: 300-311 [PMID: 18851995 DOI: 10.1016/j.bbamcr.2008.08.013]

56 **Hoxha E**, Lambers E, Wasserstrom JA, Mackie A, Ramirez V, Abramova T, Verma SK, Krishnamurthy P, Kishore R. Elucidation of a novel pathway through which HDAC1 controls cardiomyocyte differentiation through expression of SOX-17 and BMP2. *PLoS One* 2012; **7**: e45046 [PMID: 22984607 DOI: 10.1371/journal.pone.0045046]

57 **Hoxha E**, Lambers E, Xie H, De Andrade A, Krishnamurthy P, Wasserstrom JA, Ramirez V, Thal M, Verma SK, Soares MB, Kishore R. Histone deacetylase 1 deficiency impairs differentiation and electrophysiological properties of cardiomyocytes derived from induced pluripotent cells. *Stem Cells* 2012; **30**: 2412-2422 [PMID: 22915496 DOI: 10.1002/stem.1209]

58 **Lu Y**, Yang S. Angiotensin II induces cardiomyocyte hypertrophy probably through histone deacetylases. *Tohoku J Exp Med* 2009; **219**: 17-23 [PMID: 19713680 DOI: 10.1620/tjem.219.17]

59 **Lewandowski SL**, Janardhan HP, Smee KM, Bachman M, Sun Z, Lazar MA, Trivedi CM. Histone deacetylase 3 modulates Tbx5 activity to regulate early cardiogenesis. *Hum Mol Genet* 2014; **23**: 3801-3809 [PMID: 24565863 DOI: 10.1093/hmg/ddu093]

60 **Zhang LX**, DeNicola M, Qin X, Du J, Ma J, Tina Zhao Y, Zhuang S, Liu PY, Wei L, Qin G, Tang Y, Zhao TC. Specific inhibition of HDAC4 in cardiac progenitor cells enhances myocardial repairs. *Am J Physiol Cell Physiol* 2014; **307**: C358-C372 [PMID: 24944198 DOI: 10.1152/ajpcell.00187.2013]

61 **Ha CH**, Kim JY, Zhao J, Wang W, Jhun BS, Wong C, Jin ZG. PKA phosphorylates histone deacetylase 5 and prevents its nuclear export, leading to the inhibition of gene transcription and cardiomyocyte hypertrophy. *Proc Natl Acad Sci U S A* 2010; **107**: 15467-15472 [PMID: 20716686 DOI: 10.1073/pnas.1000462107]

62 **Chang S**, McKinsey TA, Zhang CL, Richardson JA, Hill JA, Olson EN. Histone deacetylases 5 and 9 govern responsiveness of the heart to a subset of stress signals and play redundant roles in heart development. *Mol Cell Biol* 2004; **24**: 8467-8476 [PMID: 15367668 DOI: 10.1128/MCB.24.19.8467-8476.2004]

63 **Miller TA**, Witter DJ, Belvedere S. Histone deacetylase inhibitors. *J Med Chem* 2003; **46**: 5097-5116 [PMID: 14613312 DOI: 10.1021/jm0303094]

64 **Itoh Y**, Suzuki T, Miyata N. Isoform-selective histone deacetylase inhibitors. *Curr Pharm Des* 2008; **14**: 529-544 [PMID: 18336298]

65 **Haggarty SJ**, Koeller KM, Wong JC, Grozinger CM, Schreiber SL. Domain-selective small-molecule inhibitor of histone deacetylase 6 (HDAC6)-mediated tubulin deacetylation. *Proc Natl Acad Sci U S A* 2003; **100**: 4389-4394 [PMID: 12677000 DOI: 10.1073/pnas.0430973100]

66 **Zeng L**, Zhang Y, Chien S, Liu X, Shyy JY. The role of p53 deacetylation in p21Waf1 regulation by laminar flow. *J Biol Chem* 2003; **278**: 24594-24599 [PMID: 12716906 DOI: 10.1074/jbc.M301955200]

**P-Reviewer:** Gunther T, Schmelzer E **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table1 Summary of histone deacetylases’ effect on endothelial cell, smooth muscle cell and cardiomyocyte differentiation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Commitment** | **HDACs** | **Characterization** | **Ref.** |
| **EC** | HDAC1 | EC differentiation markers ↓ | [[28](#_ENREF_28)] |
| HDAC 3 | EC differentiation markers ↑  *In vitro* and *in vivo* angiogenesis  *In vivo* ability to repair injured vessels | [[29](#_ENREF_29)]  [[31](#_ENREF_31)] |
| HDAC 4 | EC differentiation | [[33](#_ENREF_33),[34](#_ENREF_34)] |
| HDAC 5 | Endothelial colony forming cells differentiation | [[37](#_ENREF_37)] |
| HDAC 7 | EC differentiation  Maintenance of vascular integrity  Promote angiogenesis | [[33-35](#_ENREF_33)] |
| **SMC** | HDAC2 | Involved in suppressing SMC differentiation | [[43](#_ENREF_43),[44](#_ENREF_44)] |
| HDAC3 | Neural crest-derived smooth muscle cell differentiation ↓ | [[43](#_ENREF_43)] |
| HDAC4 | Involved in suppressing SMC differentiation | [[44](#_ENREF_44)] |
| HDAC5 | Involved in suppressing SMC differentiation | [[44](#_ENREF_44)] |
| HADC7 | Full splicedHDAC7 SMC differentiation markers ↑ | [[50](#_ENREF_50)] |
| HADC7 | Unspliced HDAC7 SMC differentiation markers ↓ | [[50](#_ENREF_50)] |
| HDAC8 | Marker of smooth muscle differentiation | [[13](#_ENREF_13)] |
| **CM** | HDAC1 | CM differentiation ↑ | [[56](#_ENREF_56), [57](#_ENREF_57)] |
| HDAC1 | CM differentiation ↓ | [[52-55](#_ENREF_52)] |
| HDAC2 | Induce CMs hypertrophy | [[58](#_ENREF_58)] |
| HDAC3 | Regulate early cardiogenesis | [[59](#_ENREF_59)] |
| HDAC4 | CSC-derived cardiac regeneration  Restoration of cardiac function ↑ | [[60](#_ENREF_60)] |

EC: Endothelial cell; SMC: Smooth muscle cell; CM: Cardiomyocyte; CSC: Cardiac stem cell; HDAC: Histone deacetylase.