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Review

Epigenetics and autosomal dominant polycystic kidney disease ☆

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ABSTRACT

The roles of epigenetic modulation of gene expression and protein functions in autosomal dominant polycystic kidney disease (ADPKD) have recently become the focus of scientific investigation. Evidence generated to date indicates that one of the epigenetic modifiers, histone deacetylases (HDACs), are important regulators of ADPKD. HDACs are involved in regulating the expression of the *Pkd1* gene and are the target of fluid flow-induced calcium signal in kidney epithelial cells. Pharmacological inhibition of HDAC activity has been found to reduce the progression of cyst formation and slow the decline of kidney function in *Pkd1* conditional knockout mice and *Pkd2* knockout mice, respectively, implicating the potential clinical application of HDAC inhibitors on ADPKD. Since the expression of HDAC6 is upregulated in cystic epithelial cells, the potential roles of HDAC6 in regulating cilia resorption and epidermal growth factor receptor (EGFR) trafficking through deacetylating α-tubulin and regulating Wnt signaling through deacetylating β-catenin are also discussed. This article is part of a Special Issue entitled: Polycystic Kidney Disease.

1. Introduction

ADPKD is one of the most common hereditary disorders in humans, affecting 1/500 in the United States [1]. The hallmark of the disease is the development of multiple bilateral renal cysts that replace normal renal parenchyma, resulting in end-stage renal disease (ESRD) in approximately 50% of the individuals with ADPKD by the age of 50. Cyst formation is thought to start early in development and to continue throughout the entire life of the affected individual. In addition to renal manifestations, ADPKD patients also suffer from various extra-renal manifestations including hepatic cysts, intracranial aneurysms and cardiac vascular abnormalities. Most cases of ADPKD are caused by mutations in one of two genes: *PKD1*, accounting for 85–95% of the cases; and *PKD2*, accounting for most of the remainder [2]. The gene product of *PKD2*, polycystin-2 (PC2), either alone or in complex with the gene product of *PKD1*, polycystin-1 (PC1), appears to function as a calcium-permeable cation channel [3–6]. The unexpected association of the primary cilium with several inherited cystic kidney diseases and localization of cystoproteins including PC1 and PC2 to the cilia has led to the "primary cilia" hypothesis. Simply stated, the hypothesis is that structural or functional abnormalities in the primary apical cilia of tubular epithelia play a role in renal cyst development and may represent a unifying mechanism of cyst formation. Growing genetic evidence also suggests that polycystin expression must be finely tuned in order to achieve and maintain terminal epithelial differentiation to prevent cyst formation and growth [7,8]. Elucidation of the complex pathways that regulate the expression of polycystins or the signaling pathways downstream of polycystin signaling are critical for achieving a full understanding of ADPKD pathogenesis and for identification of crucial regulatory or structural components that may be useful as therapeutic targets.

Epigenetic modulation of gene expression is as an important regulatory process in cell biology [9]. Developmental and regulatory processes within the cell are strongly influenced by histone modification, which includes acetylation, methylation, and phosphorylation [10]. These post-translational modifications increase accessibility of transcription factors to gene promoter regions by changing the secondary structure of the histone protein tails in relation to the DNA strands within the nucleosome, composed of a DNA strand wound around a core of eight histone proteins [11,12]. Deacetylation, demethylation, and dephosphorylation of histones have the opposite effect of decreasing access of transcription factors to promoter regions. Histone acetylation is mediated by histone acetyl transferases [13,14], while acetyl groups are removed by histone deacetylases (HDACs) [15]. This review will focus on the functional roles of HDACs in regulating the cellular processes of renal

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epithelia and the potential of HDAC inhibitors for treatment of ADPKD. Although histone methylation [16] and phosphorylation [17] are the subjects of intense research, there is little evidence to date connecting these types of modifications to ADPKD; thus, they will not be discussed here.

2. Classification of HDACs

To date, eighteen mammalian HDACs have been identified and are grouped into classes I–IV based on their homology to their respective yeast orthologues [18–20]. Classes I, II, and IV consist of 11 family members and all contain a zinc (Zn) molecule in their active site. Classes I, II, and IV are referred to as "classical" HDACs and are inhibited by the pan-HDAC inhibitor trichostatin A (TSA). Class I HDACs (HDACs 1, 2, 3 and 8) show homology to the yeast HDAC, *Rpd3*, are ubiquitously expressed and predominantly localized in the nucleus [21,22]. Class II HDACs (HDACs 4, 5, 6, 7, 9 and 10) are expressed in a tissue-specific manner and have a high degree of homology with the yeast HDAC *Hda-1* [23]. Class II HDACs are expressed in both the nucleus and cytoplasm. The shuttling of class II HDACs in and out of the nucleus is regulated by 14-3-3 proteins and is a major mechanism by which their activity is regulated [23]. Class I and II HDACs share significant homology at the deacetylase domain but differ in their N-terminal sequence. Class IV HDAC only has one member, HDAC11, which shares some homology to both class I and II HDACs [24]. The seven different class III HDACs, also known as sirtuins, are NAD^+-dependent deacetylases (distinct from the zinc-dependent class I and II HDACs) [25]. Sirtuins are homologous to the yeast Sir2 gene, from which the family derives its name [26]. Class III HDACs share little homology to the first two classes, and are not inhibited by any known HDAC inhibitors [27].

3. Mechanisms of action of class I and II HDACs

HDACs regulate cellular functions through transcription-dependent or transcription-independent mechanisms. In the transcription-dependent mechanism, HDACs regulate gene expression through deacetylation of either histones or non-histone transcriptional factors [28,29]. First, upon recruitment by sequence-specific transcription factors to specific gene promoters, HDACs deacetylate specific lysine residues in the DNA-bound core histone proteins creating a positive charge on histone proteins to enhance their affinity for negatively charged DNA. This modification alters the conformation of the nucleosome and reduces accessibility of the transcriptional regulatory machinery to the DNA template repressing the transcription of specific genes [28]. Second, HDACs deacetylate sequence-specific transcription factors such as p53 [30], E2F [31], c-Myc [32], nuclear factor-κB (NF-κB) [33], hypoxia-inducible factor 1α (HIF-1α) [34], Sp1 and Sp3 [35,36], TFIIEβ and TFIIF [37], GATA-1 [38], TCF [39], and HMG-1 [40], to decrease their DNA binding activity, and subsequently repress transcription of specific genes [37]. Individual HDACs are responsible for regulating different transcription factors, i.e., deacetylation of p53 by HDAC1 [41], deacetylation of glucocorticoid receptor by HDAC2 [42], and deacetylation of myocyte enhancer factor 2 (MEF2) by HDAC3 [43]. In the transcription-independent mechanism, HDACs regulate specific cellular functions through deacetylation of a number of cytoplasmic proteins, such as tubulin [44] and HSP90 [45], which are the substrates of HDAC6. HDAC6 mediated deacetylation of α-tubulin helps to regulate protein trafficking [46], cell motility [47] and the cilia disassembly during the cycle [48]. HDAC6-mediated deacetylation of HSP90 enhances its chaperone function [49]. The potential contribution of transcription-dependent versus independent mechanisms of HDACs in regulation of cystic epithelial cell biology is discussed below.

4. Function of class I and II HDACs in ADPKD

4.1. HDACs are involved in p53-mediated repression of the PKD1 gene expression

The growing genetic evidence suggests that polycystin expression must be finely tuned in order to achieve and maintain terminal epithelial differentiation and to prevent cyst formation [7,8]. Increased *Pkd1* expression can be achieved from enhanced expression of transcriptional activators. Decrease *Pkd1* expression has been found to be regulated through p53-mediated repression of the *PKD1* promoter, and HDACs as the negative regulators are involved in this process [50]. The *PKD1* gene promoter which contains a hybrid p53-Sp1-binding motif has been shown to bind p53 *in vivo*. However, the interaction between p53 and Sp1 does not fully account for p53-induced repression of *PKD1* since a pan-HDACs inhibitor TSA further attenuated p53-induced repression of the *PKD1* promoter. This evidence together with the finding that p53 is downregulated in *Pkd1* mutant kidney epithelial cells suggest a model in which polycystin signaling activates p53, which in turn, in cooperation with HDACs, controls *PKD1* gene expression. However, which HDAC (s) is involved in p53-mediated repression of *Pkd1* gene expression is unknown. Since HDAC1 is able to deacetylate p53 [41] and has been found to bind with Sp1 [51], it may be directly involved in p53-mediated repression of the *PKD1* gene expression. Using siRNA to knockdown HDAC1 may clarify its function in this process.

4.2. HDAC5 is the target of fluid flow-induced calcium signal in kidney epithelial cells

To identify downstream targets regulated by the mechanosensory function of the polycystins, we performed an expression microarray analysis designed to detect genes that are differentially expressed in response to fluid flow shear stress in a PC1-dependent manner in polarized renal epithelial cells. This analysis identified HDAC5 and myocyte enhancer factor 2C (MEF2C), two key regulators of cardiac hypertrophy, as targets of polycystin-dependent fluid stress sensing in renal epithelial cells [52]. We demonstrated that fluid flow stimulation of polarized epithelial monolayers results in increased PC2 calcium channel activity and results in calcium influx into the cells. Increasing intracellular calcium activates protein kinase C (PKC), which then directly or indirectly phosphorylates HDAC5 at two 14-3-3 binding sites, an event that leads to disruption of HDAC5–MEF2C interaction and translocation of HDAC5 from the nucleus to the cytosol [53]. Nuclear export of HDAC5 releases its inhibition on MEF2C-based transcription. MEF2 targets include not only structural proteins important for cardiac muscle differentiation, but also members of the MEF2 and class II HDAC families through positive feedback loops [54,55]. A recent study demonstrated that fluid shear stress-induced HDAC5 phosphorylation and nuclear export also occurred in endothelial cells [56]. Thus, HDAC5 may be a common target of multiple mechanosensory pathways that respond to fluid flow or other mechanical stresses. However, the details of this fluid flow sensing pathway in renal epithelial cells remain to be elucidated.

To determine if Mef2C-based transcription is an important factor in the regulation of renal epithelial cell function, we disrupted Mef2C in the kidney through crossing a *Mef2C* conditional knockout mice [57] with *Sglt2* promoter-driven Cre mice [58], which results in decreased expression in renal tubules and glomeruli. In 5-month or older *Mef2C$^{flox/flox}$:Sglt2-Cre* mutant mice renal abnormalities including broadly distributed dilated tubules, and small bilateral cysts with flat lining cells were observed in 9 out of 12 mice, [52].

To test if loss-of-function mutations in HDAC5 alleviate cyst formation in *Pkd2$^{-/-}$* mice, we crossed pairs of *Pkd2$^{+/-}$Hdac5$^{+/-}$* double mutant mice, and embryonic kidneys were analyzed at 18.5 dpc. *Pkd2$^{-/-}$* embryos die before or immediately after birth with many

large renal cysts [59]. We found that kidneys of *Pkd2*$^{-/-}$*Hdac5*$^{+/-}$ embryos ($n=7$) exhibited noticeably reduced cyst formation, compared to *Pkd2*$^{-/-}$*Hdac5*$^{+/+}$ kidneys from embryos of *Pkd2*$^{+/-}$*Hdac5*$^{+/+}$ parents of the same genetic background [52]. This data suggests that *Hdac5* heterozygosity reduces cyst formation in *Pkd2*$^{-/-}$ mouse embryos and inhibition of HDAC5 with HDAC inhibitor may prevent cyst formation.

To test the possibility that reduced activity of HDAC5 would suppress cystogenesis in *Pkd2*$^{-/-}$ mice, TSA was administered to pregnant *Pkd2*$^{+/-}$ female mice (mated with *Pkd2*$^{+/-}$ males) from embryonic day (E) 10.5 through E17.5 and embryonic kidneys were analyzed at 18.5 dpc. In all *Pkd2*$^{-/-}$ embryos ($n=7$) from TSA-injected mothers, kidney cyst formation was drastically reduced compared to those from control DMSO-injected mothers. This finding suggests that HDACs are the potential therapeutic targets for the treatment of ADPKD [52].

Although the reduction in cyst severity in *Pkd2*$^{-/-}$ embryonic kidneys caused by *Hdac5* heterozygosity or inhibition of HDAC5 activity with TSA is consistent with our proposed epistatic relationship between *Pkd2* and HDAC5 [52], this result does not rule out possible regulation by other members of the class II HDAC family. Furthermore, since HDAC5 lacks intrinsic enzymatic activity and requires to form a complex with HDAC3, a class I HDAC that is also sensitive to TSA, for their transcriptional repression activity [60], the reduction in cyst severity in *Pkd2*$^{-/-}$ embryonic kidneys caused by TSA also does not rule out possible regulation by class I HDACs. In supporting that cystogenesis might also be regulated by class I HDACs and HDACs are the potential therapeutic targets for the treatment of ADPKD, Cao et al. [61] reported that valproic acid (VPA), a class I HDAC specific inhibitor, was able to reduce the progression of cyst formation and slow the decline of kidney function in another mouse ADPKD model.

5. Other potential functions of HDACs in PKD

5.1. HDAC6 regulates cilia disassembly during the normal cell cycle

Renal epithelial cells possess a single non-motile hair-like structure called the primary cilium, which functions as a mechanosensor detecting fluid flow through the renal tubule. Cilia consist of a microtubule-based axoneme covered by a specialized plasma membrane. The ciliary axoneme is built from one of the two basal bodies (centrioles) that form the core of the centrosome [62]. The centrosome directs assembly of the bipolar spindle during mitosis. Thus, cilia have also been suggested to passively affect the cell cycle for their requirement for one of the centrioles of the centrosome. Since the membrane of primary cilia is attached to the distal end of one of the centriole, it is necessary to disassemble the primary cilium to liberate the captive centriole for cell division [63]. It has been demonstrated that HDAC6 regulates the stability of microtubules through deacetylation of α-tubulin and regulates cilia disassembly during the normal cell cycle [48]. HDAC6 specific inhibitor, tubacin, stabilizes cilia from regulated resorption cues. We have found that HDAC6 is upregulated in the *Pkd1* mutant mouse embryonic renal epithelial cells (unpublished data). These data demonstrate that the functional role of HDAC6 in ciliogenesis and cyst formation warrants further investigation.

5.2. HDAC6 regulates β-catenin nuclear translocation and EGFR trafficking

In normal tissues, the primary cilium coordinates a complex series of signal transduction pathways, including Hedgehog, Wnt, and integrin signaling [64]. Abnormal activation of the Wnt/beta-catenin-dependent pathway resulting in nuclear translocation of β-catenin is characteristic of ADPKD [65–67]. In addition to the canonical Wnt pathway ligands, growth factors such as epidermal growth factor (EGF) also induce β-catenin dissociation from the adherens junction complex, translocation into the nucleus, and activation of target genes such as c-*myc* [68]. Published reports demonstrate that EGF-induced nuclear localization of β-catenin is regulated by HDAC6-dependent deacetylation of β-catenin at lysine 49 [69], a site often mutated in cancers [70]. This modification inhibits β-catenin phosphorylation at serine 45. The authors further show that inhibition of HDAC6 blocks EGF-induced β-catenin nuclear localization and decreases c-Myc expression, leading to inhibition of epithelial cell proliferation. These results together with the increased expression of HDAC6 in *Pkd1* mutant cystic epithelia suggest that HDAC6 regulates Wnt signaling through deacetylating β-catenin.

EGF has a documented role in the expansion of renal cysts. Cystic epithelial cells from patients with ARPKD or ADPKD are unusually susceptible to the proliferative stimulus of EGF [71]. EGFR has been demonstrated to promote epithelial hyperplasia in cystic epithelia, resulting in renal cyst formation and progressive enlargement in murine PKD and human ADPKD and ARPKD [72–77]. In all animal models studied to date, abnormal expression and localization of members of the EGFR have been reported [71]. HDAC6 has recently been found to negatively regulate EGFR endocytosis and degradation by controlling the acetylation status of α-tubulin and, subsequently, receptor trafficking along microtubules [46]. In addition, a negative feedback loop existed between HDAC6 and EGFR in that EGFR-mediated phosphorylation of HDAC6 resulted in reduced deacetylase activity and increased acetylation of α-tubulin. It has also been shown that stable knockdown expression of HDAC6 causes a decrease in the steady-state level of EGFR in A549 lung cancer cells [78]. The decreased levels of EGFR in HDAC6-knockdown cells correlated with increased acetylation of microtubules, resulting in increased turnover of EGFR protein. These studies imply a connection between HDAC6, EGFR activity and cyst formation.

6. The potential clinical implications of HDAC inhibitors on ADPKD

To date, an array of drugs with HDAC inhibitory effects have been described and more than 15 HDAC inhibitors are currently being tested in clinical trials for a number of disease states [79]. However, the Federal Drug Enforcement Agency (FDA) approved only one HDAC inhibitor, vorinostat (also known as SAHA), for treatment of cutaneous T-cell lymphoma. We and others have reported that class I HDAC inhibitor, VPA, and class II HDAC inhibitor, TSA, reduce the progression of cyst formation and slow the decline of kidney function in *Pkd1* conditional knockout mice and *Pkd2* knockout mice, respectively [52,61]. VPA belongs to the short-chain fatty acids derived HDAC inhibitors, which also includes sodium phenylbutyrate and sodium butyrate. TSA belongs to the hydroxamic acids derived HDAC inhibitors, which also includes vorinostat (SAHA), panobinostat, and belinostat. Before considering potential implications of HDAC inhibitors in human ADPKD, studies of other members of these two classes of HDAC inhibitors, especially SAHA, in preventing cyst formation in animal models of ADPKD would be extremely useful.

Recent studies demonstrate that HDAC6-knockdown cells are more sensitive than control cells to the MEK inhibitor U0126 [78]. MEK inhibition has been suggested as a possible therapy to prevent cyst formation in *Pkd* animal model [80]. These data and studies in cancer biology suggest that a combination of HDAC inhibitors along with the inhibitors of growth factor signaling may provide an effective therapy for prevention of cyst formation.

7. Conclusions

The roles of epigenetic modulation of gene expression and protein functions in ADPKD have recently become the focus of scientific

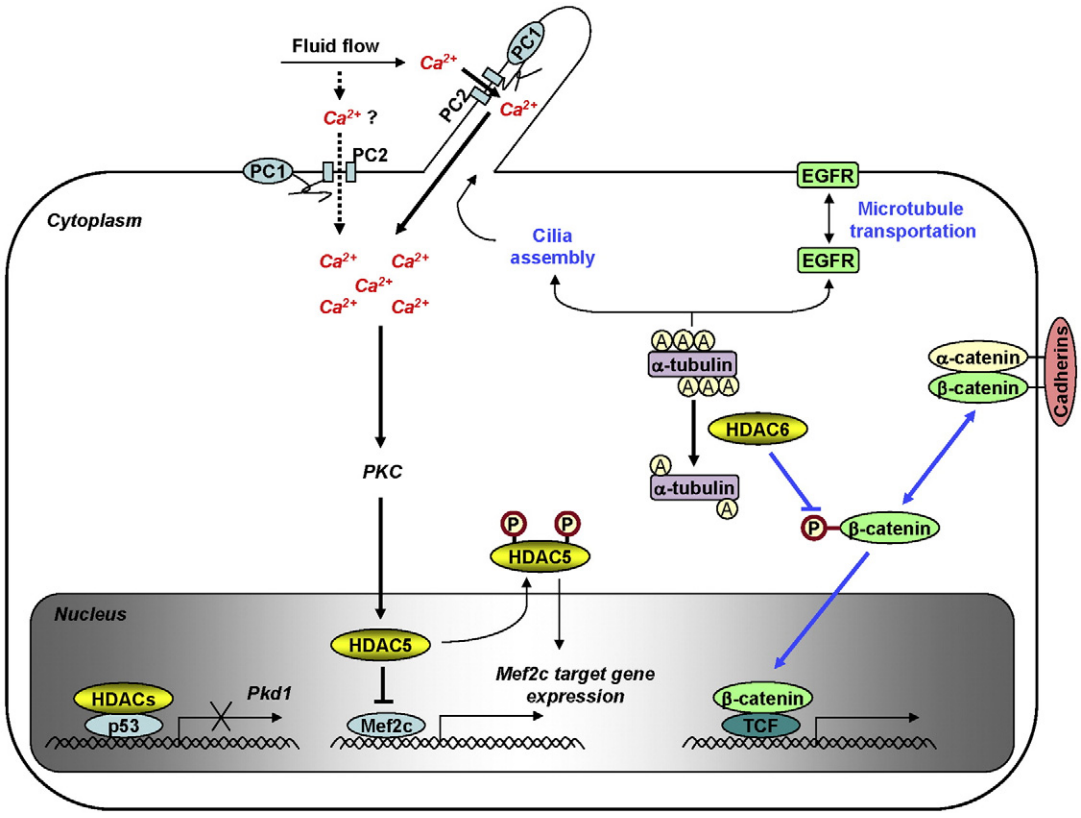

Fig. 1. Actions of HDACs in kidney epithelial cells. In this schematic diagram, we have depicted the function of HDACs in ADPKD and the potential roles of HDAC6 in ADPKD/PKD. The functions of HDACs in ADPKD include: i) HDACs together with *p53* repress *Pkd1* gene expression; ii) HDAC5 is the target of fluid flow-induced calcium signal in kidney epithelial cells. The potential roles of HDAC6 in ADPKD/PKD include: i) HDAC6 regulates cilia disassembly through deacetylation of α-tubulin during the normal cell cycle; ii) HDAC6 regulates EGFR trafficking through deacetylation of α-tubulin; iii) HDAC6 either alone or with EGF regulates β-catenin nuclear translocation.

investigation. Evidence generated to date indicate that HDACs are involved in regulating the expression of the *Pkd1* gene and HDAC5 is the target of fluid flow-induced calcium signal in renal epithelia (summarized in Fig. 1). HDACs may also be involved in regulating ciliogenesis and EGFR trafficking through deacetylating α-tubulin and regulating Wnt signaling through deacetylating β-catenin (Fig. 1). Consistent with such a role, pharmacological inhibition of HDAC activity has been found to reduce the progression of cyst formation and slow the decline of kidney function in *Pkd1* conditional knockout mice and *Pkd2* knockout mice, respectively. To date, only a single HDAC inhibitor, SAHA, has been approved by FDA for the treatment of cutaneous T-cell lymphoma. Preclinical trials examining the utility of SAHA in preventing cyst formation and growth in animal models of ADPKD may offer an exciting and novel therapeutic target for the treatment of ADPKD.

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References

[1] P.A. Gabow, Autosomal dominant polycystic kidney disease, Am. J. Kidney Dis. 22 (1993) 511–512.
[2] D.J. Peters, L.A. Sandkuijl, Genetic heterogeneity of polycystic kidney disease in Europe, Contrib. Nephrol. 97 (1992) 128–139.
[3] X.Z. Chen, P.M. Vassilev, N. Basora, J.B. Peng, H. Nomura, Y. Segal, E.M. Brown, S.T. Reeders, M.A. Hediger, J. Zhou, Polycystin-L is a calcium-regulated cation channel permeable to calcium ions, Nature 401 (1999) 383–386.
[4] S. Gonzalez-Perrett, K. Kim, C. Ibarra, A.E. Damiano, E. Zotta, M. Batelli, P.C. Harris, I.L. Reisin, M.A. Arnaout, H.F. Cantiello, Polycystin-2, the protein mutated in autosomal dominant polycystic kidney disease (ADPKD), is a Ca2 + -permeable nonselective cation channel, Proc. Natl Acad. Sci. USA 98 (2001) 1182–1187.
[5] K. Hanaoka, F. Qian, A. Boletta, A.K. Bhunia, K. Piontek, L. Tsiokas, V.P. Sukhatme, W.B. Guggino, G.G. Germino, Co-assembly of polycystin-1 and -2 produces unique cation-permeable currents, Nature 408 (2000) 990–994.
[6] P. Koulen, Y. Cai, L. Geng, Y. Maeda, S. Nishimura, R. Witzgall, B.E. Ehrlich, S. Somlo, Polycystin-2 is an intracellular calcium release channel, Nat. Cell Biol. 4 (2002) 191–197.
[7] C. Thivierge, A. Kurbegovic, M. Couillard, R. Guillaume, O. Cote, M. Trudel, Overexpression of PKD1 causes polycystic kidney disease, Mol. Cell. Biol. 26 (2006) 1538–1548.
[8] M.Y. Chang, E. Parker, S. Ibrahim, J.R. Shortland, M.E. Nahas, J.L. Haylor, A.C. Ong, Haploinsufficiency of Pkd2 is associated with increased tubular cell proliferation and interstitial fibrosis in two murine Pkd2 models, Nephrol. Dial. Transplant. 21 (2006) 2078–2084.
[9] R.S. Jones, Epigenetics: reversing the 'irreversible', Nature 450 (2007) 357–359.
[10] B.D. Strahl, C.D. Allis, The language of covalent histone modifications, Nature 403 (2000) 41–45.
[11] K. Luger, Structure and dynamic behavior of nucleosomes, Curr. Opin. Genet. Dev. 13 (2003) 127–135.
[12] P.D. Gregory, K. Wagner, W. Horz, Histone acetylation and chromatin remodeling, Exp. Cell Res. 265 (2001) 195–202.
[13] S.Y. Roth, J.M. Denu, C.D. Allis, Histone acetyltransferases, Annu. Rev. Biochem. 70 (2001) 81–120.
[14] D.Y. Lee, J.J. Hayes, D. Pruss, A.P. Wolffe, A positive role for histone acetylation in transcription factor access to nucleosomal DNA, Cell 72 (1993) 73–84.
[15] S.G. Gray, B.T. Teh, Histone acetylation/deacetylation and cancer: an "open" and "shut" case? Curr. Mol. Med. 1 (2001) 401–429.
[16] Y. Shi, Histone lysine demethylases: emerging roles in development, physiology and disease, Nat. Rev. Genet. 8 (2007) 829–833.
[17] M. Oki, H. Aihara, T. Ito, Role of histone phosphorylation in chromatin dynamics and its implications in diseases, Subcell. Biochem. 41 (2007) 319–336.

[18] S. Thiagalingam, K.H. Cheng, H.J. Lee, N. Mineva, A. Thiagalingam, J.F. Ponte, Histone deacetylases: unique players in shaping the epigenetic histone code, Ann. NY Acad. Sci. 983 (2003) 84–100.
[19] J.E. Bolden, M.J. Peart, R.W. Johnstone, Anticancer activities of histone deacetylase inhibitors, Nat. Rev. Drug Discov. 5 (2006) 769–784.
[20] J.M. Mariadason, HDACs and HDAC inhibitors in colon cancer, Epigenetics 3 (2008) 28–37.
[21] J. Taplick, V. Kurtev, K. Kroboth, M. Posch, T. Lechner, C. Seiser, Homo-oligomerisation and nuclear localisation of mouse histone deacetylase 1, J. Mol. Biol. 308 (2001) 27–38.
[22] J. Taunton, C.A. Hassig, S.L. Schreiber, A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p, Science 272 (1996) 408–411.
[23] N.R. Bertos, A.H. Wang, X.J. Yang, Class II histone deacetylases: structure, function, and regulation, Biochem. Cell Biol. 79 (2001) 243–252.
[24] L. Gao, M.A. Cueto, F. Asselbergs, P. Atadja, Cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family, J. Biol. Chem. 277 (2002) 25748–25755.
[25] S. Michan, D. Sinclair, Sirtuins in mammals: insights into their biological function, Biochem. J. 404 (2007) 1–13.
[26] G. Blander, L. Guarente, The Sir2 family of protein deacetylases, Annu. Rev. Biochem. 73 (2004) 417–435.
[27] W.S. Xu, R.B. Parmigiani, P.A. Marks, Histone deacetylase inhibitors: molecular mechanisms of action, Oncogene 26 (2007) 5541–5552.
[28] S.G. Gray, T.J. Ekstrom, The human histone deacetylase family, Exp. Cell Res. 262 (2001) 75–83.
[29] M.A. Glozak, N. Sengupta, X. Zhang, E. Seto, Acetylation and deacetylation of non-histone proteins, Gene 363 (2005) 15–23.
[30] W. Gu, R.G. Roeder, Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain, Cell 90 (1997) 595–606.
[31] G. Marzio, C. Wagener, M.I. Gutierrez, P. Cartwright, K. Helin, M. Giacca, E2F family members are differentially regulated by reversible acetylation, J. Biol. Chem. 275 (2000) 10887–10892.
[32] J.H. Patel, Y. Du, P.G. Ard, C. Phillips, B. Carella, C.J. Chen, C. Rakowski, C. Chatterjee, P.M. Lieberman, W.S. Lane, G.A. Blobel, S.B. McMahon, The c-MYC oncoprotein is a substrate of the acetyltransferases hGCN5/PCAF and TIP60, Mol. Cell. Biol. 24 (2004) 10826–10834.
[33] L. Chen, W. Fischle, E. Verdin, W.C. Greene, Duration of nuclear NF-kappaB action regulated by reversible acetylation, Science 293 (2001) 1653–1657.
[34] J.W. Jeong, M.K. Bae, M.Y. Ahn, S.H. Kim, T.K. Sohn, M.H. Bae, M.A. Yoo, E.J. Song, K.J. Lee, K.W. Kim, Regulation and destabilization of HIF-1alpha by ARD1-mediated acetylation, Cell 111 (2002) 709–720.
[35] S. Ammanamanchi, J.W. Freeman, M.G. Brattain, Acetylated sp3 is a transcriptional activator, J. Biol. Chem. 278 (2003) 35775–35780.
[36] H. Braun, R. Koop, A. Ertmer, S. Nacht, G. Suske, Transcription factor Sp3 is regulated by acetylation, Nucleic Acids Res. 29 (2001) 4994–5000.
[37] A. Imhof, X.J. Yang, V.V. Ogryzko, Y. Nakatani, A.P. Wolffe, H. Ge, Acetylation of general transcription factors by histone acetyltransferases, Curr. Biol. 7 (1997) 689–692.
[38] J. Boyes, P. Byfield, Y. Nakatani, V. Ogryzko, Regulation of activity of the transcription factor GATA-1 by acetylation, Nature 396 (1998) 594–598.
[39] L. Waltzer, M. Bienz, Drosophila CBP represses the transcription factor TCF to antagonize Wingless signalling, Nature 395 (1998) 521–525.
[40] N. Munshi, M. Merika, J. Yie, K. Senger, G. Chen, D. Thanos, Acetylation of HMG I(Y) by CBP turns off IFN beta expression by disrupting the enhanceosome, Mol. Cell 2 (1998) 457–467.
[41] A. Ito, Y. Kawaguchi, C.H. Lai, J.J. Kovacs, Y. Higashimoto, E. Appella, T.P. Yao, MDM2-HDAC1-mediated deacetylation of p53 is required for its degradation, EMBO J. 21 (2002) 6236–6245.
[42] K. Ito, S. Yamamura, S. Essilfie-Quaye, B. Cosio, M. Ito, P.J. Barnes, I.M. Adcock, Histone deacetylase 2-mediated deacetylation of the glucocorticoid receptor enables NF-kappaB suppression, J. Exp. Med. 203 (2006) 7–13.
[43] S. Gregoire, L. Xiao, J. Nie, X. Zhang, M. Xu, J. Li, J. Wong, E. Seto, X.J. Yang, Histone deacetylase 3 interacts with and deacetylates myocyte enhancer factor 2, Mol. Cell. Biol. 27 (2007) 1280–1295.
[44] C. Hubbert, A. Guardiola, R. Shao, Y. Kawaguchi, A. Ito, A. Nixon, M. Yoshida, X.F. Wang, T.P. Yao, HDAC6 is a microtubule-associated deacetylase, Nature 417 (2002) 455–458.
[45] J.J. Kovacs, P.J. Murphy, S. Gaillard, X. Zhao, J.T. Wu, C.V. Nicchitta, M. Yoshida, D.O. Toft, W.B. Pratt, T.P. Yao, HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor, Mol. Cell 18 (2005) 601–607.
[46] Y.L. Deribe, P. Wild, A. Chandrashaker, J. Curak, M.H. Schmidt, Y. Kalaidzidis, N. Milutinovic, I. Kratchmarova, L. Buerkle, M.J. Fetchko, P. Schmidt, S. Kittanakom, K.R. Brown, I. Jurisica, B. Blagoev, M. Zerial, I. Stagljar, I. Dikic, Regulation of epidermal growth factor receptor trafficking by lysine deacetylase HDAC6, Sci. Signal. 2 (2009) ra84.
[47] A. Valenzuela-Fernandez, J.R. Cabrero, J.M. Serrador, F. Sanchez-Madrid, HDAC6: a key regulator of cytoskeleton, cell migration and cell-cell interactions, Trends Cell Biol. 18 (2008) 291–297.
[48] E.N. Pugacheva, S.A. Jablonski, T.R. Hartman, E.P. Henske, E.A. Golemis, HEF1-dependent Aurora A activation induces disassembly of the primary cilium, Cell 129 (2007) 1351–1363.
[49] P. Bali, M. Pranpat, J. Bradner, M. Balasis, W. Fiskus, F. Guo, K. Rocha, S. Kumaraswamy, S. Boyapalle, P. Atadja, E. Seto, K. Bhalla, Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: a novel basis for antileukemia activity of histone deacetylase inhibitors, J. Biol. Chem. 280 (2005) 26729–26734.
[50] D. Van Bodegom, Z. Saifudeen, S. Dipp, S. Puri, B.S. Magenheimer, J.P. Calvet, S.S. El-Dahr, The polycystic kidney disease-1 gene is a target for p53-mediated transcriptional repression, J. Biol. Chem. 281 (2006) 31234–31244.
[51] K. Enya, H. Hayashi, T. Takii, N. Ohoka, S. Kanata, T. Okamoto, K. Onozaki, The interaction with Sp1 and reduction in the activity of histone deacetylase 1 are critical for the constitutive gene expression of IL-1 alpha in human melanoma cells, J. Leukoc. Biol. 83 (2008) 190–199.
[52] S. Xia, X. Li, T. Johnson, C. Seidel, D.P. Wallace, R. Li, Polycystin-dependent fluid flow sensing targets histone deacetylase 5 to prevent the development of renal cysts, Development 137 (2010) 1075–1084.
[53] T.A. McKinsey, C.L. Zhang, E.N. Olson, MEF2: a calcium-dependent regulator of cell division, differentiation and death, Trends Biochem. Sci. 27 (2002) 40–47.
[54] M. Haberland, M.A. Arnold, J. McAnally, D. Phan, Y. Kim, E.N. Olson, Regulation of HDAC9 gene expression by MEF2 establishes a negative-feedback loop in the transcriptional circuitry of muscle differentiation, Mol. Cell. Biol. 27 (2007) 518–525.
[55] D.Z. Wang, M.R. Valdez, J. McAnally, J. Richardson, E.N. Olson, The Mef2c gene is a direct transcriptional target of myogenic bHLH and MEF2 proteins during skeletal muscle development, Development 128 (2001) 4623–4633.
[56] W. Wang, C.H. Ha, B.S. Jhun, C. Wong, M.K. Jain, Z.G. Jin, Fluid shear stress stimulates phosphorylation-dependent nuclear export of HDAC5 and mediates expression of KLF2 and eNOS, Blood (2009).
[57] L.H. Vong, M.J. Ragusa, J.J. Schwarz, Generation of conditional Mef2cloxP/loxP mice for temporal- and tissue-specific analyses, Genesis 43 (2005) 43–48.
[58] I. Rubera, C. Poujeol, G. Bertin, L. Hasseine, L. Counillon, P. Poujeol, M. Tauc, Specific Cre/Lox recombination in the mouse proximal tubule, J. Am. Soc. Nephrol. 15 (2004) 2050–2056.
[59] G. Wu, V. D'Agati, Y. Cai, G. Markowitz, J.H. Park, D.M. Reynolds, Y. Maeda, T.C. Le, H. Hou Jr., R. Kucherlapati, W. Edelmann, S. Somlo, Somatic inactivation of Pkd2 results in polycystic kidney disease, Cell 93 (1998) 177–188.
[60] W. Fischle, F. Dequiedt, M.J. Hendzel, M.G. Guenther, M.A. Lazar, W. Voelter, E. Verdin, Enzymatic activity associated with class II HDACs is dependent on a multiprotein complex containing HDAC3 and SMRT/N-CoR, Mol. Cell 9 (2002) 45–57.
[61] Y. Cao, N. Semanchik, S.H. Lee, S. Somlo, P.E. Barbano, R. Coifman, Z. Sun, Chemical modifier screen identifies HDAC inhibitors as suppressors of PKD models, Proc. Natl Acad. Sci. USA 106 (2009) 21819–21824.
[62] H.A. Praetorius, K.R. Spring, A physiological view of the primary cilium, Annu. Rev. Physiol. 67 (2005) 515–529.
[63] J. Pan, W. Snell, The primary cilium: keeper of the key to cell division, Cell 129 (2007) 1255–1257.
[64] I.R. Veland, A. Awan, L.B. Pedersen, B.K. Yoder, S.T. Christensen, Primary cilia and signaling pathways in mammalian development, health and disease, Nephron Physiol. 111 (2009) 39–53.
[65] K.M. Cadigan, M. Peifer, Wnt signaling from development to disease: insights from model systems, Cold Spring Harb. Perspect. Biol. 1 (2009) a002881.
[66] E. Kim, T. Arnould, L.K. Sellin, T. Benzing, M.J. Fan, W. Gruning, S.Y. Sokol, I. Drummond, G. Walz, The polycystic kidney disease 1 gene product modulates Wnt signaling, J. Biol. Chem. 274 (1999) 4947–4953.
[67] X. Song, V. Di Giovanni, N. He, K. Wang, A. Ingram, N.D. Rosenblum, Y. Pei, Systems biology of autosomal dominant polycystic kidney disease (ADPKD): computational identification of gene expression pathways and integrated regulatory networks, Hum. Mol. Genet. 18 (2009) 2328–2343.
[68] Z. Lu, S. Ghosh, Z. Wang, T. Hunter, Downregulation of caveolin-1 function by EGF leads to the loss of E-cadherin, increased transcriptional activity of beta-catenin, and enhanced tumor cell invasion, Cancer Cell 4 (2003) 499–515.
[69] Y. Li, X. Zhang, R.D. Polakiewicz, T.P. Yao, M.J. Comb, HDAC6 is required for epidermal growth factor-induced beta-catenin nuclear localization, J. Biol. Chem. 283 (2008) 12686–12690.
[70] S. Amit, A. Hatzubai, Y. Birman, J.S. Andersen, E. Ben-Shushan, M. Mann, Y. Ben-Neriah, I. Alkalay, Axin-mediated CKI phosphorylation of beta-catenin at Ser 45: a molecular switch for the Wnt pathway, Genes Dev. 16 (2002) 1066–1076.
[71] W.E. Sweeney Jr., E.D. Avner, Molecular and cellular pathophysiology of autosomal recessive polycystic kidney disease (ARPKD), Cell Tissue Res. 326 (2006) 671–685.
[72] J. Du, P.D. Wilson, Abnormal polarization of EGF receptors and autocrine stimulation of cyst epithelial growth in human ADPKD, Am. J. Physiol. 269 (1995) C487–C495.
[73] V.H. Gattone 2nd, K.A. Kuenstler, G.W. Lindemann, X. Lu, B.D. Cowley Jr., C.A. Rankin, J.P. Calvet, Renal expression of a transforming growth factor-alpha transgene accelerates the progression of inherited, slowly progressive polycystic kidney disease in the mouse, J. Lab. Clin. Med. 127 (1996) 214–222.
[74] J. Nauta, W.E. Sweeney, J.C. Rutledge, E.D. Avner, Biliary epithelial cells from mice with congenital polycystic kidney disease are hyperresponsive to epidermal growth factor, Pediatr. Res. 37 (1995) 755–763.
[75] S.A. Orellana, W.E. Sweeney, C.D. Neff, E.D. Avner, Epidermal growth factor receptor expression is abnormal in murine polycystic kidney, Kidney Int. 47 (1995) 490–499.
[76] W.G. Richards, W.E. Sweeney, B.K. Yoder, J.E. Wilkinson, R.P. Woychik, E.D. Avner, Epidermal growth factor receptor activity mediates renal cyst formation in polycystic kidney disease, J. Clin. Invest. 101 (1998) 935–939.
[77] W.E. Sweeney Jr., E.D. Avner, Functional activity of epidermal growth factor receptors in autosomal recessive polycystic kidney disease, Am. J. Physiol. 275 (1998) F387–F394.
[78] K. Kamemura, A. Ito, T. Shimazu, A. Matsuyama, S. Maeda, T.P. Yao, S. Horinouchi, S. Khochbin, M. Yoshida, Effects of downregulated HDAC6 expression on the

proliferation of lung cancer cells, Biochem. Biophys. Res. Commun. 374 (2008) 84–89.
[79] A. Mai, S. Valente, A. Nebbioso, S. Simeoni, R. Ragno, S. Massa, G. Brosch, F. De Bellis, F. Manzo, L. Altucci, New pyrrole-based histone deacetylase inhibitors: binding mode, enzyme- and cell-based investigations, Int. J. Biochem. Cell Biol. 41 (2009) 235–247.
[80] W.E. Sweeney Jr., R.O. von Vigier, P. Frost, E.D. Avner, Src inhibition ameliorates polycystic kidney disease, J. Am. Soc. Nephrol. 19 (2008) 1331–1341.