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The interplay between histone deacetylases and rho kinases is important for cancer and neurodegeneration

Sonja Mertsch^{a,*}, Oliver H. Krämer^{b,*}

^aLaboratory of experimental Ophthalmology, Department of Ophthalmology, Medical Faculty, University of Düsseldorf, Merowingerplatz 1A, 40225, Düsseldorf, Germany

^bInstitute of Toxicology, University Medical Center, Obere Zahlbacher Str. 67, 55131, Mainz, Germany

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ABSTRACT

Rho associated coiled-coil containing kinases (ROCKs) respond to defined extra- and intracellular stimuli to control cell migration, cell proliferation, and apoptosis. Histone deacetylases (HDACs) are epigenetic modifiers that regulate nuclear and cytoplasmic signaling through the deacetylation of histones and non-histone proteins. ROCK and HDAC functions are important compounds of basic and applied research interests. Recent evidence suggests a physiologically important interplay between HDACs and ROCKs in various cells and organisms. Here we summarize the crosstalk between these enzymatic families and its implications for cancer and neurodegeneration.

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Abbreviations: A β , amyloid- β ; A β PP, amyloid- β protein precursor; AD, Alzheimer disease; AML, acute myeloid leukemia; APP, amyloid Precursor Protein; ARHGEF3/XPLN, rho guanine nucleotide exchange factor-3; ARHI, ras-related tumor suppressor gene aplasia Ras homolog member I; ABL, abelson murine leukemia viral oncogene homolog; BCR, breakpoint cluster region protein; BCR-ABL, tyrosine kinase leukemia fusion protein of BCR and ABL; BIM, BCL-2-like protein 11; CBP, CREB-binding protein; CD68, cluster of differentiation 68; CDC42, cell division control protein 42; CML, chronic myeloid leukemia; CHO, Chinese hamster ovary cells; CR, caloric restriction; CRD1, cell cycle regulatory domain-1; DMPK, myotonic dystrophy kinase; EGF, epidermal growth factor; ELK1, ETS domain-containing protein-1; ERK, extracellular regulated kinase; FDA, Food and Drug Administration; FOXO3, forkhead box O3; GAP, GTPase-activating protein; GATA2, GATA binding factor-2; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factor; GH, growth hormone; GTP, guanosine triphosphate; HDAC, histone deacetylase; HAT, histone acetyltransferase; HDM2, human double minute-2; HeLa, Henrietta Lacks; HH3, histone H3; HSP70, heat shock protein 70; IL-6, interleukin-6; IPF, idiopathic pulmonary fibrosis; iPSCs, induced Pluripotent Stem Cells; JAK, janus kinase; MCF7, Michigan Cancer Foundation-7 (breast cancer cell line); MDM2, murine double minute-2; MLC, myosin light chain; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mSIN3a/mSIN3b, mammalian SIN3a/Sin3b SWI/SNF

interacting protein; MYPT, myosin phosphatase target subunit-1; NAD, nicotinamide adenine dinucleotide; NCoR, nuclear corepressor; NET1A, protein networked-1A; NF- κ B, nuclear factor 'kappa-light-chain-enhancer' of activated B cells; NUR77/NR4A1, nuclear receptor subfamily-4 group-A member; OPHN1, oligophrenin-1; PC, pheochromocytoma; PD, Parkinson disease; PDGF, platelet-derived growth factor; p53, tumor protein 53 kDa; PH, pleckstrin homology; PLK1, polo-like kinase 1; PK, protein kinase; PTM, posttranslational modification; Ras, rat sarcoma; RBD, rho-binding domain; RhoA, Ras homolog gene family member A; RhoGDI α , rho guanine nucleotide dissociation inhibitor α ; rDNA, ribosomal DNA; rRNA, ribosomal RNA; ROCK, rho associated coiled-coil containing protein kinase; RBD, rho binding domain; SAH, subarachnoid hemorrhage; SAHA, suberoylanilide hydroxamic acid; SIRT, silent information regulation/sirtuins; SMRT, silencing mediator for retinoic and thyroid/Nuclear corepressor 2; STAT, signal transducer and activator of transcription; SUMO1, small ubiquitin-like modifier-1; TGF β , transforming growth factor; TNF- α , tumor necrosis factor α ; TPPP1/p25, tubulin polymerization promoting protein-1; TSA, trichostatin A; VPA, valproic acid.

* Corresponding authors.

E-mail addresses: Sonja.Mertsch@med.uni-duesseldorf.de (S. Mertsch), okraemer@uni-mainz.de (O.H. Krämer).

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1. Rho kinases: ROCK1 and ROCK2

1.1. Structure of ROCKs

ROCK1 and ROCK2 are serine/threonine protein kinases of the AGC kinase family, which is named after the protein kinase (PK) families PKA, PKG, and PKC [1,2] (Fig. 1a). ROCKs share a high phylogenetic homology with the myotonic dystrophy kinase (DMPK), DMPK-related cell division control protein 42 (CDC42)-binding kinase, and citron kinase [3]. ROCK2, originally called ROK α , was identified in 1996 as a guanosine triphosphate (GTP)-binding protein by affinity column chromatography using a GST-bound version of the small GTPase Ras homolog gene family member A (RhoA) [1,2]. ROCK1, originally called ROK β /p160ROCK, was identified one year later as isoform of ROCK2, with 90% similarity in the kinase domain and 64% overall amino acid identity [4]. ROCKs have a molecular mass of ~158 kDa and several functionally relevant domains [3] (Fig. 1a).

1.2. Localization of ROCKs

Despite the high sequence similarity in the kinase domains of ROCK1 and ROCK2, their tissue distributions are rather different. The mRNAs encoding these kinases are expressed ubiquitously, but the ROCK2 protein is mainly found in the heart and brain and only weakly in lung tissue. In contrast, non-neuronal tissues, such as kidney, pancreas, skeletal muscle, heart, lung, liver, and placenta express ROCK1 at high levels [5–7]. ROCK2 is present in the nucleus and in the cytoplasm, where it co-localizes with the cytoskeletal protein vimentin and filamentous actin [2,8]. ROCK1 shows a cytosolic localization and is associated with the plasma membrane, cell–cell contacts, cell adhesion sites, and vesicles [9]. These differences between ROCK1 and ROCK2 presumably rely on the binding preferences of their pleckstrin homology (PH) C1 domains, which selectively bind to defined sets of membrane lipids. The PH-C1 domain of ROCK2 specifically binds to phosphatidylinositol (3, 4, 5)-trisphosphate and phosphatidylinositol (4, 5)-bisphosphate

[10] (Fig. 1). Due to their high homology, both ROCKs also have common substrates *in vitro*. The occurring difference in substrate specificity and biological activity presumably results from the variable subcellular localization of ROCK1 and ROCK2 in different cell types [5–7].

1.3. Functions and regulation of ROCKs

The molecular actions of ROCKs and their effects on cell migration are cell type specific. For example, the inhibition of ROCK in endothelial cells decreases migration, while such effects do not occur in fibroblasts [11]. The N-terminal regions of ROCKs are composed of an amino-terminal kinase domain, which is followed by the Rho binding domain (RBD) containing a coiled-coil region in the middle [5]. Furthermore, ROCKs contain PH domains with internal cysteine-rich domains (Fig. 1a). Such domains serve as autoregulatory inhibitors, which are modulated through interactions with lipid mediators and the plasma membrane as well as by proteolytic cleavage [12].

The RBDs of ROCK1 and ROCK2 bind specifically and with almost equal affinities to the switch I and II regions of GTP-bound active RhoA, RhoB, or RhoC [13]. The C-termini of ROCKs function in an auto-inhibitory manner [14]. They restrict kinase activity through an association with the kinase domains (Fig. 1b). In contrast, the N-terminal kinase domains increase ROCK auto-phosphorylation and activity by the homodimerization of ROCK proteins [15]. The interaction of active GTP-bound Rho proteins with the RBD activates ROCKs by disrupting the inhibitory interaction between the kinase domain and the C-terminal autoinhibitory domain [3,6]. This conformational change frees the kinase domain (Fig. 1c).

As downstream effectors of the small GTPase Rho, ROCKs crucially control cytoskeletal remodeling, cell motility, proliferation, and cell adhesion [16,17]. Accordingly, one of the first identified functions of ROCKs was the formation of stress fibers and focal adhesion complexes by the phosphorylation of the myosin light chain (MLC) [18]. ROCKs also regulate the actomyosin

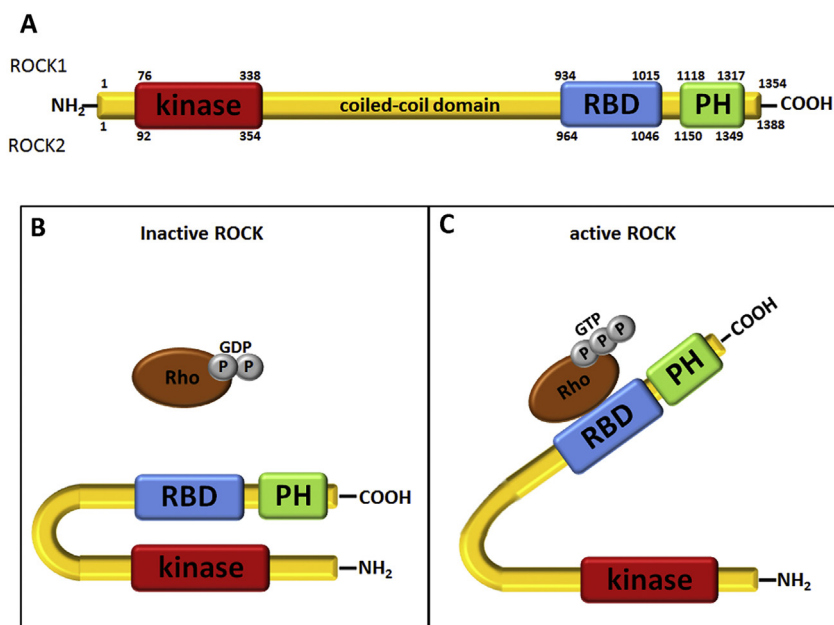


Fig. 1. Protein structures of ROCK1 and ROCK2. A) structure of ROCK1 and ROCK2 in comparison, numbers denote amino acids of the ROCKs. b) inactive ROCK and c) active ROCK with binding of phosphorylated Rho.

cytoskeleton via serine phosphorylation of MLC, myosin phosphatase, and LIM kinase [3].

1.4. Control of ROCKs by external and internal stimuli

The growth factors platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin promote stress fiber and focal adhesion formation in the presence of RhoA in murine 3T3 fibroblasts [19]. The cytokine transforming growth factor (TGF)- β induces epithelial-to-mesenchymal transition, which plays a role in embryogenesis, wound healing, metastasis and other essential biological processes [20]. TGF- β upregulates the protein expression and activity of RhoA, which in turn activates ROCKs [21]. Beside the effect of TGF β on Rho/ROCK-mediated stress fiber formation, TGF β has an influence on macrophage cell migration mediated by RhoA [22]. In a possible negative feedback, ROCK2 antagonizes TGF β signaling by its ability to promote lysosomal degradation of TGF β 1 receptors in mammalian cells [23].

There are additional pathways of ROCK activation. During apoptosis, ROCK1 is activated by the cleavage and removal of the auto-inhibitory domain by caspase-2 and caspase-3. Consequently, actin-myosin contractions become altered through increased MLC phosphorylation by ROCKs [24]. Furthermore, during the activation of the apoptotic pathway, ROCK2 can be activated by Granzyme B-mediated cleavage, which leads to caspase activation and an ensuing ROCK1 activation [25].

In contrast to most other members of the AGC family kinases, ROCKs do not require phosphorylation for activity [15]. However, other kinases modulate ROCK signaling by phosphorylation. An example for such an enzyme is the Polo-like kinase I (PLK1) [26], which is controlled by growth factors, cell cycle progression, and DNA damage. PLK1 phosphorylates ROCK2 at Thr-967, Ser-1099, Ser-1133, or Ser-1374, in a synergistic manner with RhoA, to enhance ROCK2 activity [26] (Fig. 2).

PLK1 is responsible for a variety of essential functions during mitosis such as centrosome maturation, separation and microtubule nucleation during late prophase and prometaphase [27].

Furthermore, it plays an important role in cytokinesis. The interaction between PLK1 and ROCK2 is a direct and also an indirect interaction, as PLK1 also binds to MLCK and influences ROCK via MLCK-RhoA. Additionally it binds to Citron Rho-interacting kinase (CIT) which plays a role to Myosin regulatory light chain 2, ventricular/cardiac muscle isoform (MLC-2) and therefore again to MLCK and both PLK1 and ROCKs bind to vimentin (Fig. 2) [26]. Cytokinesis is known to play an important role in cancer development due to occurring genome instability in cytokinesis failure [28]. Furthermore PLK1, ROCKs and some of their associated proteins are known to be deregulated in different cancer types. These findings showed the importance of the interaction between ROCK and PLK1.

1.5. ROCK inhibitors

In addition to the actomyosin cytoskeleton [3], ROCKs influence gene transcription, proliferation, differentiation, apoptosis, and oncogenic transformation (Table 1). Chemical inhibitors, such as Y-27632, H-1152, Wf-536, HA-1100 (hydrofasudil), and HA-1077 (fasudil), allow an assessment of the functions of ROCK. Y-27632 as well as siRNA-based, specific knockdowns of ROCK1 and ROCK2 illustrate that both kinases differentially regulate proliferation and migration based on the substrate cells grow on [29,30].

Such knowledge is important, as ROCK1 and ROCK2 have different functions in various cell types. Examples are glioblastoma cells and keratinocytes [30,31]. In glioblastoma cells, a ROCK1 knockdown reduces the substrate-dependent cell migration, whereas a ROCK2 knockdown does not produce this effect [30]. In keratinocytes, the reduction of ROCK1 promotes an inhibition in focal adhesion maturation with an increase in cell adhesion to fibronectin, while a reduction of ROCK2 leads to the formation of large focal adhesions with increased stability [31]. Such different functions of ROCKs in the regulation of cell detachment also occur in mouse embryonic fibroblasts [32]. The different functions of ROCK1 and ROCK2 presumably rely on different subcellular localizations and alternative types of regulation.

PLK and ROCK network

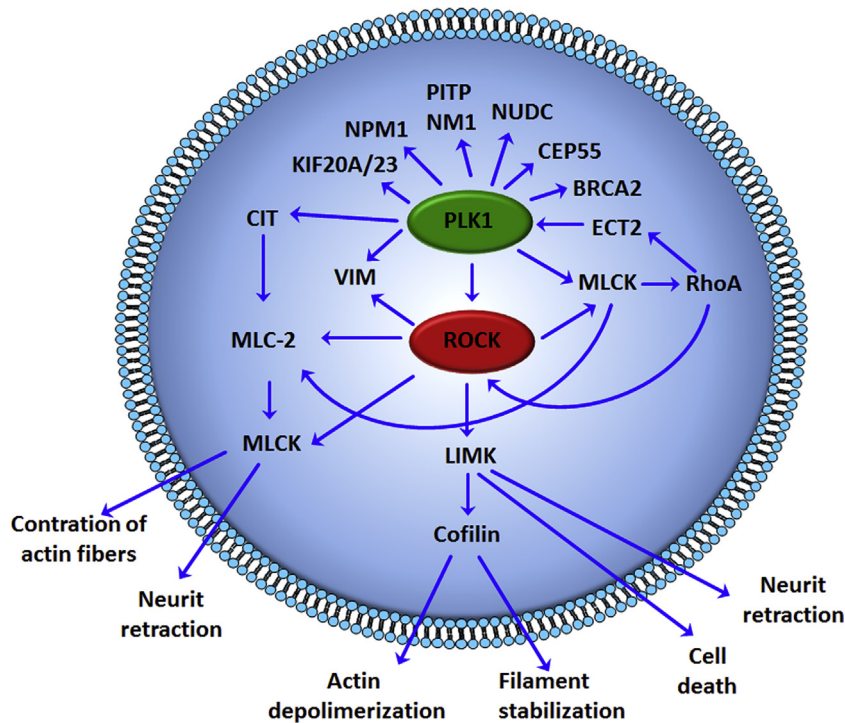


Fig. 2. PLK and ROCK network. ROCK and PLK1 display a network of similar protein interactions with myosin light chain kinase (MLCK), RhoA, Myosin regulatory light chain 2, ventricular/cardiac muscle isoform (MLC-2), vimentin (VIM) and also direct interactions. Furthermore pathways of PLK1 and ROCKs are shown. Kinesin Family Member (KIF), Nucleophosmin 1 (NPM1), Phosphatidylinositol transfer protein (PITP), Nuclear migration protein nudC (NUDC), Centrosomal Protein 55 (CEP55), breast cancer 2 (BRCA2), epithelial cell transforming 2 (ECT2), Citron Rho-interacting kinase (CIT), LIM domain kinase 1 (LIMK1). Figure modified from [26].

1.6. ROCKs in cancer

The involvement of ROCKs in different cancer types has been evaluated extensively, with a specific focus on motility, invasion, and metastasis (Table 1). Such studies revealed that ROCK inhibitors are potential cancer therapeutics [33–36].

Accordingly, ROCKs are expressed in several cancer types, such as prostate cancer [33], renal cancer [37], breast cancer [38], gastric cancer [39], and glioblastoma [30]. Furthermore, ROCKs are often found to be upregulated in different tumor entities where they contribute to a metastatic behavior [40]. ROCK expression levels negatively correlate with patient outcome in renal cell

carcinoma [41], breast cancer [42,43], colorectal cancer [44], glioblastoma [45], and hepatocellular carcinomas [46].

As ROCK signaling was found to be either pro- or anti-apoptotic depending on the cell type, the inhibition of ROCKs can lead to both apoptotic “blebbing” of the plasma membrane as well as to protective effects [47]. Such data suggest that ROCK inhibitors are potential anti-cancer drugs. Using Y-27632 and fasudil, several studies accordingly observed a promising effect of ROCK inhibition on cancer proliferation and progression [30,48]. As these inhibitors target both ROCKs, these works did not analyse functional differences between the isoforms. Therefore, recent research had begun to elucidate the role of each ROCK separately and

Table 1
Interplay between ROCKs and deacetylases/acetylation-dependent mechanisms in cancer cells and fibroblasts. The table sums up pharmacological inhibitors of ROCKs and HDACs. Abbreviations and explanations: Ø, not tested; C3 exoenzyme adds ADP-ribose moieties to Rho proteins.

Model	Signaling pathway	ROCK inhibitor	HDAC inhibitor	Reference
Murine 3T3 fibroblasts	Growth hormone signaling	C3 exoenzyme (indirect)	TSA	[79]
Human gastric adenocarcinoma cells	Histone acetylation	Y-27632	TSA	[86]
Human cervix carcinoma cells	Genesis of ribosomal RNA	Y-27632	TSA	[87]
Human breast and cervix carcinoma cells	EGF signaling	Ø	TSA, nicotinamide	[88]
Human epithelial kidney and cervix carcinoma cells	Actin filament formation	Ø	SAHA, TSA, nicotinamide, sirtinol, sodium butyrate	[89,90]
Human epithelial kidney and osteosarcoma cells	Tubulin network cell migration and proliferation	Y-27632	Ø	[95,96]
Rat mammary carcinoma cells	Durotaxis	Y-27632	MS-275, VPA	[100]
Murine pancreatic adenocarcinoma cells	Invasion and proliferation	Y-27632, C3 exoenzyme (indirect)	Ø	[102]
Human thyroid cancer cells	Growth, migration, mitotic catastrophe, senescence	Y-27632, SP600125	TSA	[107]
Human leukemia cells	Differentiation	Y-27632	MS-275	[116]
Human leukemia cells	Cell adhesion	Y-27632	SAHA	[117]

found functional difference of both ROCKs in the same cell types [30,48].

In Japan, clinicians use fasudil for vasodilatation in angina pectoris patients as well as for the treatment of cerebral vasospasm after subarachnoid hemorrhage, but not as a cancer treatment [49–51]. Other ROCK inhibitors have not entered the clinic, but some are potential agents to treat cancer in combinatory schedules [40].

Despite the enormous knowledge about ROCKs to date, there are still unidentified contributions of ROCKs to different pathways or diseases. This renders them interesting candidates for future research.

2. Histone deacetylases: classes I-IV

2.1. Acetylation and deacetylation are important regulators of protein functions

The sequence of nucleotides as well as epigenetic modifications determine cell fate and ultimately homeostasis [52]. The phosphorylation of serine, threonine, and tyrosine residues is probably the most common posttranslational protein modification (PTM) [53]. However, other PTMs such as the acetylation, sumoylation, and ubiquitinylation of lysine residues as well as their crosstalk equally control signaling and gene expression in response to extra- and intracellular stimuli and conditions [53].

The acetylation of lysine residues was first identified in the early 1960s [54]. Recent research shows that dynamic acetylation/deacetylation cycles are physiologically relevant regulators of cell growth and development [52,55]. However, the physiological relevance of only about 1–2% of the cellular acetylation patterns has been functionally characterized yet [56]. Future research will decipher how acetylation and deacetylation cycles determine cell fate decisions in more detail. Such knowledge could allow an improved and tailored therapy of patients.

2.2. The HDAC family

Such enzymes catalyze the Zn²⁺- or NAD⁺-dependent removal of acetyl groups from lysine residues in histones and non-histone proteins (Table 2). Therefore, HDACs are also termed protein deacetylases or PDACs. While this term appears more logical, because HDACs do not restrict their activities to histones, we stick to the more commonly used term HDACs. Mammalian HDACs fall into four classes (I, IIa/IIb, III, IV; Table 2) and their discovery was preceded by the identification of transcriptional repressors in yeast [57].

2.2.1. Zn²⁺-dependent HDACs

These enzymes catalyze the removal of the acetyl group from lysine residues in proteins according to the equation ϵ -N-acetylated lysine residue + H₂O → lysine residue + acetate. They represent the HDAC class I, IIa/b, and IV subfamilies [58].

In 1996, Stuart Schreiber's group isolated HDAC1, the founding member of the mammalian Zn²⁺-dependent HDACs [59]. These researchers used an affinity-matrix containing the irreversible HDAC inhibitor trapoxin to isolate HDAC1 from mammalian cell lysates. In the following years, 10 further Zn²⁺-dependent HDACs were discovered [60] (Table 2).

Class I HDACs have a size around 55 kDa and one catalytic domain (Table 2). While HDAC1 and HDAC2 mainly locate to the nucleus and bind the corepressors mammalian SIN3A/SIN3B, HDAC3 shuttles between the nucleus and cytoplasm and binds to the nuclear corepressors-1 and -2 (NCoR/SMRT) [60–62]. HDAC8 seems to be functional independent of corepressor binding [63].

Class II HDACs are larger with around 110 kDa and the subfamily IIb has two catalytic domains (Table 2). This class is frequently

found in the cytoplasm and some members undergo signal-dependent translocation to the nucleus [60,64,65].

Isoenzyme-specific biological functions of the 11 Zn²⁺-dependent HDACs exist [64–66]. There is consensus that the elimination of cancer cells by HDAC inhibitors is often due to an inhibition of class I HDACs (i.e. HDAC1, -2, -3, and -8) [58,65,67].

2.2.2. NAD⁺-dependent HDACs

The sirtuins (SIRT) form the class III subgroup of the HDAC family [55,68] (Table 2). These enzymes catalyze the removal of the acetyl group and of bulkier acyl groups from lysine residues in proteins according to the equation ϵ -N-acetylated lysine residue + NAD⁺ + H₂O → lysine residue + nicotinamide + 2'-O-acyl-ADP-ribose [69]. The fact that the SIRT-mediated deacetylation requires NAD⁺ [69] directly links SIRT activity to the cellular energy status [55,68].

Sirtuins were discovered as homologs of *Saccharomyces cerevisiae* Sir2 [70] and a large number of studies concerning their disease relevance were published [71]. Mammalian cells express SIRT1–7, which share a catalytic core domain [55,68]. SIRT1, which shares the highest homology with yeast Sir2, occurs mainly in the nucleus, but also in the cytoplasm [55,68]. SIRT1 is associated with differentiation, apoptosis, and oncogenic transformation. SIRT2 is located in the cytoplasm where it deacetylates α -tubulin. Furthermore, a nucleo-cytoplasmic shuttling mechanism possibly regulates SIRT2 [55,68]. SIRT3, -4, and -5 locate to mitochondria, where SIRT3 functions as a major deacetylase. SIRT4 is a ADP-ribosyltransferase lacking any deacetylase activity and SIRT5 functions as deacetylase and deacylase [55,68]. SIRT6 is a nuclear, chromatin-associated protein with NAD⁺-dependent deacetylase and ADP-ribosyltransferase activity. SIRT7 regulates ribosomal DNA gene expression in the nucleus [55,68] (Table 1).

2.3. Inhibitors of HDACs and SIRTs

The majority of HDAC inhibitors mimics the acetylated lysine and thereby blocks access of this substrate to the catalytic cleft of HDACs. Moreover, high affinity HDAC inhibitors bind and complex the Zn²⁺ ion at the bottom of the catalytic cleft. Consequently, it cannot polarize H₂O for the nucleophilic attack on the acetyl-lysine

Table 2

The HDAC family falls into four classes. HDACs are listed in the order of their isolation; see text for references; aa, amino acids, sizes of isoforms and splice variants may vary, numbers taken from the NCBI data bank for human HDACs; ✓, yes, ∅, no; *only one domain catalytically active, **has ADP-ribosyltransferase activity, N/A, not applicable.

HDAC	HDAC class	Active deacetylase	HDAC domains	Deacetylation cofactor	Size Protein (aa; NCBI)
HDAC1	I	✓	1	Zn ²⁺	482
HDAC2	I	✓	1	Zn ²⁺	488
HDAC3	I	✓	1	Zn ²⁺	428
HDAC4	IIA	✓	1	Zn ²⁺	1084
HDAC5	IIA	✓	1	Zn ²⁺	1123
HDAC6	IIIB	✓	2	Zn ²⁺	1215
HDAC7	IIA	✓	1	Zn ²⁺	991
HDAC8	I	✓	1	Zn ²⁺	377
HDAC9	IIA	✓	1	Zn ²⁺	1011
HDAC10	IIIB	✓	2; *	Zn ²⁺	669
HDAC11	IV	✓	1	Zn ²⁺	347
SIRT1	III	✓	1	NAD ⁺	747
SIRT2	III	✓	1	NAD ⁺	389
SIRT3	III	✓	1	NAD ⁺	399
SIRT4	III	∅	∅; **	N/A	314
SIRT5	III	✓	1	NAD ⁺	310
SIRT6	III	✓	1	NAD ⁺	355
SIRT7	III	✓	1	NAD ⁺	400

moiety [58,65]. HDAC isoenzyme-selective inhibitors might be promising drugs with lower side effects [58,65]. Such drugs can for example be generated for HDAC6, because its catalytic cleft is broader and shallower than the one of class I HDACs [65].

Several compounds act on SIRT6, but their pharmacological and clinical assessment lags behind the development of drugs against the Zn²⁺-dependent HDACs [55,66,68,69]. Resveratrol is a leading example of a natural compound that activates SIRT1 [72]. This agent occurs in at least 72 plant species. Despite initial euphoria about resveratrol, it rapidly became obvious that only a massive and excessive consumption of such plants would achieve significant levels of this agent *in vivo* [55,68]. While caution has been raised about a multitude of studies that assessed the functions of SIRT1 [73], there is ample evidence that SIRT6 are drug targets [69,74]. This has led to the characterization of new SIRT inhibitors of which some block individual members of the seven sirtuins [69].

The FDA has recently approved four HDAC inhibitors (Panobinostat (LBH589), Depsipeptide (FK228), Vorinostat (suberoylanilide hydroxamic acid (SAHA)), and Belinostat (PXD101)), which all inhibit Zn²⁺-dependent HDACs, for the treatment of hematologic disorders [75]. In addition, several combinations of HDAC inhibitors and chemotherapeutic drugs act additively/synergistically against cancer cells [58,65,67,75]. Inhibitors against HDACs are also possible treatment options for inflammatory conditions and neurodegeneration [52,76].

A large number of not exclusive mechanisms can explain the beneficial effects of HDACi. These are for example, altered gene expression, modulation of protein degradation, cell cycle arrest, differentiation, senescence, reversal of tumor-induced immune suppression, repression of angiogenesis, modulation of cytokine and hormone signaling, and other molecular and cellular pathways [66,67,77,78].

3. Regulation of signaling, gene expression, and cell fate decisions by HDAC/ROCK interactions in solid tumor cells and fibroblasts

Deacetylases and ROCKs are pivotal regulators of cell fate *in vitro* and *in vivo*. In the following section, we summarize the interplay between these two classes of enzymes (Table 1).

3.1. STAT signaling

Cytokines and growth factors activate latent, cytoplasmic transcription factors of the signal transducer and activator of transcription (STAT) family [77]. Key kinases for the phosphorylation-dependent activation of STATs are the Janus kinases (JAKs) (Fig. 3). Human growth hormone (GH) activates JAK-STAT signaling as well as the loading of RhoA with GTP and the phosphorylation of the ROCK target myosin phosphatase target subunit 1 (MYPT1) in murine 3T3 fibroblasts [79]. This activation of RhoA/ROCK depends on JAK2 and the GTPase-activating protein (GAP) p190 RhoGAP (Fig. 3 and Table 1). GAPs promote the transition from GTP-bound RhoA to its inactive GDP-binding form and catalytically active JAK2 promotes the dissociation of RhoA from its inhibitor p190 RhoGAP [79].

While JAK2 activates RhoA/ROCK, there seems to be no reverse signaling. Inhibition of RhoA with the *Clostridium botulinum* C3 exoenzyme does not affect the GH-induced phosphorylation of JAK2, STAT5, and the extracellular regulated kinase (ERK)-dependent phosphorylation of the transcription factor mitogen-activated protein kinase ETS domain-containing protein (ELK1). Instead, RhoA/ROCK signaling interferes with a negative effect of the class IIb deacetylase HDAC6 on STAT5-dependent signaling (Fig. 3). RhoA/ROCK activation blocks the interaction between HDAC6 and catalytically active or inactive histone acetyltransferase (HAT) p300 and could thereby promote STAT5 activity [79].

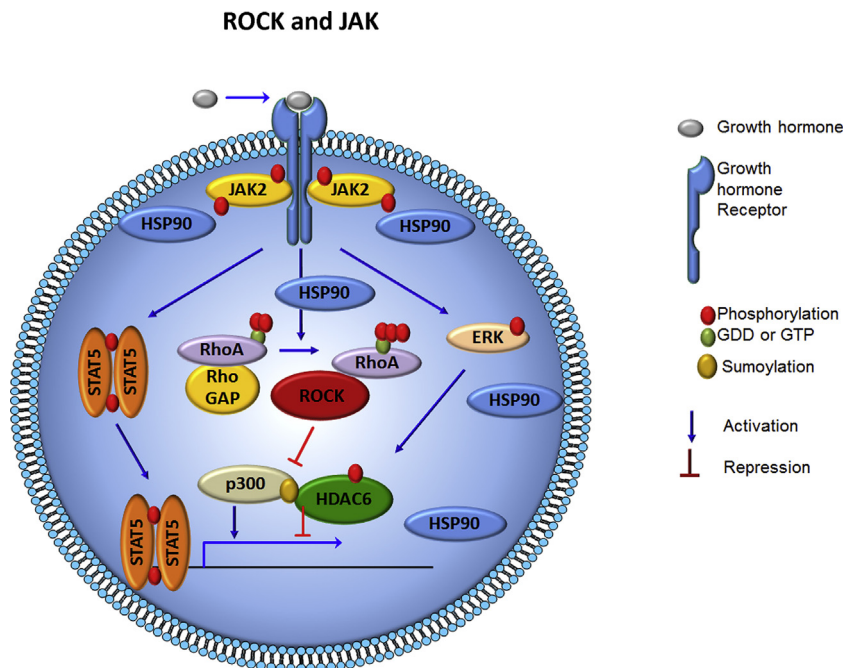


Fig. 3. Growth hormone activates STAT5 via JAK and ROCK signaling.

Binding of GH to its cognate receptor triggers a JAK2-dependent phosphorylation cascade that activates the transcription factor STAT5, the RhoA/ROCK signaling node, and signaling activating ERK. The HAT p300 and HDAC6 affect STAT5 signaling in a rather uncommon mode of action. While p300 rather acts as a transcriptional activator, the recruitment of the otherwise cytoplasmic HDAC6 causes transcriptional repression. Sumoylation of p300 appears as a regulator of this process. ERK and the chaperone HSP90 could mediate several steps of the GH-dependent signaling.

Since the cell cycle regulatory domain-1 (CRD1) of p300 recruits HDAC6 dependent on the small ubiquitin-like modifier-1 (SUMO1) [80], the authors speculated that p300 without CRD1 would be neutral for the GH-induced STAT5 reporter. Indeed, such a p300 mutant failed to attenuate the reporter. The observation that the pan-HDAC inhibitor trichostatin A (TSA) antagonized negative effects of HDAC6 on the STAT5-dependent reporter system further suggest that HDAC6 negatively regulates STAT5 activity in fibroblasts [79] (Fig. 3). This work was one of the first linking ROCK signaling to HDAC functions.

Evidence accumulating in the following years revealed that HATs and HDACs control STAT5 itself [77]. Therefore, one cannot exclude that ROCK signaling also affects the acetylation-dependent control of STAT5. It may also be relevant that the chaperone heat shock protein 90 (HSP90) controls several steps of the GH-induced JAK- and ROCK-dependent signaling (Fig. 3) [65,81,82]. Drugs targeting the ATPase activity of HSP90 have been developed and gave promising results in some settings [83]. Moreover, HDACi can trigger an inactivating acetylation of HSP90 [65]. Further analyses are necessary to clarify the role of HSP90 for GH-induced signaling pathways.

An interplay between ROCKs and STATs operates in further systems. For example, an inhibition of ROCK2 promotes the activity of STAT5 in human T cells or peripheral blood mononuclear cells from patients with the autoimmune disorder systemic lupus erythematosus [84]. Moreover, mutant JAK2 contributes to leukemogenesis via constitutive STAT activation and this may also involve Rho- and ROCK-dependent signaling networks [85]. Whether ROCK signaling represents a novel pharmacological target in such diseases is currently an interesting, open question.

3.2. Histone acetylation

ROCK signaling also affects PTMs at the very global level of histone acetylation. Gastric adenocarcinoma cells that adhere to fibronectin have higher levels of acetylated histone H3 (HH3) than cells growing in suspension [86] (Table 1). This is linked to a differential activity of HDACs under these two conditions. While HH3 and HDACs are expressed to comparable levels under each condition, there is an about two fold higher ROCK1 mRNA and protein expression in suspended cells [86]. Moreover, manipulation of RhoA/ROCK signaling with dominant negative RhoA, siRNA against ROCK1, Y-27632, and Rac1QL (a constitutive active mutant form of Rac1) illustrates that ROCK activity is necessary for basal and TSA-increased acetylation of HH3 in suspension cells. While TSA cannot augment the levels of acetylated HH3 in fibronectin-attached cells, acetylation of HH3 increases with the actin depolymerase inhibitor cytochalasin D [86].

It is surprising that fibronectin-attached cells cannot accumulate hyperacetylated HH3 in response to TSA, because a multitude of reports unequivocally demonstrates that adherent cells can accumulate hyperacetylated histones in response to HDAC inhibitors (for example, works cited in [52,55,58]). Additional data are required to explain such a phenomenon. Perhaps, PTMs of HDACs and/or specific complex formation protect fibronectin-adherent cells from TSA. Alternatively, fibronectin might alter the uptake of TSA.

3.3. Synthesis of rRNA

A further global process that the HDAC/ROCK interplay controls is the synthesis of ribosomal RNA (rRNA). ROCK and HDAC1 determine the genesis of rRNA in HeLa cervix carcinoma cells [87] (Table 1). Expression of a hyperactive ROCK mutant, which causes cytoskeletal stress, increases the binding of HDAC1 to ribosomal RNA (rDNA) genes. This reduces H3K9/14 acetylation, which is a

positive histone modification mark for rDNA transcription. The authors verified the specificity of the ROCK/HDAC1 interplay for rDNA transcription with RNAi against HDAC1, TSA, and Y-27632 [87]. Further research will elucidate details on the interactions of HDAC1 and ROCK in this process. HDAC1 and ROCK might be substrates for each other and further HDACs may regulate rDNA transcription.

3.4. Acetylation-dependent control of ROCK signaling

Direct acetylation/deacetylation cycles can equally affect Rho-dependent signaling (Table 1). For example, the RhoA guanine nucleotide exchange factor (GEF) NET1A is controlled by acetylation and its N-terminal acetylation is required for EGF-induced extranuclear relocalization and activation of RhoA in human breast and cervix carcinoma cells [88].

Rho guanine nucleotide dissociation inhibitors (RhoGDIs) maintain Rho GTPases in an inactive, cytosolic form that is protected from proteasomal degradation. Rho proteins are consequently unable to interact with activating GEFs, but they are still rapidly inducible upon appropriate stimuli [89,90]. The ubiquitously expressed chaperone RhoGDI α is controlled by acetylation at several lysine moieties and the HATs CBP and p300 regulate the acetylation of RhoGDI α antagonistically with HDAC2 and SIRT2 [89,90] (Table 1). Accordingly, HDAC inhibitors can augment the acetylation of RhoGDI α [90].

The studies [89,90] used a number of state-of-the-art techniques to elaborate how site-specific lysine acetylation determines the interactions of RhoGDI α with RhoA and CDC42, the antagonistic interplay with RhoGDI α sumoylation at the lysine residue K138, and actin filament formation in recombinant assays and in HeLa cells. Apparently, HeLa and human epithelial kidney cells modulate endogenous RhoA dynamically through acetylation and deacetylation of RhoGDI α at eight sites [89,90]. Acetylation of K127/K141 increases the hydrophobicity of RhoGDI α and likely interrupts its electrostatic interaction with RhoA [89]. Furthermore, mutation of K141 to a lysine-mimicking glutamine moiety thickens actin stress fibers in HeLa cells [91]. The frequently observed alterations of cell morphology in the presence of HDAC inhibitors may hence relate to effects of these drugs on RhoGDI α [58,65].

Notably, direct acetylation modifies multiple factors that control the actin cytoskeleton in human cancer cells (HeLa, U2OS osteosarcoma, A549 lung cancer cells, MV4-11 acute myeloid leukemia cells) when they are exposed to HDAC inhibitors (MS-275 or SAHA) or DNA damage (Etoposide, UV-light, or gamma-irradiation) [92–94]. Among these molecules are ROCK1 and ROCK2. Thus, further analyses could identify an acetylation-dependent control of ROCK-dependent signaling cascades.

3.5. Regulation of microtubuli

HDAC/ROCK interactions also control the tubulin network and thereby the migration and proliferation of permanent human cell lines (Table 1). Such processes involve the control of the microtubule network by phosphorylation of the tubulin polymerization promoting protein-1 (TPPP1/p25). ROCK-mediated phosphorylation of TPPP1 disrupts its interaction with HDAC6, which is a major deacetylase for tubulin [95]. Since TPPP1 blocks HDAC6 activity, inhibition of ROCKs with Y-27632 increases the acetylation of microtubuli [96].

3.6. The tumor suppressor p53

The tumor-suppressive transcription factor p53 regulates cell growth, DNA repair, apoptosis, metabolism, and several other key

cell fate decisions. Accordingly, p53 is functionally lost or mutated in most human tumors in adults [97,98]. Furthermore, mutant p53 has not only lost the anti-tumorigenic properties of wild-type p53, but acts as an oncogenic driver and promoter of invasion and metastasis [97,98].

Overexpression of p53 reduces ROCK1 and ROCK2 expression and RNAi against p53 increases both ROCKs in human keratinocytes [99] (Fig. 4). This mechanism of ROCK1 regulation involves a p53-dependent induction of the transmembrane receptor Notch-1. The activation of its downstream targets occurs via an intracellular form of Notch-1. This molecule is generated proteolytically by γ -secretase, upon the association of Notch-1 with its membrane-bound ligands [99–101]. Since class I HDACs and SIRT1/SIRT2 regulate the acetylation of p53, which controls its stability and the expression of its target genes [69], HDAC and SIRT inhibitors might regulate p53-dependent effects on ROCKs [97].

In pancreatic cancer cells, there is an interplay between ROCKs and HDACs at the level of mutant p53 (Fig. 4). A positive regulation of RhoA by mutant p53^{R172H} (which corresponds to the human Li-Fraumeni mutation in tumors) contributes to the invasive properties of murine pancreatic ductal adenocarcinoma cancer cells [102]. The authors assessed the interplay between mutant p53^{R172H} and ROCK signaling with imaging experiments *in vivo* and they compared non-invasive, p53 null and invasive p53 mutant pancreatic ductal adenocarcinoma cancer cells. The study demonstrates that the ROCK inhibitor Y-27632 attenuates the invasiveness of p53^{R172H}-positive pancreatic ductal adenocarcinoma cancer cells [102] (Table 1).

Class I HDAC inhibitors could be an option to target the expression of mutated p53, which is positively regulated by HDAC1/HDAC2 and HDAC8 in various tumor cells [82,103–105]. A resulting beneficial suppression of RhoA/ROCK-dependent signaling on tumor cell migration may not be restricted to pancreatic cancers, as mutant p53 also promotes RhoA activity in colon, lung, breast tumors, melanoma cells, and embryonic fibroblasts

[97,98,106]. It remains to be shown whether ROCK inhibitors affect the expression and stability of wild-type and mutant p53.

An interplay between p53, HDACs, and ROCKs also exists in thyroid cancers [107]. The c-Jun N-terminal kinase (JNK) inhibitor SP600125, which has also activity against ROCK2 and several other kinases, is an effective drug against this cancer type [107] (Table 1). At the molecular level, SP600125 blocks the ROCK/HDAC6 interaction through an increased interaction between HDAC6 and TPPP1. Consequently, the HDAC6 targets tubulin and β -catenin show augmented acetylation. Moreover, SP600125 promotes p53 DNA binding, the induction of its growth inhibiting target gene p21^{WAF/CIP1}, and cellular senescence [108].

The efficiency of chemotherapy often depends on the p53 status of the tumor [97,98]. HDACs and SIRT2s reduce p53-dependent transcriptional activation and apoptosis through the deacetylation of p53. Therefore, agents antagonizing these enzymes can activate p53 signaling and tumor cell death [97,98,109,110]. Different HDAC inhibitors enhance p53 expression through a reduction of the E3 ubiquitin ligase murine/human double minute-2 (MDM2/HDM2) (Fig. 4), which negatively regulates the stability of p53 [97,98]. Acetylation and phosphorylation of p53 abrogate the binding between p53 and HDM2 [97,98]. On the other hand, HDAC inhibitors reduce the expression of the *TP53* gene [82,103–105]. It therefore appears that the less stable wild-type p53 is transiently stabilized and that the more stable mutant p53 becomes reduced in HDAC inhibitor-treated cells [82,103–105]. The acetylation of p53 might be a rheostat for ROCK signaling.

3.7. Durotaxis

In rat mammary adenocarcinoma cells grown on high-density collagen matrices, Notch-1 is important for the suppression of ROCK1 mRNA and protein expression by the class I HDACi MS-275 and valproic acid (VPA) [100]. Increased stiffness of the extracellular matrix also increases ROCK2 expression in the breast cancer cell line MCF7 [111]. Such substrates promote durotaxis, the

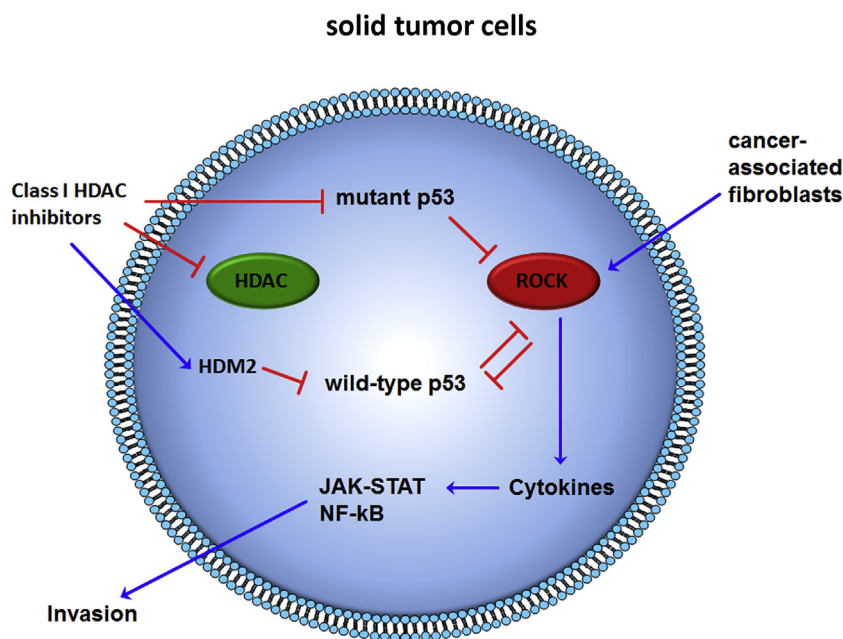


Fig. 4. HDAC/ROCK interactions in solid tumor cells.

Wild-type and mutant p53 as well as NF- κ B and JAK-STAT signaling interact with ROCKs and modulate cell fate decisions in tumor cells and surrounding cells. Class I HDACi suppress the transcription of the *TP53* gene in its wild-type and mutant form. These drugs also decrease the expression of the E3 ubiquitin ligase HDM2, which accelerates the proteasomal degradation of wild-type p53. In an indirect feedback mechanism, HDACi could modulate invasive properties of cancer cells.

attraction of tumor cells to stiffer matrices. The mechanism by which these HDACi repress ROCK1 involves an upregulation of Notch-1 and *de novo* protein synthesis [100].

A recent report though shows that ROCK2 is required for the induction of p53 in MCF7 cells that are exposed to the DNA-damaging chemotherapeutic drug doxorubicin [111]. While it cannot be judged if HDAC inhibitors represent a valid option in such a combinatorial setting, it is well established that MS-275 and VPA suppress breast cancer cell growth *in vivo* [112,113].

3.8. Tumor-associated cells

One should additionally consider that ROCK inhibitors restrict cancer cell growth and development through their effects on stromal cells [40]. ROCK activity in cancer-associated fibroblasts is necessary for the invasiveness of squamous cell carcinoma cells [114]. This may be mediated by pro-inflammatory cytokines, including TNF- α , IL-6, and Oncostatin M, and an ensuing activation of the cytokine-regulated STAT and NF- κ B signaling pathways [114,115]. Since acetylation-deacetylation balances critically regulate these factors [77], HDAC/ROCK inhibitor combinations might be a valid option to block cancer cell invasiveness and inflammation linked to these signaling molecules.

4. HDAC/ROCK interaction in leukemic cells

4.1. Transcriptional control of the GTP/GDP cycle by HDACi

Recent publications report that HDAC inhibitors modulate ROCK signaling in leukemic cells [116,117] (Fig. 5 and Table 1). A global transcriptome analysis of U937 histiocytic lymphoma cells revealed that Rho guanine nucleotide exchange factor-3 (ARHGEF3/XPLN) and the monocyte/macrophage marker cluster of

differentiation 68 (CD68) were among the most strongly upregulated genes in response to 5 μ M of the HDAC1-3 selective benzamide HDAC inhibitor MS-275 after 6 and 24 h incubation periods [116].

ARHGEF3 is a GEF that specifically activates RhoA and RhoB [118]. Within minutes, ARHGEF3 translocates from the nucleus to the cytoplasm in response to MS-275. This alteration of its localization correlates with morphological changes and alterations in the actin cytoskeleton [116]. This rapid redistribution of ARHGEF3 precedes the increase in its expression [116], which may indicate that PTMs (e.g., acetylation) of ARHGEF3 or its import/export factors are involved (Fig. 5).

The authors link ARHGEF3 to the differentiation response as they demonstrate that an RNAi-mediated attenuation of ARHGEF3 decreased the expression of CD68 on the surface of MS-275-treated U937 cells as well as the phosphorylation-dependent activation of the JNK [116]. JNK is a downstream target of ROCK and the ROCK inhibitor Y-27632 could prevent the surface expression of CD68 in MS-275-exposed U937 cells [116]. These data suggest that the increased levels of ARHGEF3 contribute to a monocyte-like maturation of U937 cells. Such effects are highly relevant in light of the fact that leukemic cells cannot fully mature into functionally competent, mature blood cells [116,117,119]. The induction of ARHGEF3 by MS-275 may also promote erythroid differentiation [120].

ARHGEF3 and its target RhoA are necessary for the uptake of iron by normal erythroid precursors of *Danio rerio* and by human erythroleukemic K562 cells. The uptake of iron is a prerequisite for hemoglobin synthesis and erythroid maturation [120] and class I HDAC-selective HDAC inhibitors including the benzamide MS-275 and the cyclic peptide apicidin promote a p38 MAPK-dependent accumulation of fetal hemoglobin in K562 cells [121]. In contrast to these rather class I HDAC-selective agents, the hydroxamic-acid

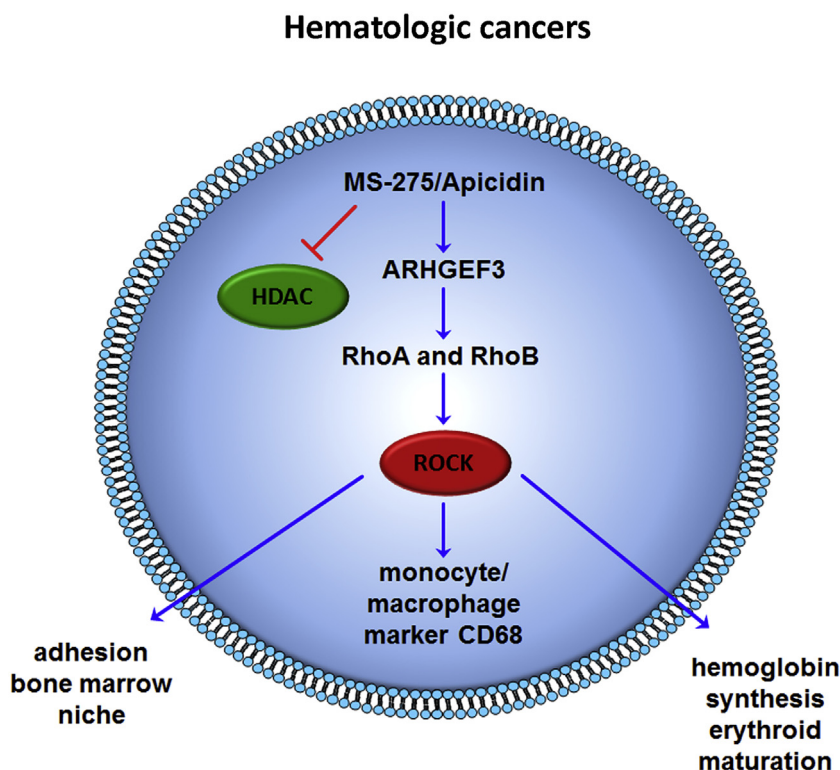


Fig. 5. HDAC/ROCK interactions in leukemic cells.

The HDAC inhibitor-induced differentiation program and the adhesion of leukemic cells are associated with ROCK signaling. Inhibitors of class I HDACs induce ARHGEF and thereby ROCK signaling in leukemic cells. While differentiation of leukemic cells is desired, their attachment to stroma promotes chemotherapy resistance.

based pan-HDAC inhibitors SAHA and TSA failed to induce fetal hemoglobin in K562 cells. This study ruled out that a massive induction of cell death by these compounds was the reason for this unexpected finding. SAHA could also not promote the differentiation of U937 cells; unfortunately, apoptosis was not assessed in this context [116].

The inability of hydroxamic acids to propel differentiation may result from a failure of SAHA to induce a persistent histone hyperacetylation after a 4-day exposure [121]. Congruent with this idea, the HDAC1/HDAC2-selective benzamide compound-60 also evoked a more stable histone hyperacetylation than SAHA in human epithelial kidney cells [122]. Perhaps, the more reactive hydroxamic acids cannot persist in a stable manner for such extended treatment periods and therefore fail to activate the erythroid differentiation program. One though cannot exclude that apoptosis overrides differentiation, as seen in other cellular systems [119].

HDACs and SIRT6 critically contribute to a methylation-dependent epigenetic control of gene expression, which might affect ROCK signaling [52,55,58]. The Rho inhibitor and tumor suppressor ARHGAP26/Graf1 is frequently methylated in leukemic patients [40,123] and HDACs and SIRT6 may regulate this epigenetic silencing mechanism.

4.2. Modulation of cell adhesion by HDAC/ROCK interactions

Adhesion of cells to the extracellular matrix and to other cells regulates growth, metastasis, drug sensitivity, and other key cellular processes [124]. HDAC inhibitor- and cell type-specific effects determine whether HDAC inhibitors alter the adhesion of human hematopoietic cancer cells to fibronectin [117]. While SAHA enhances the expression of integrin- β 1 and paxillin- α , which are constituents of the focal adhesion complex, TSA and sodium butyrate failed to produce such effects (Table 1). Concerning ROCK, its inhibition with Y-27632 impaired the SAHA-induced adherence of the chronic myeloid leukemia (CML) T lymphoid cell line CML-T1, but not of four other leukemia/lymphoma cell lines, to fibronectin [117].

This finding is surprising as ROCK1/ROCK2 generally promote the adherence of adherent cells to fibronectin [125]. However, CML-T1 is equally an exceptional cell line, as there usually is no clear T cell involvement in CML, which is usually driven by the leukemia fusion protein BCR-ABL [126]. Whether this observation is valid for other blood cancers of this type and whether it has *in vivo* significance remains unclear. If this pathway operates as a druggable mechanism *in vivo*, a possible benefit could be the

detachment of blood cancer cells from the cytoprotective bone marrow niche by ROCK inhibitors, in order to sensitize such cells to cytotoxic chemotherapy [117,127]. Since this attachment is mediated by the secreted factor wingless-type MMTV integration site family member-3, the integrins β 1/ α 6, and ROCKs, agents against these signaling molecules may equally be used in combinatorial approaches with HDAC and ROCK inhibitors [127].

Interestingly, ROCK1 is an already validated drug target in AML and CML cells *in vitro* and *in vivo* [48,127]. Thus, a combination between inhibitors of ROCKs and HDACs may abrogate protective cancer cell attachment, while pro-apoptotic effects of the inhibitors kill the malignant cells.

5. Deacetylase/ROCK interactions in neurodegenerative diseases

ROCKs regulate key neuronal processes, such as growth cone dynamics, stability of synapses, and axogenesis [128]. An upregulation of ROCK expression occurs in neurodegenerative diseases [129,130]. Moreover, ROCKs hamper axonal regeneration and pro-survival pathways [131].

The roles of HDACs and SIRT6 in neuronal diseases are in the focus of current research. It is known that HDACi regulate transcriptional activators of neuronal survival genes and provide neuroprotective mechanisms in Parkinson Disease (PD) and Alzheimer Disease (AD) [132]. SIRT6 directly deacetylate different proteins to evoke beneficial effects in neurodegenerative diseases [133]. In the following section, we summarize the interplay between ROCKs and deacetylases in PD and AD (Table 3).

5.1. Sirtuins and ROCK in Parkinson disease

PD is a chronic and progressive disease of the central nervous system that mainly affects the motor system [134]. Several mechanisms contribute to PD, such as dopaminergic neuron degradation in the *substantia nigra* in the brain, intracellular development of Lewy bodies, an abnormal protein aggregation, as well as an impaired ubiquitin-proteasome system. The accumulation of α -synuclein and the occurrence of Lewy bodies are characteristic for PD [134,135]. A recent study shows that the inhibition of RhoA significantly reduces α -synuclein expression levels, which are mediated by the transcription factors serum response factor (SFR) and megakaryoblastic leukemia 1 (MLK1) [136,137] (Table 3). Similar to the known influence of ROCK inhibition on HSP70 and the resulting neuro-protective effects [137], SIRT6 significantly affect α -synuclein and the heat shock protein 70 (HSP70) in PD. SIRT1 suppresses the formation

Table 3
Interplay between ROCKs and deacetylases/acetylation-dependent mechanisms in neuronal diseases. The table sums up pharmacological inhibitors or activators of ROCKs and Sirtuins. Abbreviations and explanations: \emptyset , not tested; CR, caloric restriction.

Model	Signaling pathway	ROCK inhibitor/activator	SIRT inhibitor/activator	Reference
SK-N-BE (human neuroblastoma cell line)	α -synuclein toxicity (via HSP70)	\emptyset	Resveratrol (activator)	[72,139]
MN9D cells (Model for dopamine neurons)	Neurit extension	C3 transferase (indirect)	\emptyset	[136]
Mouse model of PD	Axon degeneration (via HSP70)	Fasudil (inhibitor)	\emptyset	[137]
primate model (<i>Macaca mulatta</i>)	α -synuclein toxicity (via HSP70)	\emptyset	CR (activator)	[140]
Drosophila melanogaster PD model	α -synuclein toxicity	\emptyset	siRNA SIRT2 and AGK2 (inhibitor)	[144]
AD Mouse Model	Decreased A β levels.	isoform-selective small molecule (SR3677, ROCK2 inhibitor)	\emptyset	[151]
PC12 cells as AD model	Attenuated A β induced cell death	\emptyset	Resveratrol (activator)	[155– 157]
AD Mouse model and Chinese hamster ovary (CHO) cells	SIRT1-mediated decrease of ROCK1	Constitutively active ROCK1	CR	[161]

α -synuclein in an *in vivo* PD model of *Caenorhabditis elegans* [138]. Furthermore, resveratrol, an indirect activator of SIRT1, protects the human neuroblastoma cell line SK-N-BE against α -synuclein toxicity [72,139] (Table 3). In a primate model (*Macaca mulatta*) of PD, caloric restriction (CR), which upregulates SIRT1, leads to an improvement of the locomotor functions and increases dopamine neuronal survival after treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [140]. Different studies have shown that in these PD models, SIRT1 plays a role in the activation of heat shock factor 1 (HSF1), which transcriptionally upregulates heat shock protein (HSP) genes, including HSP70 [141,142]. HSP70 expression protects dopaminergic neurons from neurodegenerative cell death by α -synuclein [143] (Fig. 6), which leads to the indirect protective effect of SIRT on dopaminergic neurons.

SIRT2 also plays a role in PD. A SIRT2 inhibitor produces a dose-dependent reduction of α -synuclein toxicity in an *in vitro* model. Moreover, the SIRT2 inhibitor can protect dopaminergic neurons from cell death in a *Drosophila melanogaster* fly model of PD [144] (Table 3). These findings lead to the hypothesis that SIRT1 and ROCK, both regulating α -synuclein and HSP70 in PD, interact and play an important role in this neurodegenerative disease (Fig. 6).

Furthermore, an indirect link between ROCKs and HDAC6/TPPP1 operates in human kidney cells and osteosarcoma cells. ROCKs phosphorylate TPPP1, which in turn disrupts the interaction of TPPP1 with HDAC6, a major deacetylase for tubulin. Consequently, the enhancement of HDAC6 activity results in a decreased microtubule acetylation [95,96]. An increased acetylation through the inhibition of HDAC6 and of SIRT2 via an inhibition of ROCK activity results in restored axonal transport and a recovery of locomotor ability in a *Drosophila melanogaster* PD model; these flies develop PD through a Leucine-rich repeat kinase-2 mutations that commonly occurs in humans [145] (Fig. 6). This finding indicates a promising use for ROCK inhibitors in PD.

5.2. Sirtuins/HDACs and ROCK in Alzheimer disease

AD is a chronic neurodegenerative disease, which leads to severe cognitive syndromes, such as loss of memory,

disorientation, problems with language, and behavioral issues. In addition, body functions are lost at the late stage of this disease. The dementia, which occurs at a middle stage of AD, associates with synaptic injury and neuronal loss [146]. Further characteristics of the AD pathology are amyloid- β (A β) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau [147]. Several gene mutations occur in AD patients, such as the amyloid precursor protein (APP), presenilin-1, and presenilin-2. The proteolytic enzyme α -secretase cleaves within APP to generate the A β protein. This factor is primarily responsible for the development of A β plaques. Aggregation of the A β protein in the brain plays an important role in the initial phase of AD. Abnormal accumulation of A β , which is based on an imbalance between A β production and clearance, results in the formation of toxic oligomers in the brains of patients [148]. Different studies have already shown a significant influence of ROCK inhibition on AD through a direct modulation of A β levels [149–151]. Additionally, different animal models show that CR, which shifts the balance from NADH to NAD⁺, has beneficial effects on AD pathology [152] (Fig. 7). SIRT1 plays an important role in the CR-induced increase in lifespan in a variety of animal models [153]. This relies on the increase of NAD⁺, which is a cofactor for SIRT1. The SIRT activator resveratrol is able to attenuate A β induced cell death [154–156] (Table 3). Other studies confirmed that resveratrol could reduce the A β plaque formation *in vivo* by using a transgenic mouse model [157–159]. Additionally, SIRT1 plays an important role in neuroprotection by a reversible, inactivating deacetylation of NF- κ B p65 at K310 upon its activation by A β [160]. Inhibitions of this acetylation by SIRT1 or its agonist resveratrol exert neuroprotective effects. This leads to the hypothesis that SIRT1 and resveratrol are possible therapeutic compounds for AD treatment [160] (Fig. 7). A combination of *in vitro* and *in vivo* models confirmed this neuroprotective effect of SIRT [149,161] (Table 3). The inhibition of ROCK2 leads to a suppression of the β -site APP cleaving enzyme-1, leading to a reduced A β production in mouse brain [151]. Interestingly, the effect of SIRT1 on AD relies on the influence of SIRT1 on ROCKs. In an AD mouse model, SIRT1 downregulates ROCK1, and this leads to enhanced α -secretase activity [161]. In an *in vitro* model, the expression of constitutive

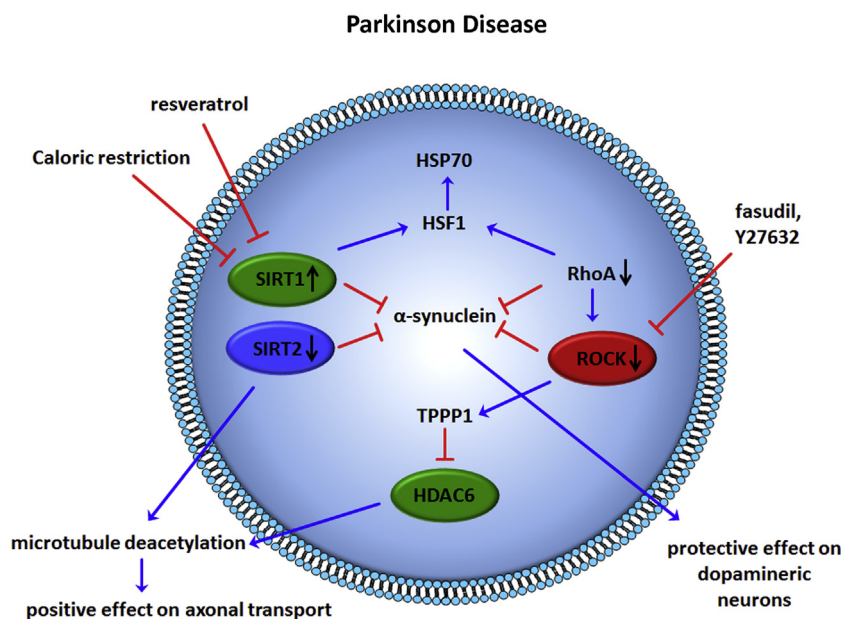


Fig. 6. SIRT and ROCK interactions in Parkinson Disease.

In Parkinson Disease, SIRT1 upregulation and SIRT2 downregulation show an inhibitory effect on α -synuclein. ROCKs as well as RhoA inhibition impair α -synuclein aggregation, which results in a positive effect on dopaminergic neurons.

active ROCK1 in CHO-APP_{swe} cells (Chinese hamster ovary cells expressing human APP with the Swedish mutation) leads to a significant reduction in sAPP α [161]. Furthermore, a stable hSIRT1 expression in a transgenic mouse model results in a significant reduction of ROCK1 expression. These results were the first showing an influence of SIRT1 on the expression of ROCK1 [161] (Fig. 7).

Resveratrol also inhibits neuronal apoptosis in AD through the SIRT-ROCK1 signaling pathway in PC12 cells, which are derived from murine adrenal gland. In this model for neuronal cells, resveratrol increases cell viability *in vitro* [162]. Furthermore, resveratrol reduces apoptosis through the activation of SIRT1, which in turn leads to an inhibition of ROCK1. To elucidate the SIRT-ROCK interplay, this study used the SIRT inhibitor nicotinamide and the ROCK inhibitor Y-27632. It turned out that SIRT1 inhibition augments ROCK1 expression, but the inhibition of ROCK1 does not interfere with SIRT expression levels in PC12 cells. These data indicate that SIRT1 acts upstream of ROCK and directly regulates its expression [162].

The beneficial effect of CR in AD also occurs in a monkey (*Saimiri sciureus*) model [163]. In a group with CR, 30% of the animals show a reduction in A β ^{1–40} and A β ^{1–42} peptides as analyzed by ELISA assay. Furthermore, in the brain area with reduced A β peptides, an increased amount of SIRT1 protein is detectable, but there are no changes in the full-length amyloid- β protein precursor (A β PP). Congruent with previous findings using the Tg2576 AD mouse model (mice expressing mutant APP with the Swedish mutation), ROCK1 expression was decreased in the same brain regions [161]. This finding again indicates the influence of the SIRT-ROCK

pathway in AD pathology [163] (Fig. 7). An abnormal microtubule association through the protein tau leads to intracellular neurofibrillary tangles and A β plaques, characteristics of AD [147]. This relies on hyperphosphorylated tau, resulting in a low tubulin-binding activity and microtubule destabilization. Microtubules are composed of α - and β -tubulin heterodimers. There are many posttranslational modifications of the C-terminal end of α -tubulin, such as deetyrosination, acetylation, and postglutamylation [164]. It was also shown that there is a reduction in total α -tubulin and an increase in the acetylated α -tubulin level compared to remaining total α -tubulin in AD brains [165]. The authors of this work suggest that the increase in acetylated α -tubulin is a compensatory mechanism for the loss of microtubules to stabilize the remaining network. The connection between HDAC6 inhibition and an increase in acetylated α -tubulin improved memory in a tau AD mouse model and reduce cognitive defects [166,167].

Remarkably, HDAC6 inhibition by soluble A β was found to increase the levels of heterodimeric acetylated tubulin and tau, which are both important factors for the pathogenesis of AD [168]. HDAC6 deacetylates both tau and tubulin and consequently, the binding between tau and microtubuli becomes impaired [169,170]. Additionally, the contact between A β and the plasma membrane induces growth cone collapse by the activation of the RhoA/ROCK pathway [168]. The activation of this pathway, together with the inhibition of HDAC6 by intracellular A β , results in cytoskeletal instability of neurites and the loss of neuronal polarity [168]. These findings lead to the conclusion that the inhibition of the ROCK pathway, as well as the inhibition of HDAC6, may be a useful tool to enhance the treatment of AD.

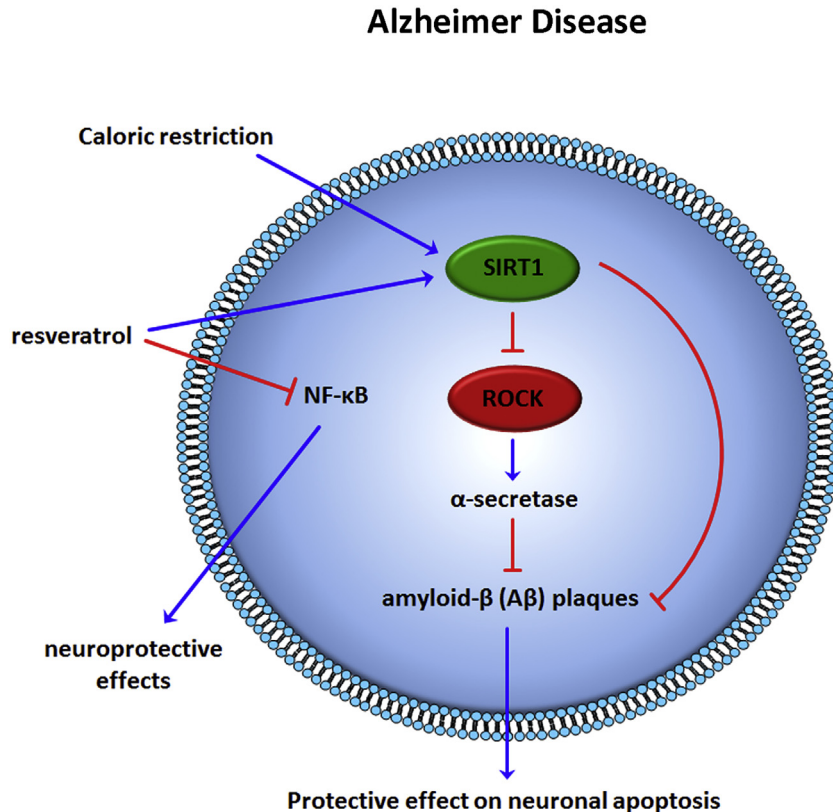


Fig. 7. SIRT and ROCK interactions in Alzheimer Disease.

In AD, there is a direct link between SIRT1 and ROCKs. The upregulation of SIRT1 results in an inhibition of ROCK activity, which in turn influences α -secretase. Upregulation of α -secretase leads to an impairment of A β plaque formation and an ensuing protective effect on neurons. SIRT1 also inhibits A β plaque formation directly.

6. Putative HDAC/ROCK interaction in other diseases

6.1. X-linked intellectual disability and cerebellar hypoplasia

Oligophrenin-1 (OPHN1) is a Rho GTPase activating factor. A functional loss of OPHN1 contributes causally to X-linked intellectual disability and cerebellar hypoplasia [171]. Such cells display ROCK hyperactivity and neuronal maturation defects [172]. Recent work shows that OPHN1 and its impact on ROCK control the phosphorylation of HDAC7 [173], which belongs to the subgroup of class IIa HDACs [174]. Using induced pluripotent stem cells (iPSCs) from OPHN1-mutated patients and healthy individuals, the authors demonstrate that a loss of OPHN1 leads to a hyperphosphorylation of HDAC7 and its accumulation in the nucleus [173]. Since a MYPT1/phosphatase-1 β complex can dephosphorylate HDAC7 in thymocytes [175], hyperphosphorylation of HDAC7 could be due to a ROCK-dependent, inactivating hyperphosphorylation of MYPT1 [176]. As a result, the expression of the nuclear receptor subfamily-4 group-A member/nuclear hormone receptor (NUR77/NR4A1; a steroid-thyroid hormone-retinoid orphan receptor) and the apoptosis of thymocytes are suppressed [175]. Also in iPSCs, the phosphorylation of HDAC7 inversely correlates with the levels of NUR77/NR4A1 [173]. These data support the notion that HDAC7 controls the expression of this orphan receptor in blood cells and suggest the validity of this finding in other cell types [175].

6.2. Fibrosis

The interaction between ROCKs, HDAC7, and NUR77/NR4A1 may also have relevance for further severe diseases. For example, NUR77/NR4A1 blocks TGF- β target gene expression and fibrotic diseases in a complex with various transcriptional corepressors [177]. Primary tissues from patients suffering from idiopathic pulmonary fibrosis (IPF) overexpress HDAC7 and several other HDACs [178]. ROCK activation occurs in patients with IPF and inhibitors of ROCK are beneficial for this detrimental lung disease [179]. Therefore, further studies could address whether the interplay between dysregulated HDAC expression patterns, excessive ROCK signaling, and NUR77/NR4A1-dependent processes is therapeutically relevant and druggable.

6.3. Niemann-Pick type C disease

In a mouse model of progressive Niemann-Pick Type C disease, the inhibition of ROCK increases p53 phosphorylation in neurons. The finding let the authors speculate that ROCK signaling promotes the MDM2-mediated degradation of p53 in this model system [180,181]. Furthermore, the ROCK inhibitor Y-27632 rescues the effect of growth cone collapse induced by p53 inhibition. The authors of the study revealed that p53 acts upstream of ROCKs and suppresses their activity through local interaction in the growth cones. [181].

7. Conclusion

Despite the ongoing research on ROCKs HDACs, additional research is necessary to fully identify their physiological functions. HDAC inhibitors undergo testing in clinical trials and some of these agents are approved for the treatment of hematopoietic malignancies. ROCK inhibitors may become relevant as drugs against various cancer types. Since there is an intense crosstalk between ROCKs and HDACs at several levels of signaling and in various types of human ailments, drugs that are effective against these enzymatic classes should be considered further as innovative, single or combined treatment options. Furthermore, the interactions in the signaling pathways of ROCKs and HDACs/SIRT1s in

neuronal disorders, such as PD and AD, suggest that both inhibitor classes could be useful as new drug combinations for these severe diseases.

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Sonja Mertsch focuses on understanding the role of Rho Kinases in different diseases such as glioblastoma and other neuronal diseases. Furthermore, she is working on the roles of different cell signaling cascades on corneal nerve regeneration. She studied biology at the Westfälische Wilhelms-University Münster, Germany. She obtained her PhD for her work on molecular mechanisms of tumor cell migration in the Institute of Neuropathology Münster. After a postdoctoral trainee time on the area of chorioid plexus tumors, she joined the Institute of experimental Ophthalmology as a group leader for glioblastoma and nerve regeneration research. In 2015 Dr. Mertsch was appointed as an lab head and working group leader in the Eye Clinic Düsseldorf, Laboratory of Experimental Ophthalmology where she has since worked.



Oliver H. Krämer investigates epigenetic modifiers of the histone deacetylase (HDAC) family, HDAC inhibitors, the crosstalk between posttranslational modifications, and cancer-relevant transcription factors. He studied biology and pharmacology at the Ruprecht-Karls-University Heidelberg, Germany. In addition, he studied biochemistry and molecular biology at the University of Adelaide, Australia. He investigated how valproic acid acts as HDAC inhibitor at the Georg-Speyer-Haus in Frankfurt/Main, Germany. For these works, he obtained his Ph.D. in biochemistry from the Johann-Wolfgang-Goethe University in Frankfurt/Main, Germany. He then joined the Center for Molecular Biomedicine, Friedrich-Schiller-University Jena, Germany, where he worked as post-doctoral fellow and later as group leader and associate professor. In 2013, he moved to the Department of Toxicology of the University Medical Center, Mainz, Germany, where he has since worked as a full professor.