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Review

Histone deacetylase 2 controls p53 and is a critical factor in tumorigenesis

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ABSTRACT

Histone deacetylase 2 (HDAC2) regulates biological processes by deacetylation of histones and non-histone proteins. HDAC2 is overexpressed in numerous cancer types, suggesting general cancer-relevant functions of HDAC2. In human tumors the *TP53* gene encoding p53 is frequently mutated and wild-type p53 is often disarmed. Molecular pathways inactivating wild-type p53 often remain to be defined and understood. Remarkably, current data link HDAC2 to the regulation of the tumor suppressor p53 by deacetylation and to the maintenance of genomic stability. Here, we summarize recent findings on HDAC2 overexpression in solid and hematopoietic cancers with a focus on mechanisms connecting HDAC2 and p53 in vitro and in vivo. In addition, we present an evidence-based model that integrates molecular pathways and feedback loops by which p53 and further transcription factors govern the expression and the ubiquitin-dependent proteasomal degradation of HDAC2 and of p53 itself. Understanding the interactions between p53 and HDAC2 might aid in the development of new therapeutic approaches against cancer.

Contents

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1. The epigenetic regulator histone deacetylase 2 (HDAC2)

Deacetylases are often dysregulated in cancer [1,2] and HDAC overexpression disturbs cell cycle control and differentiation [3,4]. HDAC2 is one of the HDACs most frequently overexpressed in tumors [3].

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Table 1
Clinical studies on HDAC2 expression in human cancers.

	Major finding	Patients	Method(s)	Reference
Hematological disorders				
Acute lymphoblastic leukemia (ALL)	HDAC2 expression elevated	93	qPCR	[185]
ALL	High HDAC2 without prognostic difference	94	qPCR	[186]
ALL	Elevated HDAC2 expression compared to control	30	qPCR	[187]
Acute myeloid leukemia (AML)	Significant differences in HDAC2 expression between two subgroups of AML patients defined by gene-expression patterns	132	qPCR	[188]
AML	Overall increase in mean HDAC2 expression when compared to controls, but large individual differences in HDAC2 levels	23	qPCR	[64]
Hodgkin's lymphoma (HL)	High HDAC2 expression in Hodgkin and Reed–Sternberg cells, correlation with worsened outcome	293	TMA	[189]
Peripheral T-cell lymphoma (PTCL), diffuse large B-cell lymphoma (DLBCL)	Overexpression of HDAC2 compared to normal lymphoid tissue, but no correlation to survival	31 DLBCL; 45 PTCL	IHC	[190]
DLBCL, PTCL, NK/T-cell lymphomas (NKTCL), reactive lymphoid hyperplasia (RLH)	High IHC scores for HDAC2 in RLH, NKTCL and PTCL	9 RHL; 78 DLBCL; 13 PTCL; 13 NKTCL	IHC	[191]
Colon and colorectal cancer				
	58% HDAC2-positive	140	IHC	[69]
	>2-fold upregulated compared to normal mucosa	16	qPCR	[70]
	ca. 2-fold upregulation compared to normal mucosa	86	qPCR	[71]
	82% show HDAC2 overexpression (compared to normal tissue)	57	IHC	[44]
	HDAC2 score increased with dedifferentiation	91	TMA	[72]
Colonic adenomas (CAD) Colorectal carcinoma (CRC)	Stronger expression of HDAC2 in adenoma and carcinoma than normal tissue, correlation to CRC progression	134 CAD; 59 CRC	TMA	[192]
Pancreatic cancer				
Pancreatic (ductal) adenocarcinoma (PDAC)	Increase of HDAC2 compared to normal tissue, correlation of HDAC2 with dedifferentiation; meta-analysis of microarray sets shows HDAC2 correlation with cytological grade	35	TMA	[105]
PDAC	Subset of PDACs (63%; 51/81) HDAC2 positive	81	IHC	[104]
Gastric cancer				
	Patients examined after conventional neoadjuvant chemotherapy, 85% (108/128) high HDAC2 expression; no association with response to chemotherapy or overall survival	128	IHC	[99]
	143/293 HDAC2-positive, HDAC2 overexpression associated with decreased long term survival	293	TMA	[100]
	62% (44/71) moderate to strong expression of HDAC2, associated with aggressiveness (lymph node metastasis)	71	IHC	[101]
	57% (11/19) HDAC2 level upregulated compared to surrounding non-tumor tissue	19	IHC	[102]
	Meta-analysis of NCBI GEO database with cohorts of gastric cancer patients (accession numbers GSE24375 and GSE13196); HDAC2 expression enhanced in gastric adenoma and adenocarcinoma compared to normal tissue, confirmed at 12 randomly selected samples with Western Blot	n/a	IB	[103]
Esophageal squamous cell carcinoma (ESCC)	Higher expression of HDAC2	6	IB	[193]
ESCC	Higher expression of HDAC2, correlation with histological grade and lymph node metastasis	69	IHC	[194]
Renal cancer				
	High expression of HDAC2 in 60% of tumors	108	TMA	[105]
Hepatic cancer				
Hepatocellular carcinoma (HCC)	Higher expression compared to normal tissue, correlation with poor prognosis	170	TMA	[98]
HCC	Upregulated in a subset of HCC	10	IB	[195]
HCC	Meta-analysis of NCBI GEO GSE14520, GSE16757 and GSE25097, significant upregulation of HDAC2 in HCC compared to normal tissue; poor prognosis for patients with high HDAC2 levels in HCC tumors	n/a 100	qPCR IHC	[97]
Lung cancer				
Lung adenocarcinoma, basaloid carcinoma, squamous cell carcinoma	77% (27/35) higher HDAC2 score compared to surrounding normal tissue	35	TMA	[120]
Non-small cell lung cancer (NSCLC)	46/95 HDAC2 positive	95	IHC	[122]
NSCLC	Elevated HDAC2 levels compared to normal tissue	18	IHC	[121]
Breast cancer				
	Intermediate to high HDAC2 expression in 56% of tumors; correlation with undifferentiated, ER negative and HER2 positive tumors; strong expression in aggressive tumors	238	IHC	[126]
Skin/epidermal cancers				
Oral squamous cell carcinoma (OSCC)	86% (80/93) positive, 54% (50/93) high HDAC2 expression	93	IHC	[144]
Mobile tongue SSC	High HDAC2 expression in 55%, no correlation with survival	49	IHC	[145]
Cutaneous T-cell lymphoma (CTCL)	Elevated HDAC2 expression, higher HDAC2 expression in aggressive CTCL subtypes	73	IHC	[196]
Keloid scars	HDAC2 score doubled in keloid scars compared to surrounding tissue	11	IHC	[146]
Central nervous system cancers				
Astrocytoma, glioblastoma	No upregulation of HDAC2 evident	43	qPCR	[152]
Gynecological malignancies				

(continued on next page)

Table 1 *(continued)*

	Major finding	Patients	Method(s)	Reference
Ovarian cancer (OC), endometrial carcinomas (EC)	OC 93% HDAC2-positive; EC 95% HDAC2-positive	465 OC; 149 EC	TMA	[161]
Cervical intraepithelial neoplasia (CIN), SCC, adenocarcinoma (AC)	HDAC2 expression ca. 2-fold elevated compared to normal tissue	50 CIN; 141 SCC; 24 AC	TMA	[165]
EC	Elevated HDAC2 expression	70	IHC	[162]
Endometrial stromal sarcoma (ESS)	Elevated HDAC2 score	24	IHC	[167]
EC, ESS	HDAC2 levels were significantly higher in endometriotic versus endometrial stromal cells	26	TMA, IB	[166]
OC	Higher HDAC2 expression compared to normal tissue	22	qPCR	[164]
OC	HDAC2 expression elevated compared to normal tissue	18	qPCR, IB	[163]
OC	Overexpression of HDAC2 (together with HDAC1/HDAC3)	115	IHC, IB	[197]
Prostate cancer				
	Strong expression of HDAC2, correlation with dedifferentiated tumors, HDAC2 independent prognostic marker	192	IHC	[157]
	Enhanced HDAC2 expression	82	IHC	[156]
Urothelial cancer	Upregulation in a subset of tumors, but no predictor of HDACi treatment efficiency	24	qPCR	[198]
Rhabdoid tumors	Overexpression of HDAC2	23	qPCR	[199]

Note: The listed studies were manually retrieved from PubMed by searching for "HDAC2 + *cancer*" in June 2013, but the list might not be complete. Expression of other HDACs was often tested together with HDAC2 expression but is not mentioned for clarity; see individual references for details. Methods' abbreviations: IHC, immunohistochemistry; TMA, tumor microarray; IB, immunoblot; and qPCR, quantitative real-time PCR.

Moreover, monitoring HDAC2 expression during treatment can serve as a marker for the efficacy of histone deacetylase inhibitors (HDACi), and HDAC2 expression levels represent an independent prognostic marker in the clinic [5,6] (Table 1).

HDACi are structurally diverse compounds which include broad range, so called pan-HDACi, and isoenzyme-selective HDACi [7,8]. Both inhibitor types are considered as promising agents for cancer therapy [9] (Table 2). Treatment with HDACi induces the accumulation of (hyper)-acetylated proteins [10]. Consequently, gene expression patterns and signaling nodes are altered in cells exposed to these agents [11,12]. There is an ongoing, intensive search for drugs that strictly target HDAC2 [7,13]. Such agents are expected to clarify the molecular functions of HDAC2 [2], and they could provide beneficial therapeutic properties while also having lesser side effects [14].

Histone deacetylase 2 (HDAC2) catalyzes the deacetylation of lysine residues in proteins [1,2,15,16]. HDAC2 is regulated by a plethora of posttranslational modifications (PTMs) (Fig. 1A and B) and it has also been clarified how HDAC2 expression is controlled by transcriptional and posttranscriptional mechanisms (Fig. 1C). For several PTMs regulating HDAC2 the responsible enzymes are known (Fig. 1B) [1,2]. Although these represent druggable factors, they have targets in addition to HDAC2.

2. The interplay between HDAC2 and the tumor suppressor p53

The tumor-suppressive transcription factor p53 [17] is currently the most intensely investigated target protein of HDAC2 (Table 3). Numerous target genes of p53 tetramers regulate growth arrest, senescence, and apoptosis to restrict cellular transformation [18]. In addition, p53 affects metabolic processes and the generation of reactive oxygen species [19]. Most tumors have a defective p53 pathway either due to a loss of *TP53* (the p53-encoding gene in humans), mutations in *TP53*, or aberrations in signaling pathways controlling the levels and activity of the p53 protein [17,20]. PTMs including phosphorylation, acetylation (depicted in detail in Fig. 2), ubiquitinylation, and sumoylation affect p53 and regulate its functions in vivo [18,21]. Interactions of p53 with other transcription factors and regulators also dictate p53 expression and activity [22,23].

Recent data show a tight link between the functions of p53 and HDAC2 (Table 3). We are beginning to understand the specific control of p53 through HDAC2 and to appreciate that PTMs precisely control this interaction (Fig. 3). Our article summarizes how interactions between HDAC2 and p53 affect tumorigenesis and how this connection might be exploited in therapeutic settings.

2.1. HDAC2 is recruited by p53 as a corepressor

HDAC2 and p53 control each other and consequently gene expression by three major processes. These are discussed in the following sections. HDAC2 is recruited to promoters of p53-dependent target genes to repress their transcription (Table 3). PTMs of HDAC2 (Fig. 1A and B) govern its interactions with specific targets. For example, while unphosphorylated HDAC2 does either not associate with chromatin or binds to regions within genes, phosphorylated HDAC2 efficiently localizes to corepressor complexes and transcription factors [24].

To regulate p53 target gene expression HDAC2 can also cooperate with peptidylarginine deiminase 4 (PAD4), which is involved in the regulation of lysine methylation by triggering arginine citrullination. HDAC2 and PAD4 serve as p53 corepressors. They suppress histone acetylation and methylation when bound to promoters [25]. Release of PAD4 and HDAC2 from the promoters of the p53 target genes *cyclin-dependent kinase inhibitor 1* (*CDKN1A*, encoding $p21^{CIP1/WAF1}$), *growth arrest and DNA-damage-inducible* (*GADD45A*), and *p53 upregulated modulator of apoptosis* (*PUMA*/*BBC3*) after genotoxic stress results in increased histone acetylation, methylation and transcription of these genes [25]. However, HDAC2 might also contribute to the regulation of p53 target genes independently of p53. For example, on the *p21* promoter, HDAC2 is recruited to two distinct binding sites by metastasis-associated protein 1 (MTA1) even in the absence of p53 [26]. This observation could provide a plausible explanation why HDACi can also induce a p53-independent induction of p21.

2.2. Regulation of p53 acetylation by HDAC2

Acetylation is indispensable for proper p53 functions [27,28]. At least 13 lysine residues of p53 are acetylated (Fig. 2) [17,27], and p53 deacetylation by HDAC2 controls p53 (Table 3). Several lines of evidence suggest that K320 acetylation is relevant for p53 signaling and that HDAC2 targets this site. We could recently show that HDAC2 deacetylates lysine residue K320 of p53 in colon cancer cells. A sumoylation-dependent interaction of HDAC2 and p53 leads to diminished acetylation of $p53^{K320}$ (Fig. 3A), reduced DNA binding of p53, and impaired transcriptional regulation of its target genes [29] (Fig. 1B). K320 is located in the linker/tetramerization domain of p53 (Fig. 2). It was accordingly found that the C-terminal region of p53 plus the tetramerization domain including K320 interacted more strongly with HDAC2 than the N-terminal part of the protein [25]. Dominant-negative effects caused by reduced acetylation at $p53^{K320}$

Table 2
Information about the HDACi that are mentioned in this review, focusing on substances inactivating HDAC2.

HDACi	Inhibitory profile	Substance class	Indications	References
Vorinostat/SAHA (suberoylanilide hydroxamic acid)	Pan-HDACi	Hydroxamic acid	Approved for CTCL, in clinical trials for other cancers	[8,200]
Romidepsin/FK288	Pan-HDACi	Depsipeptide	Approved for CTCL, in clinical trials for other cancers	[201]
VPA (valproic acid)	Class I selective	Short fatty acid	Clinical trial phase III	[202]
Entinostat/MS-275	Class I selective (HDAC1 > 2 > 3)	Benzamide	Clinical trial phase II	[203,204]
Butyrate	Pan-HDACi	Short fatty acid		[205,206]
Panobinostat/LBH-589	Pan-HDACi	Hydroxamic acid		[207,208]
Trichostatin A (TSA)	Pan-HDACi	hydroxamic acid	Model HDACi not considered for clinical use	[209,210]
BRD8430	Class I selective (HDAC1 > 2 > 3)	Lactam, ortho-amino aniline group		[153]
CG-1521 (JW-1521)	n/a	Hydroxamic acid		[158]
OSU-HDAC42 (AR-42)	n/a	Phenylbutyrate based hydroxamic acid		[211]

HDACi inhibition profile for several HDACi was recently tested for the 11 human HDACs in two studies [7,13]. CTCL: cutaneous T cell lymphoma.

could poison p53 tetramers to strongly impair p53 target gene expression [30].

Congruent with these data no transcriptional induction of the pro-apoptotic p53 targets *p53-induced gene 3* (*PIG3*, *TP53I3*) and *phorbol-12-myristate-13-acetate-induced protein 1* (*NOXA*; *PMAIP1*) was observed in p53-negative KATO-III gastric cancer cells ectopically expressing a $p53^{K320R}$ mutant after treatment with the HDACi butyrate. Accordingly, $p53^{K320R}$ cannot promote apoptosis of KATO-III cells exposed to butyrate [31]. Moreover, mimicking pseudo-acetylation at K320 with the mutant $p53^{K320Q}$ redirects p53 predominantly to high affinity binding sites like those in the *CDKN1A* promoter [32]. Acetylation of $p53^{K320}$ also controls expression of the *CCNB2* gene encoding cyclin B2. This gene is trans-repressed by p53 whereas $p53^{K320R}$ fails to repress *CCNB2*. Consistently, pseudo-acetylated $p53^{K320Q}$ is a much more potent repressor of *CCNB2* [33].

Knock-in mice carrying $p53^{K317R}$ (murine K317 corresponds to human K320) are viable and show no difference in lifespan compared to their wild-type littermates. Responses to genotoxic stress in $p53^{K317R}$ MEFs are hardly altered. However, $p53^{K317R}$ can transactivate pro-apoptotic target genes of p53, but not p53 target genes regulating the cell cycle in murine thymocytes [34]. This finding points to cell type-specific functions of HDAC2 on p53. HDAC2 is furthermore involved in the deacetylation of C-terminal lysine side chains in p53. In the hepatocellular carcinoma cell lines HepG2 and Huh7 downregulation of HDAC2 mainly affects p53 acetylation at K373 and K382, respectively [35] (Fig. 2). Furthermore, in murine keratinocytes double-negative for *Hdac1*/*Hdac2* the acetylation of p53 on K376 (corresponding to human K381) and K380 (human K386) is significantly higher than in wild-type keratinocytes [36]. Interestingly, K320 appears to be specifically targeted by HDAC1 and HDAC2 whereas C-terminal lysine residues within p53 are also targeted by SIRT1 (Fig. 2).

The reasons for diverting effects of HDAC2 activity on p53 acetylation in different systems require further investigation. It should be considered that knock-in mouse models may not reflect the human situation, especially when mutations are introduced that are not commonly found in human cancers [37]. Additionally, p53 signaling is regulated in an oscillatory way, in the steady state as well as after DNA damage [38,39]. Mutations of acetylation sites might abolish modification/removal cycles crucial for gene activation.

2.3. Cross-regulation of HDAC2 protein stability through p53

A molecular network of ubiquitin (Ub) E3 ligases connects HDAC2 and p53 (Table 3). HDAC2 is targeted for poly-ubiquitinylation and proteasomal degradation through the Ub-E3 ligase RING finger LIM domain-binding protein (RLIM/RNF12) together with the HDACi-inducible Ub-E2 conjugase UBCH8 [40] and by the MCL1 ubiquitin ligase E3 (MULE/ARF-BP1/HUWE1) [41] (Figs. 1B and 3C). The acetylation of p53 and the transcriptional activation of p53 target genes, like *p21*, are impaired in *MULE*-null mice [41]. Moreover, in $MULE^{-/-}$ cells the apoptotic p53 response after DNA damage can be rescued by HDACi or by genetic elimination of HDAC2 [41]. In murine keratinocytes, MULE deficiency additionally results in elevated levels of c-MYC and MIZ1 which can directly diminish the expression of *p21* and $p15^{INK4B}$ (*CDKN2B*) [42]. Curiously, *HDAC2* expression can be directly upregulated by c-MYC (Fig. 3B) [43,44], but HDAC2 levels in *MULE*-deficient keratinocytes are unexpectedly not changed [42]. As MULE also directs K63-linkage of Ub to c-MYC, which exerts signaling functions rather than proteasomal degradation [45], it is tempting to speculate that MULE deficiency evokes cell type-restricted effects on the regulation of c-MYC and in turn on HDAC2 and the p53 pathway (Fig. 3B).

A feedback loop from p53 towards RLIM and MULE may equally control HDAC2 and this could provide an integrating framework for the observations made (Fig. 3C). MULE directly targets p53 for proteasomal degradation [46] and RLIM is marked for degradation by poly-ubiquitinylation through the Ub-E3 ligase seven in absentia homologue 1 (SIAH1) [47]. Both, RLIM and SIAH1 are p53 target genes. p53 induces transcription of *SIAH1* [48,49] and *RLIM* expression is trans-repressed by p53 [50]. Therefore, reduced levels of MULE lead to enhanced p53 levels, which could at the same time, strengthen the repression of *RLIM* and activate *SIAH1* expression. This would stabilize HDAC2 (Fig. 3C) which could then act more efficiently on p53, for example by deacetylating K320 [29] (Fig. 3A). An additional level of control is set by SIAH1's closely related sister enzyme SIAH2 [51]. SIAH2 can reduce p53 acetylation at K320 (Fig. 3C) by promoting proteasomal degradation of the acetyltransferase PCAF, which acetylates $p53^{K320}$ [52] (Fig. 2). Furthermore, high SIAH2 levels correlate with elevated p53 levels and *SIAH2* expression is also enhanced by p53 [52–54]. SIAH1 activity on the RLIM/HDAC2 axis and SIAH2 activity on PCAF have an equal functional impact on $p53^{K320}$ acetylation. These mechanisms might work cooperatively or they might be activated separately. Further studies are needed to resolve under which conditions MULE acts directly on HDAC2, indirectly by influencing levels of RLIM and SIAH, or by both pathways. It seems plausible that multiple factors govern these decisions in certain cell types and developmental conditions.

3. HDAC2 and its connection to p53 are critical for the pathogenesis of human cancers

3.1. Role of HDAC2 in malignancies of the hematopoietic system and for immune functions

Malignancies of the hematopoietic system are often characterized by chromosomal translocations [55–57]. These result in fusion proteins,

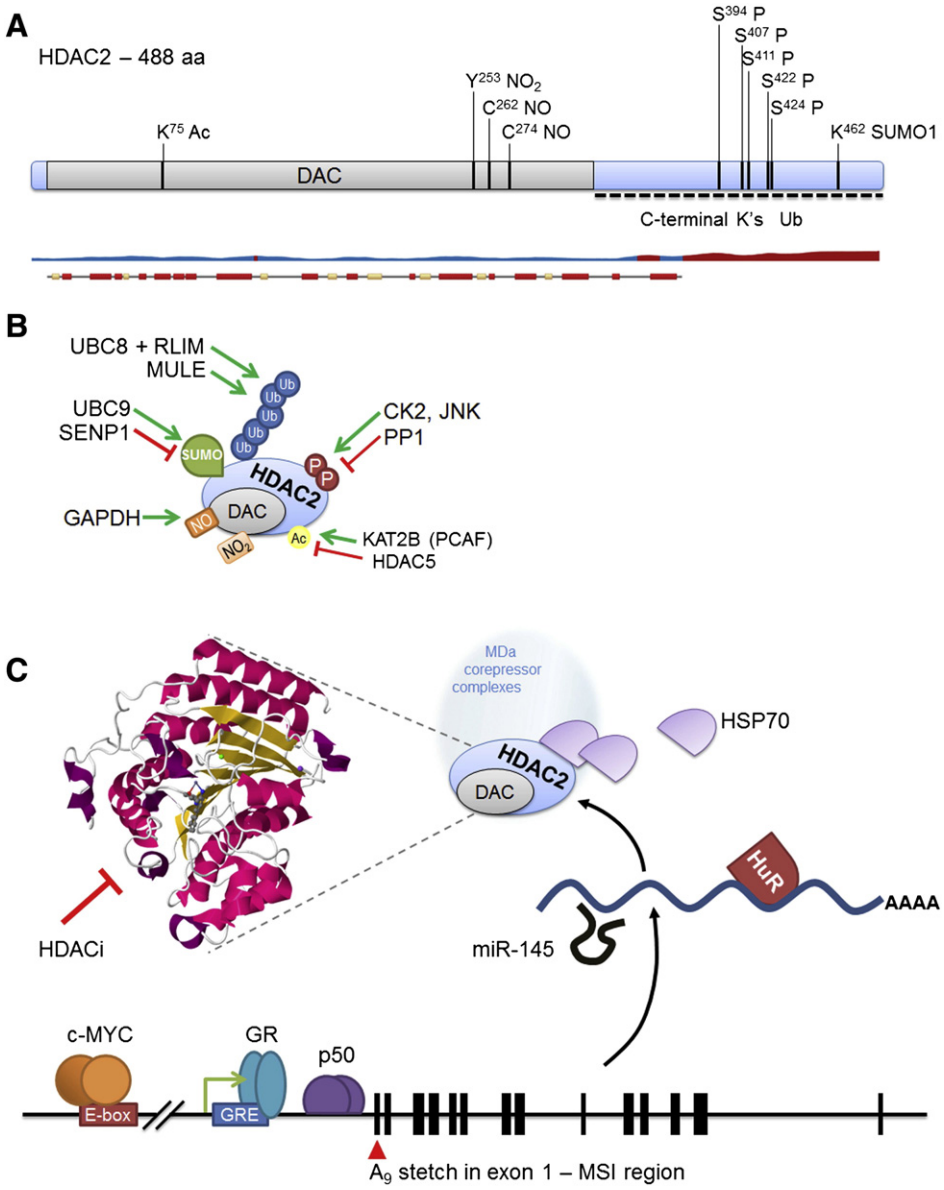

Fig. 1. Regulation of HDAC2. (A) The position of known posttranslational modifications (PTMs) of HDAC2 is shown. The histogram below is a probability prediction of protein structure disordering (red: probably disordered; calculated using JRonn) and a bar diagram with known secondary structure features of HDAC2 (yellow: strands; red: helices). Both were adopted from the PDB entry for HDAC2 (Q92769; http://www.rcsb.org/pdb/protein/Q92769 and references therein). (B) Enzymes responsible for PTMs of HDAC2 are depicted in the top panel (for references see [1,2,29,184]). (C) HDAC2 is scattered across 14 exons on chromosome 6 (not shown true to scale). An A_9 stretch in exon 1 is the region where microsatellite instability (MSI) occurs. *HDAC2* transcription is governed by the transcription factors c-MYC, NF-κB p50, and the glucocorticoid receptor (GR). Feedback loops from HDAC2 towards p50, GR, and c-MYC exist but are omitted for clarity. *HDAC2* mRNA stability is regulated by *miR-145* and the RNA binding protein HuR (ELAV1). HDAC2 structure (PDB entry 3MAX, residues 9–374; prepared using Jmol) bound by a model HDAC inhibitor (HDACi) in the catalytic cleft is shown. HDAC2 usually exists in high molecular weight complexes with other corepressors/-activators. DAC depicts the catalytic deacetylase domain. HSP70 can bind to and activate HDAC2. PTMs: Ac: acetylation; NO: S-nitrosylation; NO_2: nitration; SUMO: small ubiquitin-related modifier; Ub: ubiquitin.

Table 3
Impact of HDAC2 on p53 in tumor cell lines and murine embryo fibroblasts (MEFs).

Target(s)	Function of HDAC2	Relevance	Cell type/organ	References
p53 DNA binding and target gene expression	Repression	Chromatin/proliferation/ senescence	Breast cancer cells	[127]
p53 expression	Repression, via recruitment to CAGE and SNAIL	Chromatin/apoptosis	Melanoma and hepatic cancer cells	[147]
p53 target gene expression	Repression, in combination with PAD4	Chromatin/proliferation	diverse cancer cell lines	[25]
p53 acetylation and target gene expression	Repression, MULE-dependent proteasomal degradation of HDAC2	Chromatin/apoptosis	MEFs	[41]
p53 acetylation and target gene expression	Repression, HDAC2 sumoylation-dependent inactivation of p53	Chromatin/apoptosis	Colon cancer cells	[29]

SNAIL (Zinc finger protein SNAI1); CAGE (CAGE1, Cancer-associated gene 1; also: cancer/testis antigen); PAD4 (peptidylarginine deiminase 4); MULE (MCL1 Ubiquitin-Ligase E3; also: HUWE1, ARF-BP1).

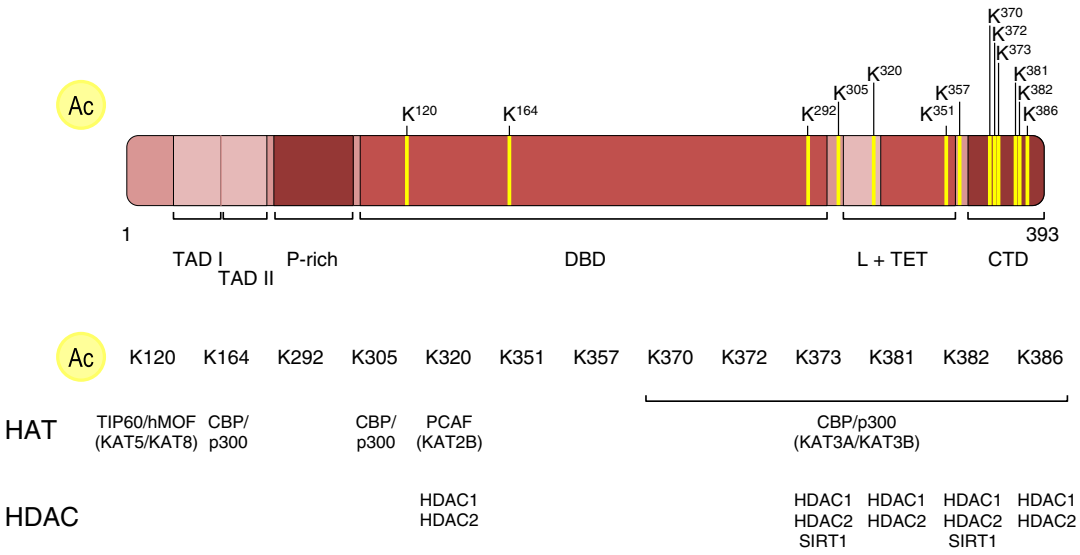

Fig. 2. Schematic representation of p53 domain structure and acetylation sites. p53 is a 393 amino acid protein. The N-terminus of p53 has two transactivation domains (TAD I, residues 20–40; TAD II, residues 40–60) and a proline-rich domain (P-rich, residues 63–97). The core DNA-binding domain (DBD) spans residues 100–300 followed by the linker and tetramerization domain (L + TET, residues 307–323–355). The C-terminal domain (CTD) spans residues 360–393. Yellow vertical marks indicate at least 13 lysine residues that can be modified by acetylation (Ac). Known lysine acetyltransferases (KATs) and HDACs regulating individual acetylation sites in vivo are stated. Of note, in vitro HDAC1 and also maybe SIRT1 are probably capable of removing acetylation from all sites. Questions marks indicate correlative evidence for the respective enzymes on p53 acetylation at the indicated sites.

which can consist of the DNA binding domain of one transcription factor fused to a protein that recruits epigenetic silencing factors including HDACs. Prominent examples are the leukemia fusion proteins PML–RARα (chromosomal translocation t(15;17)) and AML1–ETO (t(8;21)). These cause transcriptional silencing and a subsequent block in the differentiation of hematopoietic precursors. The inhibition of HDACs and the elimination of leukemogenic fusion proteins allow the differentiation of immature cells and triggers apoptosis [51].

HDAC2 and HDAC1 are also pivotal factors in normal hematopoiesis and the development of immune cells. Mice having neither *Hdac1* nor *Hdac2* show a halt in thymocyte proliferation [58,59] and a conditional knock-out of *Hdac1* and *Hdac2* in late T cell development impairs the maintenance of the CD4+ T cell lineage [60]. An inducible double knock-out of both, *Hdac1* and *Hdac2* in mature mice utilizing the *Mx–Cre* system causes thrombocytopenia by premature apoptosis of megakaryocytes [61]. Importantly, an independent knock-out of either *Hdac2* or *Hdac1* in mice is not sufficient to generate significant hematopoietic phenotypes [61]. Similar to what is seen for megakaryocytes in whole body double knock-out mice [61], a complete thymocyte-specific deletion of *Hdac1*/*Hdac2* blocks early T cell lineage development and reduces the occurrence of lymphoma [58]. In B cells, *Hdac1* and *Hdac2* have divergent effects on immunoglobulin loci recombination [62]. However, they act in concert to control cell cycle progression by repressing *p21* expression and double negativity results in a block in B cell development, similar to what is seen for T cells [63].

Whereas HDAC2 expression was found to be increased in some patients with acute myeloid leukemia (AML) [64], there was a large variability between individuals. In some patients *HDAC2* levels were lower than in control samples [64]. Using *Lck-Cre* as a thymocyte-specific knock-out system, the gradual deletion of individual *Hdac1* and *Hdac2* alleles reveals a matching increase of lymphoma frequency in mice [65]. Apparently, the less HDAC1/HDAC2 activity is present, the more rapidly lymphomas arise [58,59]. Remarkably, thymocytes with a deletion of both *Hdac1* alleles and one allele of *Hdac2* show genomic instability, accumulation of the DNA damage marker γH2AX, and the mice die of neoplastic T cell malignancies [59]. Similar results were obtained using PML–RAR expressing mice. A concomitant reduction of *Hdac1*/*Hdac2* levels by siRNA in pre-leukemic stages triggers a rapid onset of leukemia [66]. Genetic experiments with p53-deficient mice as well as with c-MYC overexpressing mice further show that diminished *Hdac1* levels increase spontaneous leukemia. Interestingly, knocking down *Hdac2* in the p53-null background does not result in a higher incidence of leukemia in these mice [66]. This finding might mean that HDAC2 is a more reliable drug target than HDAC1. Of course, additional data are required to validate this idea. A combined *Hdac1*/*Hdac2* knock-out triggers a strong G1 phase cell cycle arrest resembling senescence. This is accompanied by an increased expression of the p53 target *p21*. Nevertheless, genetic deletion of either *p53* or *p21* does not rescue the senescence-like phenotype, pointing to additional, yet to be identified HDAC1/HDAC2-dependent mechanisms [61].

Taken together, HDAC1 and HDAC2 are important for the proper development of hematopoietic cells. The finding that a deletion of *Hdac1*/*Hdac2* alleles gradually pushes the onset of lymphoma [65] is counterintuitive to the well-established role of HDACi in cancer treatment and raises caution about negative long-term effects of HDACi. However, at the moment it is not completely understood whether the genetic deletion of HDACs and treatment with HDACi cause the same effects. A deletion of HDAC1/HDAC2 leads to the loss of corepressor complex integrity, while a pharmacological inhibition would probably not affect corepressor complexes at the structural level; see [2] for further discussion. Indeed, epidemiologic studies monitoring cancer incidences for epilepsy patients long-term treated with the HDACi valproic acid (VPA) show no significant correlation between VPA uptake and risk to develop lymphoma in humans [67,68].

3.2. Digestive tract — colon and colorectal cancer

Elevated HDAC2 levels are already evident in early stages of colorectal cancer (CRC), suggesting that they are causally involved in tumorigenesis. Moreover, high HDAC2 expression characterizes strongly proliferating, dedifferentiated primary human CRCs (Table 1), as well as CRC in animal models [44,69–72]. The increased expression of HDAC2 in CRC is connected to an unbalanced regulation of the WNT/β-catenin axis and of c-MYC [44]. HDAC2 is further regulated by a stress-responsive glucocorticoid response element (GRE) in its promoter [73] (Fig. 1C). Regarding c-MYC there is a c-MYC binding site in the *HDAC2* promoter (Fig. 1C), and decreasing c-MYC levels by siRNA causes downregulation of HDAC2 [44]. The expression of c-MYC is under control of the transcription factor β-catenin, which is tightly regulated through targeted proteasomal degradation being mediated by complexes containing the adenomatous

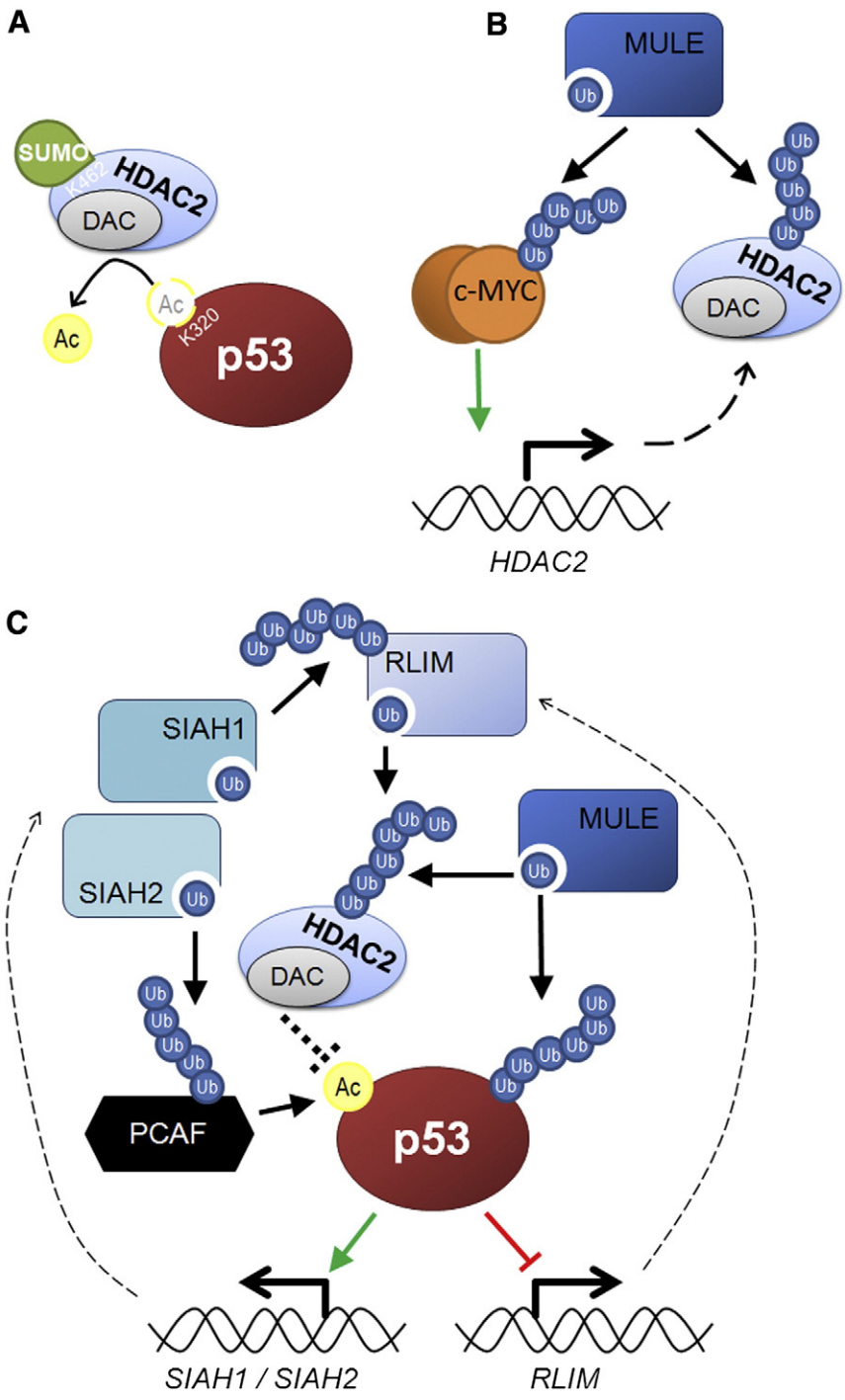

Fig. 3. Regulation of HDAC2-dependent p53^{K320} acetylation by a proteasomal degradation circuit. (A) Sumoylated HDAC2 can deacetylate K320 of p53. (B) MULE influences HDAC2 levels by regulating c-MYC, which promotes transcription of *HDAC2*. Lower HDAC2 protein levels might partially rely on the degradation of c-MYC and reduced activation of *HDAC2* expression. (C) The E3-Ubiquitin (Ub) ligases RLIM, SIAH1 and MULE regulate the degradation of HDAC2 and p53. HDAC2 proteasomal degradation is regulated by RLIM and SIAH1, which genes are under control of p53. RLIM targets HDAC2 for ubiquitinylation and is itself subject to degradation by SIAH1. While *RLIM* is repressed, the expression of *SIAH1* is enhanced by p53. *SIAH2* is possibly also activated by p53. PCAF, which acetylates p53^{K320}, is ubiquitinylated by SIAH2 and subsequently degraded by proteasomes. Thus, activated p53 can lead to diminished HDAC2 levels and consequently enhanced p53^{K320} acetylation. MULE can target both, p53 and HDAC2 directly for ubiquitinylation. This results in diminished K320 acetylation and reduced p53 levels.

polyposis coli (APC) tumor suppressor. Increased levels of APC diminish the levels of HDAC2. Consistently, transgenic mice carrying mutant APC (APC^{1638N} and APC^{min}) show higher HDAC2 expression in normal and tumor tissues [44]. Such animals develop CRC more frequently than control mice. Interestingly, crossing APC^{min} with HDAC2 mutant mice rescues the tumor-proneness of the resulting offspring to a certain degree (10–100%, dependent on the sex of the animal and location of the tumor in the intestinal tract) [74]. Congruently, the rate of tumor formation in APC^{min} mice can be significantly reduced by treatment with VPA [44]. Similar results were obtained in azoxymethane (AOM)-treated F344 rats developing CRC. Treatment with the HDACi OSU-HDAC42 diminished AOM-induced aberrant crypt foci formation and HDAC2 levels [75].

Interestingly, cancer cells may not only gain a benefit from HDAC2 overexpression, but also from a loss of HDAC2. First identified in RKO and Co-115 colon cancer cells [76,77], mono- or di-allelic loss of HDAC2 is triggered by insertion/deletion mutations due to microsatellite

instability (MSI) in a stretch with nine consecutive adenine bases in Exon 1 of the *HDAC2* gene (Fig. 1C) [78,79]. In primary tumors loss of HDAC2 sometimes affects the whole tumor, while it is restricted to specific areas in other cancers [78], being an example for intra-tumor heterogeneity [80]. MSI occurs in about 15% of all colon cancer cases [81,82] and up to half of these colon tumors show a loss of HDAC2 [77,78]. The relevance of HDAC2 deficiency is discussed controversially in respect to whether HDAC2 loss is a primary event, is reversible, or occurs as a bystander mutation in specific tumor settings [82,83]. While HDAC1 might compensate for reduced amounts of HDAC2 [61,63,84], the comparison of HDAC2-positive and -negative cells reveals aberrant expression patterns of gene products commonly associated with tumor-promoting activity. Such genes include tyrosine kinases, angiogenesis regulators, and mediators of cell cycle progression and protein stability [76]. Furthermore, enhanced expression of HDM2 and p21 is found in HDAC2-deficient colon cancer cells compared to those harboring wild-type HDAC2 [29,76]. The fact that apoptotic protease-activating factor 1 (APAF1), which is an essential mediator of cell death and directly repressed by HDAC2, is highly expressed in HDAC2 negative cells [78], illustrates that HDAC2 deficiency has to be accompanied by compensatory mutations ensuring cellular survival. It is also plausible that a loss of HDAC2 increases p53 activity on promoters of genes ensuring cell survival and repair. For example, it has been shown that the presence of wild-type p53 can protect cancer cells from chemotherapy [85], and perhaps unleashed p53 activity due to a loss of HDAC2 can promote such resistance mechanisms.

Additional mechanisms integrate the p53-HDAC2 interplay. The genotoxin-induced loss of HDAC2 sumoylation (Fig. 3A) leads to the acetylation of p53 at K320 and an increased expression of a large number of p53 target gene products. For example, expression of the pro-apoptotic apoptosis regulator BAX is reduced in the presence of HDAC2 [29]. These results illustrate that tumors could gain survival benefits through both, the overexpression and the deletion of HDAC2. Intriguingly, the colon is permanently challenged with butyrate, which is a natural occurring byproduct of digestion. The physiological levels of butyrate in the colon are sufficiently high to inhibit HDAC2 [86] and to accelerate the proteasomal degradation of HDAC2 [40]. This may influence the occurrence of tumors in the colon [87,88] and becoming independent of HDAC2 might help to subsequently evade growth-restricting effects of butyrate [2].

Evidence for a critical role of HDAC2 in CRC growth and development comes from the observation that a knockdown of HDAC2 reduces the viability of various colon cancer cell lines (CX-2, HT29, and HCT116) [69]. Interestingly, although HDAC1 and HDAC3 are also upregulated in CRCs, knockdown of HDAC1 was less effective compared to reducing HDAC2 levels, and HDAC3 had no effect on cell viability in this setting [69]. Pharmacological inhibition with the HDACi vorinostat (suberanilohydroxamic acid, SAHA) or VPA was even more potent in suppressing colon cancer cell growth [69]. In a xenograft model, administration of 100 mg/kg SAHA to nude mice significantly halted the growth of Colo 320HSR (BCRC) colon cancer cells [72]. SAHA treatment reduced the expression of the anti-apoptotic proteins survivin and BCL-x_L, of c-MYC, and of HDAC2 itself. Moreover, a portion of cells resistant to SAHA treatment showed increased expression of p53, survivin, and p21 [72,89]. In the APC^{min} mice model of colon cancer carcinogenesis VPA reduces both, the numbers and the size of adenoma polyps being pre-stages of carcinoma [44]. The loss of APC in CRC is not the only mechanism promoting HDAC2 expression. The C-terminal SRC kinase (CSK) mimics early tumorigenic events by interfering with the inhibitory CSK phosphorylation of the tyrosine kinase SRC which often promotes tumorigenesis [90]. In HT29 cells stably expressing *CSK* shRNA a more proliferative and aggressive phenotype is accompanied by increased HDAC2 expression and a global compaction of chromatin [71].

Combination treatments consisting of HDACi and classical cytotoxic chemotherapeutics also generated promising effects. The nucleotide analogues 5-fluorouracil (5-FU) and fluorodeoxyuridine (FUdR) target thymidylate synthase (TS) to trigger cancer cell apoptosis. Both drugs are used as chemotherapeutics against CRCs [91]. An increased expression of TS often evolves as a resistance mechanism against these drugs [92–94]. The pan-HDACi SAHA and LBH-589 reduce the expression of TS in both, colon cancer cell lines and xenograft models. Consequently, HDACi synergistically enhance the susceptibility of CRCs against thymidine analogues [95]. The mechanism for the HDACi-induced downregulation of TS is not completely understood but seems to be independent of both, p53 and HDAC2 [95].

3.3. Pancreatic, renal, hepatic, and gastric cancer

A large number of renal cancers [96], hepatocellular carcinoma (HCC) [97,98], gastric cancers [99–103], and subsets of pancreatic carcinoma and pancreatic ductal adenocarcinoma (PDAC) [104–106] show high expression levels of HDAC2 (Table 1). No prognostic value could be attributed to enhanced HDAC2 expression in renal cancer [96]. However, reducing HDAC2 levels in renal cancer cell lines RNAi or inhibition with VPA causes downregulation of hypoxia-inducible factor-1α and interferes with cell migration [107]. Interestingly, enhanced HDAC2 expression in HCC correlates with elevated levels of casein kinase II α, which phosphorylates and activates HDAC2 [108], possibly providing a positive feedback loop for HDAC2 activity in HCC (Fig. 1A and B). Reducing HDAC2 levels with siRNA enhances p53 acetylation in HCC cell lines HepG2 and Huh7. This results in enhanced p53 acetylation which is accompanied by a deregulation of genes associated with apoptosis, cell cycle control, and metabolic pathways [35].

Recently, a connection between HDAC2 and the mammalian target of rapamycin (mTOR) was uncovered [97]. The mTOR kinase integrates pathways sensing nutrient availability and directs cellular survival and proliferation. In HCC cell lines, HDAC2 enhances mTOR activity by altering the expression levels of several phosphoinositide signaling components. This ultimately leads to sustained AKT activation promoting cell survival and chemoresistance. Furthermore, providing a positive feedback loop to HDAC2, mTOR activity triggers NF-κB p50 nuclear localization which then binds to and activates the *HDAC2* promoter [97] (Fig. 1C).

HDAC2 expression significantly correlates with poorly differentiated PDAC tumors and worsened prognosis [104,105]. In pancreatic tumors aberrant activity of the NF-κB transcription factor family member p65 is a possible mechanism driving tumorigenesis [109]. Interestingly, HDAC expression correlates with nuclear accumulation of p65 [104] and the HDACi VPA and SAHA partially block p65 activity in pancreatic carcinoma cells [104]. Diminishing HDAC2 by siRNA or pharmacological inhibition by VPA also sensitizes the PDAC cell lines MiaPaCa2 and Panc1 towards etoposide-induced apoptosis [105]. Similarly, HDAC2 attenuation sensitizes PDAC cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) by increasing expression of the TRAIL receptor DR5 [110]. Additionally, NOXA is under the transcriptional control of HDAC2 [105]. *NOXA* is a p53 target gene and one of the executors of p53-mediated apoptosis [111,112]. However, whether the HDAC2- and p53-dependent control goes hand in hand at the *NOXA* promoter is unclear. As the Panc1 and MiaPaCa2 cell lines feature DNA-binding mutations of p53, it appears unlikely that HDAC2 regulates *NOXA* via p53 in these cells [105]. NOXA expression also seems to be critically dependent on NF-κB RelA [113], which in turn is positively influenced by HDAC2 in PDACs [104].

Remarkably, knocking down NOXA together with HDAC2 reverses the etoposide-sensitizing effect of the single HDAC2 knockdown [105,110]. These data point to an important role of HDAC2 in pancreatic cancer. High HDAC2 levels can downregulate the expression of NOXA to render pancreatic cancers more resistant to apoptosis. Thus, combining traditional DNA damaging drugs with HDACi could be a beneficial strategy for treatment of pancreatic tumors with enhanced HDAC2 expression [106].

A specific role of elevated HDAC2 in gastric cancer cells is established by its ability to repress *CITED2* and the tumor suppressor *CDKN2A* (*p16*^{INK4A}) [102,103]. HDAC2 downregulation triggers histone hyperacetylation at this promoter and restores *p16*^{INK4A} expression regardless of promoter methylation [103]. This inhibits efficient cancer cell proliferation and traps cells in senescence. Cell culture studies show that the pan-HDACi LBH-589 and SAHA suppress the growth of gastric cancer cell lines [102,114]. The efficiency of SAHA towards gastric cancer cells is inversely correlated to the activity of c-MYC and the expression levels of anti-apoptotic BCL2 family members including MCL1 and BCL-x_L [114]. In addition, CITED2 was recently identified as a key factor mediating sensitivity to the anthracyclines epirubicin and doxorubicin (DoxoR/adriamycin) [102]. Restoring *CITED2* expression by HDACi or *HDAC2* knockdown can overcome the resistance of cancer cells to anthracyclines in vitro and in the CEA/Tag mouse model for gastric cancer [102]. Treatment with butyrate can also induce *CITED2* expression. This diminished the invasiveness of cancer cells by reducing the expression of matrix metalloproteinase MMP13 [115]. As high CITED2 levels are associated with resistance to the DNA-damaging drug cisplatin (cis-Pt) [116], the use of HDACi must be carefully evaluated depending on the therapeutic regime.

Overexpression of HDAC2 increased the invasiveness of gastric cancer cells and downregulation of HDAC2 reduced the tumorigenic potential of gastric cancer cells in xenotransplanted nude mice [103]. Thus, monitoring HDAC2 expression in gastric cancers could be an important clinical parameter [117] and targeting elevated HDAC2 might reduce cancer cell proliferation and metastasis formation. The finding that after neoadjuvant chemotherapy some gastric cancers show high HDAC2 levels, but that this is not a predictor for patient survival, is puzzling at first. However, it is tempting to speculate that during drug treatment those cancer cells had acquired a set of mutations that made HDAC2 expression a secondary factor for their survival. This may argue that HDAC2 should be targeted early in therapy. Tumor cells might be dependent on a high HDAC2 expression, but further events may render them HDAC2-independent.

3.4. Respiratory system — cancers of the lung and of the upper aerodigestive tract

HDAC2 is an important factor in the development and progression of chronic obstructive pulmonary disease [118,119], and diverse types of non-small cell lung cancer (NSCLC) show HDAC2 overexpression (Table 2) [120–122]. In vitro, a knockdown of HDAC2 in A549 type II alveolar lung cancer cells increases the induction of p53-dependent gene expression patterns [120]. Likewise, treatment of human pulmonary microvascular endothelial cells with the HDACi trichostatin A (TSA) reduces HDAC2 levels and induces expression of p53 [123]. In vivo, TSA treatment of rats or subjecting neonatal mice to hyperoxia can also reduce HDAC2 levels and concomitantly increases p53 and p21 expression [123,124]. In A549 cells, attenuation of HDAC2 leads to enhanced levels of the p53 target genes *p21* and *BAX*. These evoke growth arrest and trigger apoptosis, respectively [120]. The expression of the anti-apoptotic mitochondrial protein BCL2 was reduced in this setting. Congruent with these observations xenografts using A549 cells with diminished HDAC2 levels form less and significantly smaller tumors in mice [120]. Further studies are necessary to evaluate the benefit of HDACi for lung cancer patients.

3.5. Breast cancers

Breast cancer is a heterogeneous disease with various genetic and epigenetic traits [125]. HDAC2 overexpression correlates with difficult to treat estrogen/progesterone receptor (ER/PR)-negative breast tumors and cancers with elevated expression of HER2 [126]. The knockdown of HDAC2 in the p53 wild-type, ER-positive breast cancer cell line MCF7 revealed a profound impact of HDAC2 on p53-dependent gene expression [127–129]. Decreasing HDAC2 levels reduced cell proliferation and promoted senescence. These biological effects were partially dependent on p53; interference with p53 could not rescue the phenotype induced by the HDAC2 knockdown [127]. Upon depletion of HDAC2 a subset of p53 target genes showed increased repression (*c-MYC* and *cyclin B1*), or activation (*p21*, *HDM2*, *DKK1*, *FDXR1*). While p53 protein stability was unaffected by HDAC2 knockdown, p53 occupancy at its target gene promoters was elevated [127]. This study revealed further that a concurrent HDAC2 knockdown increased the activation of p53 target genes in MCF7 cells which had been treated with cis-Pt or with the human HDM2/murine MDM2 inhibitor Nutlin-3 that stabilizes p53 [127]. HDAC2 is also important for ER and PR signaling, which are important pathways in breast cancer cells [130]. Both, the knockdown of HDAC2 and the HDACi VPA or LBH-589 can reduce ER and PR levels in T47D breast cancer cells. In contrast, HDAC1 shows an impact only on ER expression and not on the levels of PR. When ER-dependent breast cancer cells are treated with the selective ER-modulator tamoxifen and HDACi a synergistic apoptotic effect is observed. Knocking down HDAC2, but not HDAC1, generates similar effects [130].

The p53 target *MTA1* is repressed by HDAC2 recruitment after p53 activation [129]. MTA1 is a component of the nucleosome remodeling and histone deacetylase (NuRD) complex. Interaction of MTA1 with ER leads to ER target gene repression [131,132]. MTA1 is highly expressed in cancers, especially in metastatic tumors [131]. HDAC1/HDAC2 binding to the *MTA1* promoter is triggered by treatment with 5-FU and this causes H3K9 deacetylation to silence *MTA1* [129]. HDAC2 and p53 cooperate in the repression of *major vault protein* (*MVP*; also *lung resistance-related protein*, *LRP*). In breast cancer and other tumor types expression of MVP correlates with multi-drug resistance to chemotherapeutics including DoxoR, cis-Pt, and etoposide [133,134]. Recruitment of HDAC2 to the Y-box-binding protein 1 (YB1) at a Y-Box on the *MVP* promoter is mediated by p53 [128]. Treatment of MCF7 cells with anthracycline drugs relieves repression of *MVP* [128]. However, the mechanism by which this occurs is unclear and conflicting data about the role of MVP in multi-drug resistance exist [135]. MVP contributes to the functionality of signaling pathways [136] and the p53/HDAC2-mediated repression of *MVP* expression potentially influences cell fate decisions. This might indirectly regulate drug resistance.

Combinatorial regimes involving HDACi were evaluated in clinical trials with breast cancer patients [6,137]. In a phase I trial a SAHA/DoxoR combination was tested against solid tumors (breast, prostate, and melanoma). In these studies HDAC2 baseline expression emerged as a clinical predictor of HDACi therapy response: the higher pretreatment levels of HDAC2 were, the more histone hyperacetylation could be induced by SAHA treatment [6]. Matching results were obtained in a study investigating VPA/epirubicin cotreatment [137]. Furthermore, a combination of tamoxifen/SAHA in a phase II clinical trial demonstrated that efficiency of this therapy correlated with HDAC2 expression [138]. The molecular characterization of the action of HDACi together with anthracycline chemotherapeutics in the breast cancer cell lines MCF7, T47D, and MDA-486 revealed that HDAC2 inhibition regulated chromatin plasticity [139]. Moreover, depletion of HDAC2, by siRNA or treatment with VPA, reduced the expression of heterochromatin protein components like HP1 and sensitized cells for apoptosis induction by epirubicin [139]. Hence, HDACi might add up as new drugs for breast cancer treatment.

3.6. Skin and epidermal cancers

Normal skin development is strongly perturbed in *Hdac1*/*Hdac2* ectoderm-specific knock-out mice and resembles the loss of p63 [36], which plays a crucial role in skin and epidermis development [140]. Squamous cell carcinomas (SCCs) are often characterized by a dysregulation of the p53 family member p63 [140]. The versatile transcription

factor p63 can function as an activator or repressor of transcription and p53 and p63 often carry out opposing roles in transcriptional regulation [140]. Interestingly, acetylation of p53 is enhanced in *Hdac1*/*Hdac2* double-negative keratinocytes [36]. The expression of the epithelial p63 variant ΔNp63 is repressed via recruitment of HDAC2 to the *TP63* promoter by the basic helix–loop–helix protein 40 (bHLHe40/DEC1) [141]. *DEC1* in turn is a p53 target gene [142]. On the other hand, ΔNp63 recruits HDAC1/HDAC2 to exert transcriptional repression. In SCCs, especially pro-apoptotic p53 target genes such as *PUMA* are repressed in this fashion [143]. Remarkably, disrupting the p63-HDAC1/HDAC2 corepressor complex or HDACi treatment efficiently triggers apoptosis of SCC cells [143]. Thus, an exquisite balance between p53 and p63 activities might direct SCC progression.

In oral and mobile tongue SCCs HDAC2 is strongly expressed in larger tumors, and such cancers display higher invasiveness and metastasis formation [144,145]. In contrast, patients with oral epithelial dysplasia (OED), a pre-stage to SCC, have lower HDAC2 expression, pointing to a possible usage of HDAC2 as a biomarker for SCC progression [144]. However, the data are inconclusive as to whether higher HDAC2 levels present a factor determining overall patient survival [145]. HDAC2 is also upregulated in normal and keloid scars, the latter of which are benign malignancies deriving from excessive fibroblast growth [146]. The upregulation of HDAC2 especially in normal scar tissue might point to a physiological, pro-proliferative role of HDAC2 during wound healing [146].

HDAC2 also participates in the regulation of p53 expression in melanoma cell lines in vitro. In drug-resistant Malme3MR cells created by long-term exposure to the NF-κB inhibitor celastrol, HDAC2 is recruited to the *p53* promoter by cancer/testis antigen (CAGE) and participates in p53 downregulation [147]. In a surprisingly similar fashion recruitment of HDAC2 to the *p53* promoter by the transcription factor SNAIL (SNAI1) decreases p53 expression [147]. This suppression of p53 expression by CAGE- or SNAIL-dependent recruitment of HDAC2 could allow cancers cells to prevent p53-dependent apoptosis.

3.7. Central nervous system

HDAC2 acts as a negative regulator of synaptic plasticity [148] and neuronal cell growth. In PC12 cells the p53-family member ΔNp73 recruits HDAC2 to repress expression of TRKA, a nerve growth factor (NGF) receptor [149]. ΔNp73 functionally antagonizes p53 in this context. Fittingly, expression of ΔNp73 correlates with a lack of differentiation in neuronal cells and is a marker for worsened prognosis in neuroblastoma [150]. HDAC inhibition or overexpression of the acetyltransferases p300, CBP, and PCAF triggers outgrowths of neurons, at least partially by enhancing p53 acetylation [151]. No significant upregulation of HDAC2 expression was observed in astrocytoma and glioblastoma patients [152]. However, the novel HDAC1/HDAC2-selective HDACi BRD8430 induces differentiation of neuroblastoma cells in vitro and may represent an alternative to cytotoxic therapies [153].

Additionally, the tumor-suppressive micro-RNA *miR-183* is repressed in neuroblastoma by the N-MYC proto-oncogene and HDAC2-triggered epigenetic alterations [154]. Dysregulation of *miR-183* further seems to be connected to p53 signaling [155]. Interestingly, repression of *miR-183* can be relieved by HDAC2 knockdown and treatment with HDACi [154]. It is plausible that HDACi could restore functional p53-mediated gene expression in neuroblastoma by elevating of *miR-183*.

3.8. Prostate cancer, sarcomas and gynecological malignancies

HDAC2 overexpression (Table 1) represents an independent prognostic marker in prostate cancer [156,157], but the mechanisms underlying this prognosis-relevant role of HDAC2 remain to be elucidated. In the prostate cancer cell lines LNCaP and PC3 treatment with the HDACi CG-1521 and TSA potently induces p21 expression and cell cycle arrest [158]. Interestingly, only CG-1521 induces strong acetylation of p53 at K373, induction of BAX, and enhanced apoptosis of LNCaP cells. This correlates with the degradation of HDAC2 by CG-1521, but not upon TSA treatment [158]. It was similarly found that TSA failed to cause proteasomal degradation of HDAC2 in cells derived from the kidney and testis [1,2]. In p53-negative PC3 cells neither of the two HDACi triggers apoptosis, but both induce cell cycle arrest [158]. Further investigations are necessary to discriminate between p53-dependent and -independent effects of HDACi [159,160] (Table 3).

High levels of HDAC2 are found in several gynecological malignancies (Table 1) [161–167]. While a unique role of elevated HDAC2 in these studies was not identified, an overall high class I HDAC expression correlated with a lower disease-specific survival in some, but not all subtypes of ovarian and endometrial cancers [161]. HDAC2 is also upregulated in a number of sarcomas (Table 1), especially in subtypes associated with chromosomal translocations [168], and the relevance of HDAC2 has likewise not been explored in detail. In Ewing Family Tumors (EFT) sarcomas, HDACi treatment can reactivate p53 functions to trigger apoptosis. However, HDAC1 rather than HDAC2 was identified for being responsible for deacetylation of p53 at K382 [169].

Interfering with HDAC2 function seems to be a promising therapeutic strategy in several gynecological tumors. As first shown in HeLa cells, HDAC2 knockdown increases expression of the cell cycle regulator p21 and induces apoptosis [70]. In endometrial stromal sarcoma cell lines the treatment with VPA or reduction of HDAC2 levels by siRNA induces p21 expression, leads to cell cycle arrest, and induces differentiation [167]. Moreover, in cervical carcinoma cotreatment with proteasomal inhibitors and HDACi emerges as a useful combination. The etiologic agent for nearly all cervical cancers is the human papillomavirus (HPV) [170]. The HPV oncoproteins E6 and E7 can trigger degradation of p53 and utilize HDAC1/HDAC2 to disturb E2F-dependent gene expression, respectively. Combined p53 stabilization by proteasomal inhibition and TSA synergistically triggers apoptosis of HPV-positive cervical cell lines and in mouse models of cervical cancer [165]. These proof-of-principle experiments suggest that such treatment regimes restore p53 acetylation to enable pro-apoptotic p53 functions.

4. Concluding remarks

According to the COSMIC database (http://cancer.sanger.ac.uk/cancergenome/projects/cosmic; retrieved June 13th 2014) in 10,698 unique samples only 53 mutations in HDAC2 were discovered (for comparison: *TP53* shows a total of 25,071 mutations in 86,305 samples). Instead, overexpression of HDAC2 is commonly observed for a multitude of malignancies [2], as summarized in Table 1. However, as not all cancers show upregulation of all class I HDACs this finding points to specific roles of HDACs in certain tumor types (Table 1). Transformation of cells could be caused by elevated HDAC2, for example via inactivation of p53, or by a secondary event due to stress signaling after transformation [84]. HDAC2 – and other HDACs – might also integrate the crosstalk of p53 with other transcription factors, e.g., with NF-κB [22,171], STAT1 [172,173], and STAT3 [174]. Thus, even if HDAC2 does not cause cancer initiation directly but is a bystander event in tumor formation, HDAC2 seems to represent a therapeutic target. We have summarized that high HDAC2 levels can turn off pro-apoptotic functions of p53. It is interesting to see whether epidemiological studies will reveal a correlation between HDAC2 overexpression in tumors and an inactivation of wild-type p53.

As the growing evidence presented in this review suggests, our understanding of how p53 is regulated by acetylation, and how HDAC2 overexpression can have a direct impact on p53's functions, sheds new light on molecular aberrations in tumors. Numerous PTMs affect p53 functions in vivo like phosphorylation, acetylation, ubiquitinylation, and sumoylation [18]. Despite the large influence on p53 activity, mutations on p53 PTM sites are rare compared to the so-called hotspot mutations that affect the structure and DNA binding

[175–177]. Alternatively, alteration of p53 effectors, like mutated ATM phosphorylating p53 [178] or MDM2/MDMX-mediated ubiquitination of p53 changes the p53 PTM status. For example, p53 is never mutated when either MDM2 or MDMX is overexpressed in glioblastoma and well-differentiated liposarcoma [179] or in a subgroup of colorectal cancers [180].

Identifying molecular markers, such as HDAC2 overexpression, might be a next step towards personalized medicine with rationally designed therapeutic settings using highly selective or broad-range HDACi. Targeting epigenetic imbalances and PTMs in cancer cells appears as alternative or as a combinatorial strategy to the use of 'traditional' cytotoxic drugs [8,181,182]. Numerous HDACi are in clinical studies, as single compounds or in combination regimes [9,183]. Strictly selective inhibitors for HDAC2 still remain to be identified (Table 2) [7]. Drugs enhancing proteasomal degradation of HDAC2 may equally be effective against excess HDAC2 activity (Fig. 3C). Validating the connection between HDAC2 overexpression, PTMs of HDAC2 and p53, and functionality of the p53 pathway in the clinic is necessary. Furthermore, small molecules that specifically target HDAC2 to restore p53 activity might allow the transfer of recent results on p53 and HDAC2 from bench to bedside.

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