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Review

The world of protein acetylation

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ABSTRACT

Acetylation is one of the major post-translational protein modifications in the cell, with manifold effects on the protein level as well as on the metabolome level. The acetyl group, donated by the metabolite acetyl-coenzyme A, can be co- or post-translationally attached to either the α-amino group of the N-terminus of proteins or to the ε-amino group of lysine residues. These reactions are catalyzed by various N-terminal and lysine acetyltransferases. In case of lysine acetylation, the reaction is enzymatically reversible *via* tightly regulated and metabolism-dependent mechanisms. The interplay between acetylation and deacetylation is crucial for many important cellular processes. In recent years, our understanding of protein acetylation has increased significantly by global proteomics analyses and in depth functional studies. This review gives a general overview of protein acetylation and the respective acetyltransferases, and focuses on the regulation of metabolic processes and physiological consequences that come along with protein acetylation.

1. Introduction

Protein acetylation is one of the major post-translational modifications (PTMs) in eukaryotes, in which the acetyl group from acetyl coenzyme A (Ac-CoA) is transferred to a specific site on a polypeptide chain. Alongside acetylation, phosphorylation, methylation, SUMOylation, and ubiquitination have been studied intensively. These PTMs introduce new functional groups to proteins, thereby extending the repertoire of the standard amino acid residues. Most PTMs are important pillars of cell signaling and enable the cell to react specifically and rapidly to internal and external perturbations [1]. Other PTMs occur when the cell encounters specific environmental stress conditions as is the case during oxidative stress, *e.g.* carbonylation and oxidation [2]. With new techniques emerging, especially in the mass spectrometry field, hundreds of different PTMs were identified [3–5]. Protein acetylation normally occurs in two distinct forms, which combined constitute the cell-wide acetylome. In humans, 80–90% of all proteins become co-translationally acetylated at their N^{α}-termini of the nascent polypeptide chains (Fig. 1A) [6–8]. In recent years, it was shown that this N-terminal (Nt) modification also occurs post-translationally for several proteins, demonstrating that Nt-acetylation is part of a more complex system [8–11]. These reactions are catalyzed by Nt-acetyltransferases (NATs) [12]. The other common type of protein acetylation pertains to the ε-amino group of lysines (Fig. 1B). Acetylated lysine residues were first discovered in histones regulating gene transcription, which is the reason why the enzymes catalyzing lysine (K) acetylation were termed histone acetyltransferases (HATs) [13]. Nevertheless, lysine acetylation is not exclusively limited to histone proteins [14], and the enzymes have been renamed lysine (K) acetyltransferases (KATs) [15]. In contrast to Nt-acetylation, which is considered irreversible, the acetylation status of a lysine is reversible and tightly regulated. Several families of lysine deacetylases (KDACs) are counteracting KATs. KATs and KDACs developed a well-balanced and complex interaction in many cell functions. Due to the consumption of Ac-CoA during acetylation and NAD^+ during deacetylation by specific KDACs (Fig. 1C), acetylation interferes with metabolic processes and energy homeostasis. Consequently, malfunctioning acetylation machinery can lead to severe diseases such as cancer, neurodegenerative diseases and cardiovascular disorders [16–22]. The present knowledge in the field teaches us many facts about the acetyltransferases themselves, the reaction they are catalyzing, and the molecular consequences for their substrates. Nevertheless, the understanding of the physiological consequences acetylation provokes, or the overall interplay and regulation of the acetylome itself, still remain elusive.

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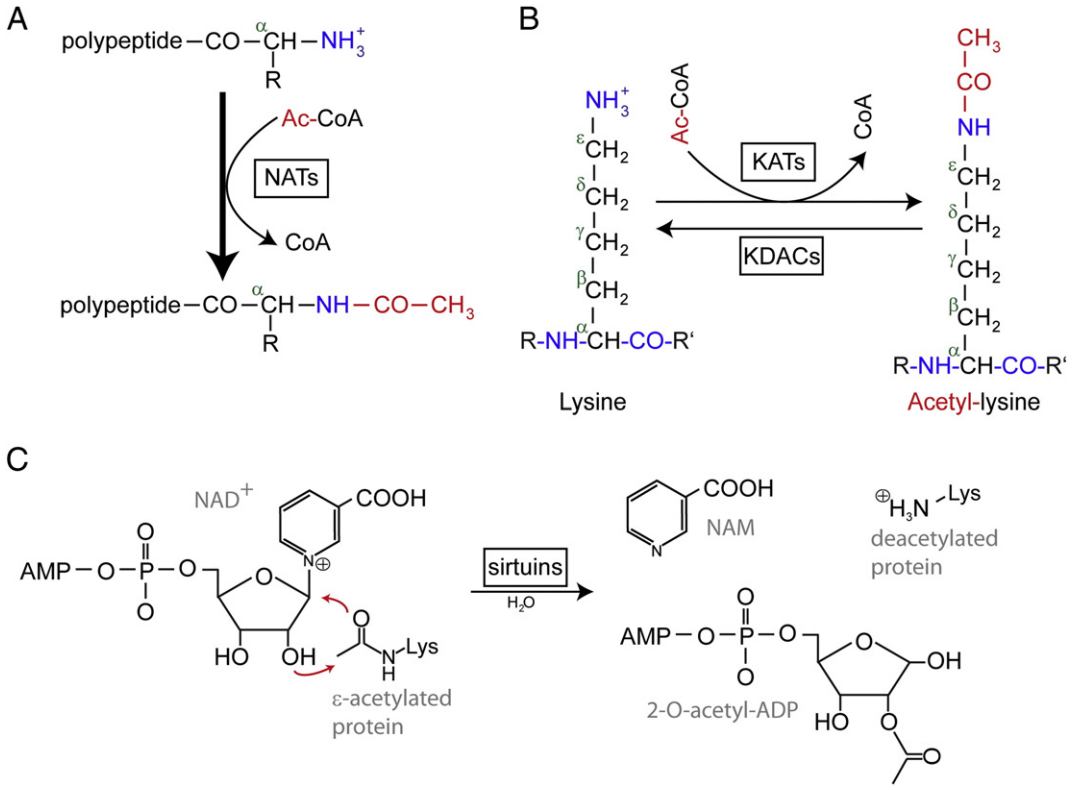


Fig. 1. Schematic overview of acetylation and deacetylation. A) Enzymatic transfer of an acetyl group from Ac-CoA to the N-terminal amino group of a polypeptide, catalyzed by N-terminal acetyltransferases (NATs). The reaction is considered to be irreversible. B) Reversible acetylation of the ε-amino group of a lysine residue by lysine acetyltransferases (KATs). The deacetylation of lysine residues is catalyzed by Lysine deacetylases (KDACs) and C) is NAD^+-dependent in case of sirtuins. NAD^+, nicotinamide adenine dinucleotide; NAM, nicotinamide.

2. N-terminal acetylation

2.1. N-terminal acetylation in general

2.1.1. Abundancy from Escherichia coli to Arabidopsis thaliana

Nt-acetylation is an abundant co- and post-translational modification, which is conserved in all branches of life. The frequency of acetylated proteins increases with the complexity of the organism [7,23,24]. In bacteria and archaea Nt-acetylation was considered to be a rare event, and it seems that this modification does not exist in all species [23]. In *Escherichia coli* only 5 proteins have long been known, mainly ribosomal subunits, to carry an acetyl group at their N-termini. However, a recent MS-based proteome-wide study in *E. coli*, analyzing PTMs under different growth conditions, identified 31 proteins being Nt-acetylated [25]. Noteworthy, these acetylation reactions all occur post-translationally [26,27]. In addition, new Nt-acetylated proteins have been identified in different bacterial species showing that Nt-acetylation occurs more frequently than first expected, actually playing important roles in these organisms [28–30]. In *Drosophila melanogaster*, 861 out of 1226 distinct N-termini identified have been found fully Nt-acetylated [31]. In yeast, the percentage of fully or partially Nt-acetylated proteins is approximately 50–70% (from 614 identified endogenous yeast proteins) [7]. Compared to that, the human Nt-acetylome consists of around 80–90% of the soluble protein fraction [7,24]. To complete the list, it should be mentioned that the abundancy of Nt-acetylation in the plant model organism *Arabidopsis thaliana* is around 72% [32].

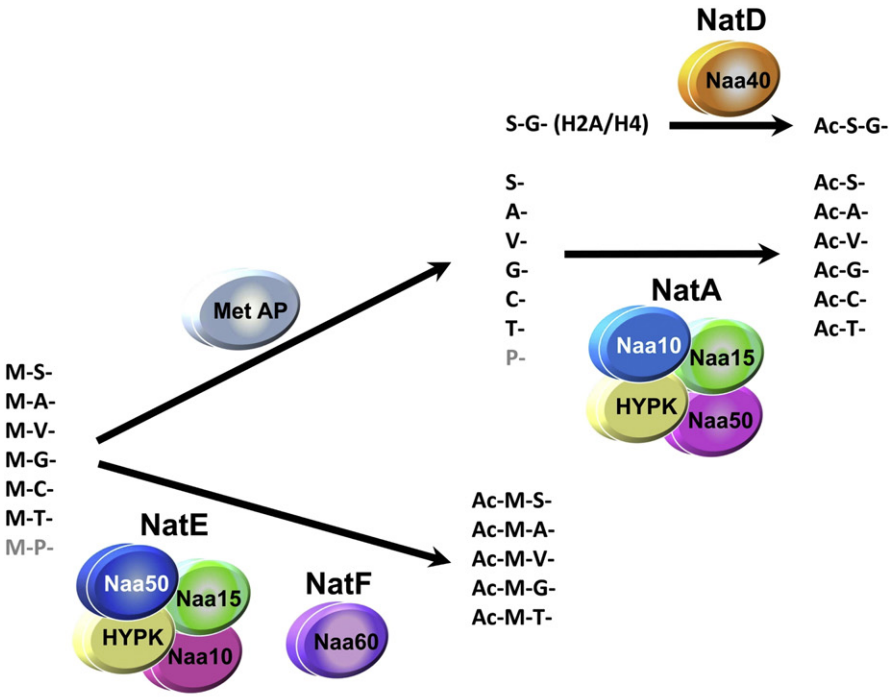
2.1.2. The reaction catalyzed by NATs

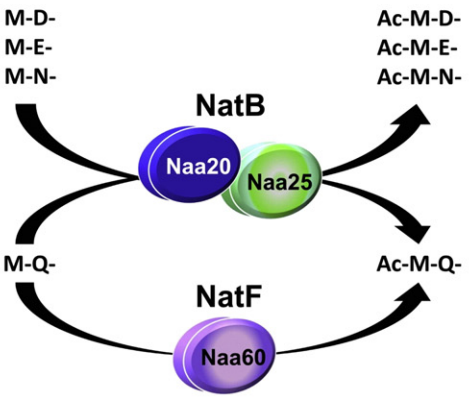
NATs transfer an acetyl moiety from Ac-CoA to the positively charged free α-amino group of a newly synthesized polypeptide chain (Fig. 1A). The attached acetyl group neutralizes this positive charge and normally blocks the N-terminus from further modifications. Dependent on the NAT, the acetyl group is transferred to the non-cleaved initial methionine residue (iMet) of the nascent polypeptide chain or the reaction occurs after the excision of the iMet by ribosomal-bound methionine aminopeptidases (MetAPs) [33–36]. The N-terminus is also subject to other PTMs, such as propionylation or arginylation [37–39]. Not all potential NAT substrates are completely Nt-acetylated. Partial Nt-acetylation is common, consequently a protein can exist in its unacetylated and its acetylated form simultaneously in the cell [12]. In recent years, structural studies delivered insights into the catalytic mechanism of NATs. In addition, several molecular consequences for proteins, becoming Nt-acetylated, were revealed by selected examples. Nevertheless, the connections between Nt-acetylation and physiological processes have not been fully elucidated. This also includes the rising numbers of cellular malfunctions and diseases that arise by NAT deficiency and mutations, respectively, and demonstrates the importance of closing these knowledge gaps.

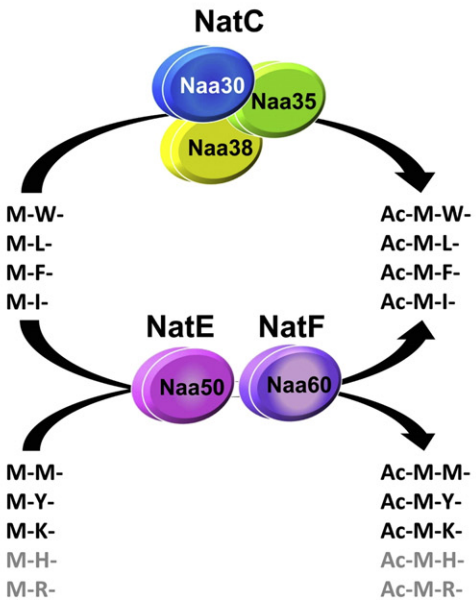
2.2. The N-terminal acetyltransferases (NATs)

2.2.1. The subunit composition of the NATs

NATs belong to the GCN5 (general control non-derepressible 5)-related acetyltransferase (GNAT) superfamily, which also include some of the well-studied KATs. The enzymes of the GNAT family share conserved sequence motifs including the recognizable Ac-CoA binding motif Q/RxxGxG/A [40,41]. NATs are mono- or multisubunit enzymes consisting of a catalytic subunit and up to two auxiliary subunits (Fig. 2). The major auxiliary subunit modulates the activity and substrate specificity of the catalytic subunit [42]. Further, the auxiliary subunits are considered to mediate, in co-translational reactions, the complex binding to the ribosome as well as to the nascent polypeptide *via* several tetratricopeptide repeat motifs [43–45]. To date, six different NATs have been identified in mammals (NatA-NatF), whereas in yeast only five NATs exist (NatA-NatE) [12]. Noteworthy, in *E. coli* the only acetyltransferases that have been identified so far are RimI, RimJ, and


NatD
Naa40
S-G- (H2A/H4)
Ac-S-G-
S-
A-
V-
G-
C-
T-
P-
Ac-S-
Ac-A-
Ac-V-
Ac-G-
Ac-C-
Ac-T-
NatA
Naa10
Naa15
HYPK
Naa50
Met AP
M-S-
M-A-
M-V-
M-G-
M-C-
M-T-
M-P-
Ac-M-S-
Ac-M-A-
Ac-M-V-
Ac-M-G-
Ac-M-T-
NatE
Naa50
Naa15
HYPK
Naa10
NatF
Naa60


M-D-
M-E-
M-N-
Ac-M-D-
Ac-M-E-
Ac-M-N-
NatB
Naa20
Naa25
M-Q-
Ac-M-Q-
NatF
Naa60


NatC
Naa30
Naa35
Naa38
M-W-
M-L-
M-F-
M-I-
Ac-M-W-
Ac-M-L-
Ac-M-F-
Ac-M-I-
NatE
NatF
Naa50
Naa60
M-M-
M-Y-
M-K-
M-H-
M-R-
Ac-M-M-
Ac-M-Y-
Ac-M-K-
Ac-M-H-
Ac-M-R-

RimL, which acetylate only a very small number of ribosomal proteins [26,46–48]. The main NAT complexes in eukaryotes, NatA, NatB, and NatC, are combined responsible for approximately 80% of all Nt-acetylation reactions in human cells [12,49]. NatA is composed of the catalytic subunit Naa10 (Ard1) and the auxiliary subunit Naa15 (Nat1) [50,51]. Naa50 co-exists in this complex [43,52,53], but possesses its own catalytic activity and is thus termed NatE [10,35,54]. Naa10 is also able to Nt-acetylate independently of Naa15 [10]. NatB is composed of the catalytic subunit Naa20 (Nat3) and the auxiliary subunit Naa25 (Mdm20) [55,56]. The catalytic subunit of NatC is Naa30 (Mak3) [57], which is associated with the two auxiliary subunits Naa35 (Mak10) and Naa38 (Mak31) [58,59]. NatD, NatE and NatF are monosubunit enzymes, composed of only their catalytic subunits Naa40, Naa50, and Naa60, respectively [8,10,24,54,60,61]. Interestingly, in contrast to the complexes NatA to NatE, which are all localized in the cytosol binding to ribosomes, NatF is associated with the Golgi apparatus [8]. Recently, a new NAT was identified in *A. thaliana*, named AtNAA70 making an exception in the NAT field due to its unique localization and activity in chloroplasts [62]. It is likely that in the upcoming years more NATs will be identified and characterized.

2.2.2. NATs vary in their substrate specificities

The various NATs differ not only in subunit composition, but also in their substrate specificity, which is determined in general by the first two amino acid residues (Fig. 2) [63]. NatA acetylates S-, A-, T-, V-, G-, and C- N-termini after iMet excision [7,64]. Naa10 is also active in the absence of Naa15, post-translationally acetylating acidic N-termini [10, 42]. NatB acetylates proteins with a retained iMet followed by an acidic or hydrophilic amino acid residue (*e.g.* D, N, E, Q) [56,64,65]. NatD has only two known substrates, the histones H2A and H4 [60,61]. NatC, NatE, and NatF have overlapping substrate specificities, potentially acetylating proteins starting with the iMet followed by amphipathic and hydrophobic amino acid residues (*e.g.* K, M, V, A, L, I, F, and Y) [8, 10,24,54,57,59]. AtNaa70 prefers chloroplast N-termini beginning with M, A, S, and T [62]. N-termini starting with a proline are never found to be Nt-acetylated [7,31].

2.3. Molecular consequences of being Nt-acetylated

The consequences of being Nt-acetylated for a protein are manifold. Nt-acetylation determines the subcellular localization for certain proteins. Arl3 and Grh1 are two Golgi-associated proteins, which are unable to associate with the Golgi apparatus when missing the Nt-acetyl group (Fig. 3A) [66–68]. Another study hypothesizes that Nt-acetylation restrains proteins in the cytosol and inhibits a post-translational translocation migration to the endoplasmic reticulum (ER) and the secretory pathway (Fig. 3B) [69]. Acetylation alters the properties of the N-terminus, and thus protein-protein interactions apparently become modulated. It was shown for several proteins that the affinity to their binding partners increased after being Nt-acetylated. The E2 ubiquitin-conjugating enzyme Ubc12 undergoes Nt-acetylation by NatC enabling an increased affinity towards its interaction partner, the E3 ubiquitin ligase Dcn1 (Fig. 3C) [70]. This Nt-acetylation-dependent interaction was found to be a conserved mechanism for the complete mammalian NEDD8 ligase family [71]. It was shown that Nt-acetylation by NatB plays an important role in tropomyosin-actin complex formation. When tropomyosin is Nt-acetylated the end-to-end bonds are stronger. Concomitantly, this increases actin binding and facilitates the regulation of specific myosin motor classes [55,72]. A recent publication showed that Nt-acetylation is also crucial for protein folding by structurally stabilizing flexible N-termini. In the absence of NatA in yeast, misfolded and aggregated proteins accumulate and result in an increased chaperone expression [73]. The most prominent effect of Nt-acetylation relates to protein stability. Nevertheless, this topic is controversial. Several examples exist showing that Nt-acetylation increases the stability and half-life of proteins such as tuberous sclerosis complex 2 (TSC2), which is involved in tumorigenic processes [74], and THO complex subunit seven homolog (THOC7) [19]. Other recent studies demonstrate that Nt-acetylated N-termini may act as proteasomal degradation signals, decreasing protein half-life and being part of the N-end rule pathway [75,76]. Certain acetylated N-termini are recognized by specific E3 ubiquitin ligases thereby opening a new branch of the N-end rule pathway, the Ac/N-end rule. This degradation pathway may in some cases regulate the stoichiometry of protein subunits of a complex when complex formation shields the N-terminal degradation signal (Fig. 3D) [76,77]. Here are only a few examples listed of the manifold effects Nt-acetylation has on proteins, and following studies will give further insights and certainly decipher new impacts and regulation mechanisms of Nt-acetylated proteins.

2.4. Putative cellular and physiological roles of NATs

2.4.1. NATs are essential for normal development

Naa10 is conserved from yeast to humans and its critical role in normal development is demonstrated in humans as well as zebrafish and different invertebrates. In a recent *Danio rerio* study, *naa10* morpholino-mediated knockdown resulted in severe phenotypes with increased lethality, developmental abnormalities and growth retardation, which emphasizes the importance of a normal Naa10 expression level for viability and early development of zebrafish [78]. Studies from other organisms demonstrate that loss of the Naa10 homolog results in lethality for *Drosophila melanogaster* [79], *Trypanosoma brucei* [80] as well as *Caenorhabditis elegans* [81]. In yeast, NatA was shown as non-essential. However, *naa10*Δ or *naa15*Δ deletion strains have defects in mating, sporulation and entry into stationary phase as well as increased sensitivity towards temperature, salt and drugs [7,50,82]. A highly regulated NAT expression is essential for human life, as demonstrated by different diseases (Section 2.5), NAT mutations (Section 2.6) and cancer studies (Section 2.7). The NATs' manifold functions in mammalian/human development and cellular regulation are further described in the following sections.

2.4.2. NAT involvement in bone and blood vessel development

Yoon et al. demonstrate Naa10 involvement in osteoblast differentiation and early phases of bone formation by control and fine-tuning of the Runt-related transcription factor 2 (Runx2) signaling [83]. Naa10 interacts with Runx2 and appears to acetylate K225 in the Runx2-domain. This disrupts Runx2/CBFβ interaction and thereby inhibits the transcriptional activity of Runx2. Runx2 on the other hand, stabilizes Naa10 in osteoblasts during bone morphogenic protein 2 (BMP-2)-induced differentiation, which in turn inhibits Runx2.

Naa15 may also play an important role in osteogenesis due to its predicted function as a nuclear transcriptional regulator. One study indicates that Naa15, Ku70 and Ku80 bind the osteocalcin promoter and activate osteocalcin expression synergistically with Runx2 [84]. However, follow up studies are necessary to confirm these observations. In contrary to Naa10 knockdown, which increases the stimulatory effects of BMP2 on osteoblastgenesis and enhances differentiation of

Fig. 2. The human N-terminal acetyltransferase machinery. The human NAT machinery consists of six different NAT complexes, NatA-F. NatA-C are multi-subunit enzymes consisting of one catalytic subunit (blue), and one or several auxiliary subunits. NatD-F are mono-subunit enzymes, with the exception of NatE/Naa50 that also can exist in complex with NatA. N-termini containing iMet followed by a small amino acid such as S-, A-, V-, G-, C-, T- and P-, often undergo iMet cleavage performed by MetAP. With the exception of P-, these are typically Nt-acetylated by NatA. NatD Nt-acetylates specifically the S-G- N-terminus of the histones H2A and H4. However, if iMet is retained in the S-, A-, V-, G-, T- N-terminus, these are Nt-acetylated by NatE or NatF. NatB Nt-acetylates M-D-, M-E-, M-N- and M-Q, however, actins are further processed by actin aminopeptidase (ActAP) and Nt-acetylated by Naa10. M-Q- is also Nt-acetylated by NatF. NatC, NatE and F have overlapping substrate profiles and demonstrate a redundancy between these NATs, Nt-acetylating hydrophobic amino acids (M-W-, M-L-, M-F- and M-I-). NatE and NatF also Nt-acetylate M-M-, M-Y-, M-K-, M-H- and M-R-, but the latter two might also be substrates for other NATs.

osteoblasts, knockdown of *NAA15* affects neither BMP2-signaling nor the Naa10-dependent lysine acetylation of Runx2 [83].

Naa15 is also suggested to be involved in blood vessel development as its expression is tightly regulated during formation and maturation of a subset of blood vessels and hematopoietic cells. The distribution and regulated expression level implicate Naa15 to play a unique role in both myelopoiesis and heart development as well as other tissues [85]. Furthermore, knockdown of *NAA15* leads to increased albumin permeability and demonstrate Naa15 as an important regulator of vascular permeability, in particular the retinal endothelial permeability of albumin [86,87]. Src and the Src substrate, cortactin, are essential factors in the signaling pathways mediating endothelial cell permeability. More specifically, cortactin regulates actin assembly, cytoskeletal remodeling and the endothelial barrier integrity and exists in complex with Naa15. Importantly, *NAA15* knockdown resulted in increased levels of activated Src family kinases as Src, Fyn and Lyn, including increased level of phosphorylated cortactin. This further explains the Naa15 regulation of albumin to go through the Src/cortactin signaling pathway, and thereby maintaining the homeostasis and vascular barrier function [88]. Loss of Naa15 expression was also reported as a contributing factor to the development of age-related retinopathy [87]. A recent study describes Nt-acetylation of phosducin-like 3 (PDCL3), a chaperone protein inhibiting proteasome degradation of vascular endothelial growth factor receptor (VEGFR)-2, both essential for angiogenesis [89]. Nt-acetylation by NatB was shown to regulate the stability of PDCL3 and as a consequence the VEGFR-2 expression.

These studies further confirm Naa10 and Naa15 to play important roles as regulators of bone differentiation, angiogenesis and retinal vascular permeability.

2.4.3. Nt-acetylation regulates blood pressure

A study by Hwang, Varshavsky and colleagues links Nt-acetylation-dependent and N-end rule-mediated degradation to blood pressure regulation [90]. Rgs2, a key G-protein regulator, lowers blood pressure in a complex process decreasing signaling through $G\alpha_q$. This protein is involved in regulation of stress responses, hormones, translation, Ca^{2+} channels, cardiac rhythms and cardiovascular homeostasis [91–98]. Human patients displaying a decreased Rgs2 signaling, due to the presence of Rgs2 mutants (ML-Rgs2 and MR-Rgs2), are hypertensive compared to humans expressing wild-type Rgs2 (MQ-Rgs2). Interestingly, different N-end rule degradation pathways target the mutant Rgs proteins [90]. Wild-type Rgs2 and ML-Rgs2 were degraded by the Ac/N-end rule pathway, recognizing Nt-acetylated proteins, acetylated by NatB and NatC, respectively. The mutant Rgs2 protein (ML-Rgs2), a relatively short-lived protein, was additionally targeted by the Arg/N-end rule degradation pathway, recognizing free N-terminal residues. This example represents a regulation mechanism mediated by Nt-acetylation of proteins with an impact at the molecular, cellular and physiological level [99].

2.4.4. NAT regulation of proteasome localization

Degradation of proteins in response to specific degradation signals as consequence of their localization, stoichiometry or misfolding, is an important aspect of a healthy cell. The proteasome localizes to nucleus and cytoplasm as well as to cytoplasmic proteasome storage granules (PSGs). The mechanism underlying the different proteasome localizations in cells involves selective Nt-acetylation as Nt-acetylation is associated with both proteasome distribution and PSG formation [100]. NatC has a specific role in nuclear enrichment of the proteasome during starvation, a phenotype correlated with replicative age. However, loss of NatC has no effect on PSG formation. In contrary, NatB knockouts demonstrate lack of PSG formation, indicating that NatB plays a specific role here. As with NatC–deficient cells, NatB-deficient cells display a nuclear enrichment of the proteasome. NatA deficiency on the other hand did not alter the proteasome distribution. While NatA and NatB control general cell fitness during starvation, NatC has a selective effect on the fitness of old cells only. This demonstrates aging as a process also affected by Nt-acetylation, at least in budding yeast.

2.4.5. NAT involvement in organelle structure and function

NatA-mediated Nt-acetylation is also linked to selective mitochondrial degradation, in particular to induction and regulation of the mitochondria-anchored receptor Atg32, a protein essential for mitophagy and formation of mitochondria-specific autosomes [101]. In addition, NatA-mediated Nt-acetylation of Brx1 is necessary for proper ribosomal biogenesis in conjunction with Ebp2 [102]. NatC Nt-acetylation of several mitochondrial proteins; Kdg1, Fum1 and Mrp has been suggested [103], as well as Nt-acetylation of the L-A gag protein, necessary for viral particle assembly and L-A viral propagation [57]. NatD-mediated Nt-acetylation of histone H4 regulate arginine methylation and thereby silence ribosomal DNA [104]. Both NatE and NatF depleted cells display chromosomal segregation defects [24,52,105]. Studies by Pimenta-Marques et al. further demonstrate Naa50 requirement for normal sister chromatid cohesion and chromosome condensation [106]. NatF is membrane-associated with the Golgi complex and essential for regulation of organelle structure and function, in particular for maintaining Golgi structural integrity [8]. The exact mechanism remains unknown, but may depend on both NatF Nt-acetylation of transmembrane proteins involved in the maintenance of Golgi as well as direct protein interaction and regulation.

2.4.6. Nt-acetylation in hormone regulation

Although Nt-acetylation occurs mainly co-translationally, it also takes place at internal sites after specific proteolytic processing of the translated protein and has profound physiological regulatory effects. This is the case for the peptide hormones α-melanocyte-stimulating hormone (α-MSH) and β-endorphin (β-END), both derived from extensive enzymatic cleavage of the precursor hormone proopiomelanocortin (POMC) and expressed in the hypothalamus, pituitary gland as well as in skin cells [107,108]. These two hormones play key roles in the regulation of a variety of physiological processes, including appetite, metabolism, sexual behavior, inflammation and pain sensation. Their biological activities are oppositely modulated by Nt-acetylation; while Nt-acetylation increases α-MSH stability and potency [109–111], this modification reduces β-END affinity to opioid receptors and results in an inactive hormone [112,113].

2.5. NATs and Nt-acetylation in neurodegenerative disease

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Lewy body dementia are characterized by formation of pathogenic fibrils composed of insoluble proteins in the brain. Dysfunctional NATs and lack of Nt-acetylation are associated with several of these neurodegenerative disorders. The Huntingtin (Htt)-interacting protein K (HYPK) act as a chaperone and prevent aggregation of polyglutamine Htt [114]. As shown in Fig. 2, HYPK exist in complex with NatA, stabilizing HYPK's functions [115]. Arnesen and colleagues, showed HYPK as essential for NatA-mediated Nt-acetylation. Interestingly, knockdown studies of *HYPK*, *NAA10* or *NAA15* further demonstrated increased aggregation of Htt. Htt is a typical NatA substrate and lack of NatA Nt-acetylation as well as destabilization of HYPK result in increased aggregation of Htt proteins, suggesting a direct link between NatA and prevention of Huntington's disease [115]. Another study links NatA activity to Alzheimer's disease [116]. Naa10 interacts with the cytoplasmic domain of the β-amyloid precursor protein (APP), a protein that is processed to the amyloid β-protein (Aβ), which is the main component of amyloid plaques contributing to the development of Alzheimer's. Co-expression of Naa15 suppresses Aβ-protein secretion, indicating that the NatA complex stabilizes APP and/or that the Nt-acetylation reduces Aβ generation. Additionally, NatA regulates protein folding through the action of chaperones in yeast, thereby promoting prion [PSI^+] propagation and further demonstrates the contribution of Nt-acetylation in amyloidogenesis [73]. In Parkinson's, α-synuclein is

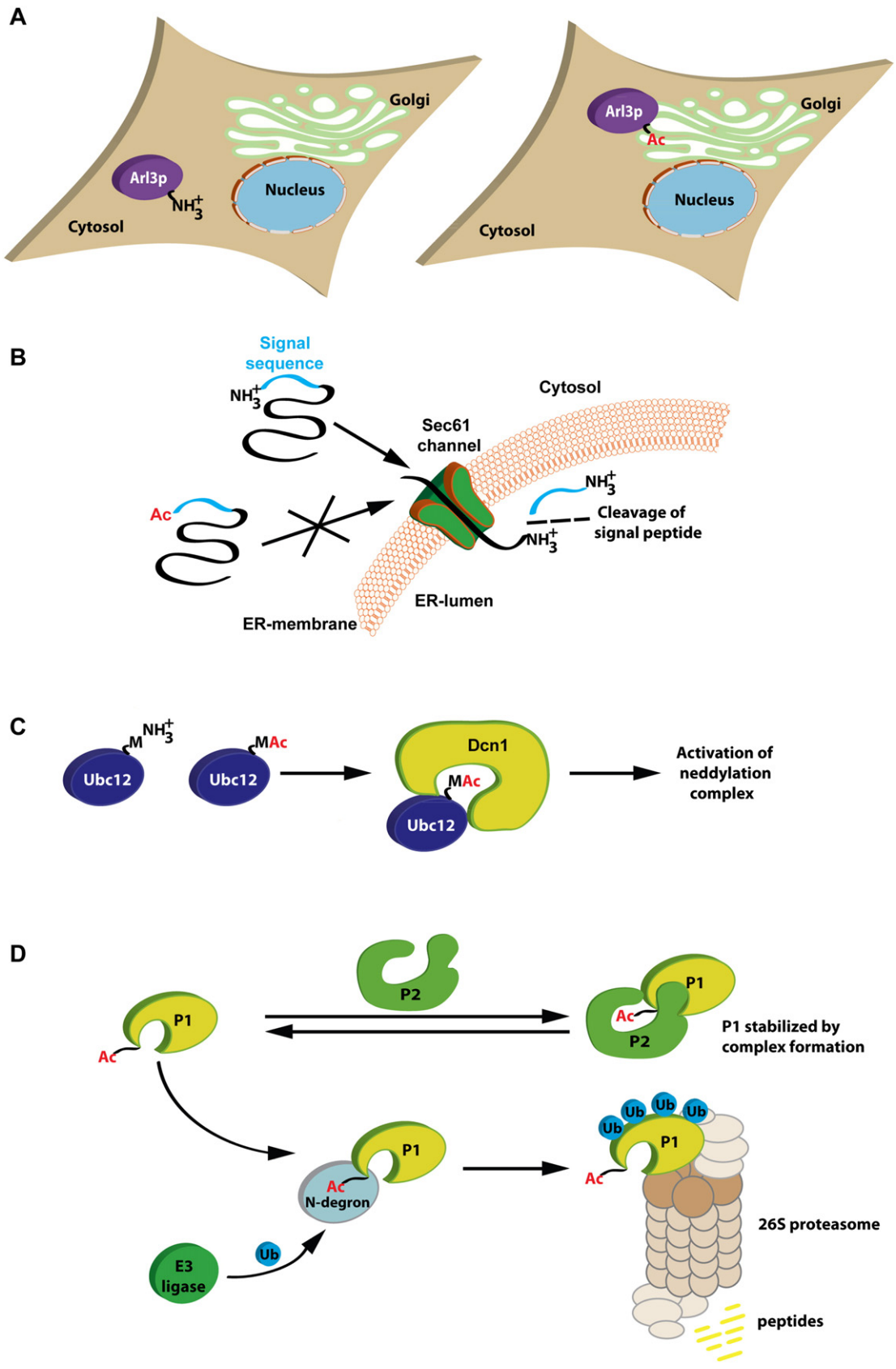


Fig. 3. Molecular effects of Nt-acetylation. Nt-acetylation has various putative roles depending on the modified protein. A) The small GTPase, Arl3p, needs Nt-acetylation for correct subcellular localization to the Golgi as the modification functions as an N-terminal membrane anchor. B) Nt-acetylation can retain proteins in cytosol and prevent their post-translational translocation to ER. C) Nt-acetylation enables protein-protein interaction as shown by the E3 ligase Ubc12, which is interacting with the E2 ubiquitin-conjugating enzyme Dcn1. The hydrophobic pocket of Dcn1 binds the Nt-acetylated methionine of Ubc12 and activates the neddylation complex. D) Nt-acetylation controls protein quality and lifetime, and regulates the protein stoichiometry by the N-end rule pathway. Nt-acetylation of protein P1 facilitates proper protein folding and thereafter stabilizes P1 in a long-lived protein complex with protein P2. When unshielded, an acetylated N-terminus can function as an Ac/N-degron, which recognized by E3 ligases. Thus, the Nt-acetylated protein is targeted for ubiquitination and following proteasomal degradation.

aggregated into insoluble fibrils called Lewy bodies [117]. α-synuclein is involved in lipid binding, synaptic vesicle trafficking as well as neuronal cell survival, but the exact mechanism remains unknown [118]. However, NatB-mediated Nt-acetylation of α-synuclein plays an essential role in folding of the stable α-helical tetramer, and makes the protein resistant for amyloid aggregation [119,120]. Nt-acetylation is a general mechanism for stabilizing α-helical structures in both proteins and peptides [121], and enhance both protein-protein and protein-membrane interaction of α-synuclein [119,120]. More specifically, Nt-acetylation mediates specificity and enhanced interaction between α-synuclein and the neuronal ganglioside GM1. This promotes membrane binding and stabilization of the helical formation of α-synuclein. Thus, Nt-acetylation may have a protective function and potentially plays an important role in preventing early development of Parkinson's.

2.6. Human disorders caused by NAT mutations

The importance of functional NATs and the physiological roles of Nt-acetylation have been further unraveled in the recently identified pathological conditions caused by a malfunctioning NAT machinery, demonstrating NATs to be essential during early embryogenesis and their important regulatory functions during tissue and organ development.

During the last five years, several mutations in the genes encoding NatA subunits have been discovered and all patients with *NAA10* mutations have some clinical features in common regardless of their syndrome. These include developmental delays (ranging from mild to severe), hypotonia, scoliosis and recurrent infections. The X-linked lethal human genetic disorder Ogden syndrome, identified in 2011 and affecting only male infants, is caused by a p. S37P mutation in exon 2 of the *NAA10* gene. [22]. The syndrome is characterized by severe developmental delay, a unique combination of craniofacial anomalies, aged appearance, hypotonia, cardiac arrhythmia followed by cardiomyopathy, being lethal during infancy. Subsequent molecular studies found Naa10 S37P cells to have both reduced complex formation with Naa15 and Naa50, and up to 80% reduced *in vitro* catalytic activity, explaining the observed decrease in NatA and NatE-type substrate Nt-acetylation [19]. The Naa10 S37P cells further showed a reduced cell proliferation *via* perturbed Rb1-pathway and dysregulated cell contact inhibition and migration. In yeast, the Naa10 S37P mutation displayed impaired functionality *in vivo*. Yeast cells expressing the mutant human Naa10-Naa15 complex displayed a reduced degree of Nt-acetylation of NatA substrates as compared to yeast cells expressing the wildtype human NatA complex [122]. Another exome sequence study identified a *NAA10* missense mutation, p. R116W (exon 5), in an intellectual disability syndrome [123]. Yet, another *de novo* missense variant in the *NAA10* gene, p. V107F (exon 6), was identified in an unrelated girl with severe global development delay [20]. Based on 3D homology modeling it was suggested that Naa10 R116W has impaired catalytic activity, due to interference with CoA binding. The V107F mutation was suggested to reduce Naa10 protein stability or enzymatic activity as the bulky side chain did not fit into the hydrophobic core of the protein. As in the case with the S37P mutation, both R116W and V107F significantly reduce the *in vitro* catalytic activity of Naa10. However, while R116W showed a 15% reduction in catalytic activity, the V107F was almost catalytically dead with a 95% reduction but still showed a milder non-lethal phenotype than the Ogden syndrome affected infants. Of notice, the girl with this severe mutation was hemizygous and additionally had a WT *NAA10* allele. A skewed X-inactivation pattern was not identified. Thevenon and colleagues report yet another *de novo* missense mutation in *NAA10*, the c. 364A > T, p. F128I in a girl which share several clinical features with the girl harboring the V107F mutation [124]. A recent study presented two brothers with another novel *NAA10* missense variant, p. Y43S (exon 3), causing an intellectual disability syndrome with facial dysmorphic features, hypotonia, scoliosis and long QT due to NAT impairment [125]. Saunier and colleagues identified three novel Naa10 mutations; the R83C mutation was detected in a male and seven girls, while the F128L mutation and F128I was detected in a girl each [126]. Both R83C and F128L demonstrated a 60–90% reduced catalytic activity. While the F128L and F128I mutation were demonstrated to interfere with the overall structure of Naa10 and destabilize the protein, the R83C mutation was shown to interfere with the Ac-CoA binding. Again moderate to severe developmental delay, intellectual disability, microcephaly, skeletal, brain and organ anomalies were observed among the affected individuals [126]. Another disease connected to a dysfunctional Naa10 is Lenz microphthalmia syndrome (LMS), characterized with congenital bilateral anophthalemia, postnatal growth failure, hypotonia and skeletal anomalies, mild to severe intellectual disability and delayed motor development, yet clinically distinct and with a milder phenotype than observed for the Ogden syndrome males [22]. The splice donor mutation (c.471 + 2T → A) in intron 7 of *NAA10* results in alternative splicing, aberrant *NAA10* transcripts and a C-terminally truncated Naa10, but a maintained NAT catalytic domain [127]. However, the mutation results in lack of wt Naa10 protein expression in addition to low expression of aberrant Naa10 transcripts, a combination that most likely results in reduced Nt-acetylation of NatA-type proteins essential for normal development. In fact, LMS fibroblasts showed similar cell proliferative defects as the Naa10 S37P mutated fibroblasts. Exon 8 in *NAA10* is conserved in mammals and suggests that loss of exon 8 could be detrimental to its function. Furthermore, the C-terminal of Naa10 (part of exon 8) has been reported to be required for interaction with TSC2, an inhibitor of the mTOR pathway [74]. The truncated Naa10 cells demonstrate both loss of Naa10-TSC2 binding and reduced TCS protein levels, and thereby a perturbed mTOR signaling. Interestingly, several genes involved in embryonic, organ, tissue, skeletal and muscular system development were differentially expressed in these splice donor mutated cells, in particular genes associated with the retinoic acid and Wnt signaling pathways, both necessary for normal eye development [127].

One study suggests an association between common birth defects and congenital heart disease and *de novo* putative frameshift mutations in *NAA15* [128]. These findings are relatively similar to the anomalies found in patients with dysfunctional Naa10, suggesting that they may be caused by lack of NatA-mediated Nt-acetylation.

It appears that only patients with mutations in the *N*-acetyl transferase domain with mutations in exon 2–6 (except from LMS patients), have cardiac arrhythmias. Future studies of Naa10 influence on arrhythmia genes either directly interaction or downstream signaling effects are therefore necessary. The *NAA10* knock-down/knock-out studies in addition to the increasing number of Naa10 mutations found in different human pathologies strengthens the notion that Naa10 and NatA are involved in signaling pathways crucial for normal development. However, the correlation between mutant NatA enzyme activity and phenotype severity is more complex than first anticipated. Viewing the Naa10 interaction complexity it is reasonable to believe that Naa10 mutants cause disease through several mechanisms and have pleiotropic effects. Thus, in-depth functional studies, both at the molecular and cellular level, are needed to understand the complex relation in human developmental diseases and provide insight into the underlying pathogenic mechanism.

2.7. NAT-involvement in tumor development

Numerous studies have linked NATs to cancer and in particular NatA is implicated in tumor development and cell survival. Naa10 is proposed to act as both an oncoprotein and a tumor suppressor [21,129]. This further manifests the complexity and difficulties, in particular related to NatA functions, as they are so diverse and target a variety of signaling pathways. In order to give a better overview of NATs involvement in tumor development, this section is separated into an oncogene and tumor suppressor section focusing on Naa10 and Naa15, as well as a section on the other NATs' (NatC-F) critical roles in tumor progression.

2.7.1. Naa10 and Naa15 function as oncogenes

Naa15, the auxiliary subunit of NatA, was initially identified in a screen for differentially expressed genes in papillary thyroid carcinoma (PTC) where it displayed elevated mRNA levels [130]. Later, overexpression of Naa15 was found in gastric cancer [131], as well as elevated Naa15 protein level in poorly or undifferentiated PTC [132] and neuroblastomas associated with a poor prognosis [133]. Naa15 was also found downregulated during differentiation of embryonal endothelial cells, pro-myeloid and myeloid leukemia cells [85,134], thus further linking the Naa15 expression pattern to both differentiation status and aggressiveness of tumors.

The role of Naa10 in cancer cells has been extensively studied and not surprisingly, Naa10 appears co-regulated with Naa15 during differentiation [134,135]. Different cancer types and tissue display elevated levels of Naa10 expression including hepatocellular carcinoma [129], colorectal cancer [136,137], lung cancer [137,138], breast cancer [137, 139] and prostate cancer [140]. Overexpression of Naa10 was also reported in urinary bladder cancer, breast cancer and cervical carcinoma [137]. As with Naa15, a high expression of Naa10 correlates to a low survival rate and aggressiveness of tumors [136,138].

Several studies have proposed various molecular explanations for Naa10's role in cancer development and cellular pathways regulating cell proliferation and cell survival. Overexpression of Naa10 increased cell proliferation in breast cancer cells by promoting the cells to pass the G1/S and G2/M cell cycle checkpoints [139]. HeLa cells depleted for NatA showed a reduced viability due to activation of p53-dependent apoptosis [141], a phenotype also found in colon carcinoma reporting a p53-independent growth inhibition [142]. Lung cancer cells depleted for *NAA10* displayed reduced cell proliferation and G1-arrest in agreement with a reduced Cyclin D1 expression [143]. This phenotype was proposed to be mediated by suppression of cyclin D1 through Naa10-mediated ε-acetylation of one or more lysine residues of β-catenin, which is a known regulator of cyclin D1. It is also known that Naa10 induces cyclin D1 transcription by activating c-Jun and c-Fos (AP-1 proteins) *via* the extracellular signal-regulated kinases (ERK) 1/2 pathway [144,145]. Gromyko and colleagues confirmed this activation of cyclin D1 in anaplastic thyroid carcinoma, but β-catenin acetylation levels remained unchanged upon Naa10 depletion [142]. Naa10 oncogenic properties are influenced by many of its interaction partners. An example is the direct interaction between Naa10 and DNA methyltransferase 1 (DNMT1) which facilitates DNMT1 binding to its substrate DNA [138]. Typically, DNMT1 binds promoters of tumor suppressor genes and silences their transcription by hypermethylation as shown for E-cadherin. Naa10 also interacts with and acetylates the androgen receptor (AR), which facilitates binding of AR to its targeted promoters and enhances gene transcription of AR-regulated genes promoting tumorigenesis [140]. This study reports that androgen induces the expression of Naa10 in an AR-dependent manner, indicating a positive feedback mechanism further explaining the oncogenic role of Naa10 in controlling proliferation, anchorage-independent growth and xenograft tumor formation in prostate cancer.

Not surprisingly, the activity of Naa10 and potency to Nt-acetylate proteins is regulated in response to the metabolic level of Ac-CoA. Cancer cells in general have a high metabolic rate [146,147]. The anti-apoptotic factor Bcl-xL promotes cancer development by regulating cell survival and influences the mitochondrial metabolism [148–150]. Studies by Yi et al. showed Bcl-xL-mediated regulation of Ac-CoA availability followed by reduced Nt-acetylation of essential apoptotic mediators [151]. Thus, regulation of protein Nt-acetylation provides a Bax/Bak-independent mechanism for Bcl-xL to regulate apoptotic sensitivity and promote cell survival. Activation of hypoxia inducible factor-1 (HIF-1α) transcriptional complex during hypoxia promotes tumor survival by induced angiogenesis, cell migration and resistance to chemotherapy [152]. HIF-1α, shown by Lim and colleagues as a regulator of Naa10, binds directly to Naa10 and blocks a following acetylation of β-catenin and thus obstructs the Wnt signaling pathway [145]. Methionine sulfoxide reductase A (MSRA) plays a crucial role in protecting proteins from oxidation and repairs damages caused by reactive oxygen species (ROS), which also crucially affects tunorigenesis [2]. A study by Shin et al. showed *in vivo* and *in vitro* Naa10 interaction with MSRA followed by K49 acetylation of MSRA, which represses its enzymatic function [153]. The authors suggest that Naa10 plays a crucial role in the cellular response to oxidative stress by regulating the MSRA activity. In contrary, an *in vitro* study of recombinant expressed proteins shows that Naa10 does not enzymatically acetylate lysine residues of Runx2, Myosin light chain kinase (MLCK) and MSRA [154]. Instead, they demonstrated *in vitro* non-enzymatic acetylation of these substrates by addition of Ac-CoA, indicating a chemically driven lysine acetylation, leaving the decipherment of this issue to upcoming studies (see Section 6.2).

Numerous cancer studies report an elevated expression level of Naa10 and Naa15, the two subunits of the NatA complex. More interestingly, this over-expression correlated with more aggressive tumors and a poor patient survival rate. Naa10 and Naa15 involvement in tumorigenesis were further demonstrated by their role in promoting cell proliferation and cell survival as well as regulating cell metabolism.

2.7.2. Naa10 - a tumor suppressor?

Contrary to Naa10's oncogenic abilities, several studies indicate that Naa10 has tumor suppressor properties. Yi et al. identified Naa10 in a genome-wide RNAi screen as necessary for DNA damage-induced apoptosis by caspase activation [155]. An elevated expression of Naa10 is also implicated in reducing breast cancer cell growth through stabilization of TSC2 by direct interaction and Nt-acetylation [74]. Stabilization and increased abundance of TSC2 suppress the mammalian target of rapamycin (mTOR) signaling pathway and thereby reduce cell proliferation. A high expression level of Naa10 has also been correlated to smaller breast tumors, fewer lymph node metastases and a better prognosis [74,156]. Zeng et al. further demonstrated Naa10 as a negative regulator of signal transducer and activator of transcription 5a (STAT5a), by direct binding to STAT5a and downregulation of inhibitors for differentiation 1 (ID1). Independent of its acetyltransferase activity, Naa10 inhibits cell migration, invasion and metastasis by antagonizing Janus Kinase 2 (JAK2)-STAT5a signaling and lowering p65-activated interleukin-1β expression [156]. The study by Hua et al. further presents Naa10 as a tumor growth and metastasis suppressor by binding of p21-activated kinase (PAK)-interacting exchange factor (PIX) proteins, thus preventing formation of the GIT-PIX-Paxillin complex and subsequent activation of Rac1/Csc42 [157]. Yet, another mechanism presented by Shin and colleagues reports that Naa10 inhibits cell motility by direct binding of MLCK and following acetylation of K608, thereby inactivating the ability of MLCK to phosphorylate MLC [158]. Studies by Park et al. showed Naa10 as required for doxorubicin NF-κB activation by its interaction with the receptor-interacting protein 1 (RIP1) [159]. Recently, *NAA10* expression in colon cancer was found regulated by microRNAs, which target *NAA10* for degradation [160].

These studies suggest Naa10 to have a more predominantly anti-proliferative and pro-apoptotic function in certain types of tumor cells in contrast to the numerous studies discussed in the previous section, reporting a pure role as an oncogene. Without doubt, Naa10 is an important protein with truly diverse functions, and the precise role of Naa10 in tumor development will remain as a major challenge for future studies. Studies need to focus more on the regulation of NatA and through which mechanisms these anti-proliferative and pro-apoptotic properties are mediated in given tissues.

2.7.3. NatC, D, E and F in tumor development

Other NATs may also be involved in oncogenesis, although most studies connecting NATs to cancer development focuses on NatA. The NatB subunits found overexpressed in hepatocellular carcinoma are implicated in cell proliferation and cell cycle progression [161]. While depletion of *NAA25* caused cell death, depletion of *NAA20* mainly results in growth arrest. However, cells depleted for NatB displayed cell cycle

arrest in conjugation with p53 induction and p21 upregulation, and sensitized cells to pro-apoptotic agents [56,161]. NatC knockdown studies by Starheim et al. demonstrated a reduced cell proliferation and p53-dependent caspase-mediated apoptosis [59]. Interestingly, activation of p53 went through another phosphorylation pathway than observed for NatA and NatB. In agreement, NatC was shown to act *via* the p53-mediated pathway in glioblastoma cancers and Naa30 depletion reduced tumorigenic features [162]. Here, NatC regulated the expression level of genes involved in cell cycle regulation, proliferation and apoptosis as well as genes involved in DNA repair and regulation of protein kinases, probably as a consequence of Nt-acetylation. NatD is downregulated in hepatocellular carcinoma, and shown to protect cells from drug induced apoptosis [163]. NatD Nt-acetylates histone H4, thereby regulating arginine methylation and ribosomal DNA silencing, and might act as a sensor for cell growth [104]. Although NatD is downregulated in hepatocellular carcinoma, its overexpression enhances apoptosis in cancerous cells [163]. Depletion of NatD further demonstrated the involvement of NatD in protecting cancer cells from drug-induced apoptosis. Recently, depletion of NatD in colon cancer was shown to induce p53-independent apoptosis by activating the mitochondrial capsase-9-mediated apoptotic cascade [164]. NatE depletion studies show that Naa50 is important for cell-cycle progression as depletion leads to M-phase cell-cycle arrest [105]. Depletion studies further demonstrate NatE function as essential for normal sister chromatid cohesion and chromosome condensation [52,105,106]. Similarly, cells depleted for NatF had abnormal chromosome segregation, which might lead to genomic instability and aneuploid cells [24].

To sum up, NATs are involved in a multitude of signaling pathways and shown to regulate cell-cycle and cell proliferation, cell survival, angiogenesis, apoptosis and to play an important role during chromosome segregation. The emerging role and involvement of all six human NATs in cancers or other pathologies are not surprising when considering that 80% of all proteins are modified by these enzymes. NATs affect other proteins either through direct Nt-acetylation of target substrate proteins, or by protein-protein interactions and subsequent suppression or activation. However, missing links exist and all NAT enzymes still deserve a significant attention in order to give a complete mechanistic explanation for the observed phenotypes.

3. Lysine acetylation

3.1. ε-Acetylation of lysine residues in general

3.1.1. The players involved in lysine acetylation

ε-amino lysine acetylation is involved in several cellular pathways and is not limited to transcriptional regulation by histone modification alone [165]. Besides phosphorylation, it is perhaps the most abundant and important PTM in cell signaling and metabolism. Lysine acetylation is dependent on Ac-CoA, while a class of KDACs, the sirtuins, use NAD^+ (nicotine adenine dinucleotide) as a co-substrate. These two metabolites are important hubs of cellular metabolism, and link cellular metabolism and cell signaling pathways (see Section 4) [165–167]. Three classes of 'players' are involved in cell signaling by lysine acetylation: KATs, KDACs, and proteins recognizing and binding acetyl-lysines. Most of these acetyl-lysine binders contain the so called bromodomain (~120 amino acids long sequence forming small helical interaction modules), including KATs and transcription factors [168]. In contrast to Nt-acetylation, lysine acetylation is reversible, making it a crucial tool for the cell to activate and deactivate certain pathways. KDACs are divided into two distinct groups with different catalytic mechanisms: Zn^{2+}-dependent HDACs (HDAC1–11) and NAD^+-dependent sirtuins (SIRT1–7) [14]. Besides KAT-catalyzed lysine acetylation, some acetylation events can also occur non-enzymatically *via* direct interaction of the protein and Ac-CoA. This reaction is favored by high pH and high Ac-CoA concentrations, conditions which certainly are present in mitochondria [169,170]. It has also been shown that other acyl-CoA or glycolytic intermediates can enzymatically or non-enzymatically bind to lysine residues in certain conditions leading to formylation, succinylation, propionylation, butyrylation, or crotonylation [167,171–175]. They are mainly determined as histone modifications (*e.g.* K23 in histone protein H3), but new non-histone target proteins such as p53, p300 and CREB are constantly being identified [174,176]. Especially propionylation and butyrylation are carried out by p300 and CREB. Thereby, they are able to autopropionylate some of their own lysine residues [175]. Further, it was demonstrated in *Salmonella enterica* that the propionylation at position K592 of the propionyl-CoA synthetase enzyme PrpE results in its inactivation [177]. Interestingly, most of these PTMs can be reversed by sirtuins, particular by SIRT1, SIRT2, and SIRT5. Further, a balanced regulation between KATs and KDACs is crucial for many cellular processes and especially for chromatin-based transcriptional regulation [178].

3.1.2. The abundance of lysine acetylation

Lysine acetylation is evolutionarily conserved. Proteome-wide studies in *E. coli* and *Saccharomyces cerevisiae* demonstrated the importance of this PTM in these organisms. Many acetylated proteins found in these studies were involved in metabolism, translational regulation or stress response. The amount of identified acetylation sites increases with the complexity of the organism, comparable to Nt-acetylation events [179–182]. In *E. coli* only 138 acetylation sites in 91 proteins have been identified [180], whereas in *S. cerevisiae* 2878 acetylation sites from 1059 proteins were determined. An organ-wide analysis of rat tissues identified 15,474 tissue-specific modifications sites in 4541 proteins, associated with various cellular functions such as gene expression, pyruvate, amino acid and glucose metabolism, apoptosis, and membrane trafficking [182]. Nevertheless, lysine acetylation is occurring more frequently than phosphorylation in bacteria. Considering the endosymbiotic theory, it is not surprising that lysine acetylation is also more abundant in mitochondria of eukaryotic cells than other PTMs [183,184]. When further comparing lysine acetylation with phosphorylation, it is remarkable that lysine acetylation sites are often found in highly structured regions (α-helices as well as β-sheets), whereas phosphorylations mainly occur in unstructured and flexible protein regions [165,185].

3.2. The lysine acetyltransferases (KATs)

3.2.1. The KAT families

Histone acetylation and the involvement of particular enzymes (KATs) were first discovered in 1964 by Allfrey and colleagues [13]. So far, 17–22 'classical' KATs have been identified in the human genome [14,15,167,186]. The exact number of KATs is controversial due to different indications in literature. The human genome (HUGO) gene nomenclature committee lists 17 different genes as KATs. This number refers to genes that have been identified and characterized as KATs as their main catalytic activity. Not listed are enzymes, which display KAT activity in addition to their previously characterized and described enzymatic activities, and when including these, the number of human KATs reaches 22. The KATs can be grouped into three major families: the GNAT (see Section 2.2) family, the MYST family and the p300/CBP (CREB-binding protein) family [15,187]. Table 1 lists the 'classical' KATs and additionally some examples of enzymes displaying additional KAT activity. The acronym MYST comes from the first four identified members: human monocytic leukemia zink finger protein (MOZ), something about silencing 3 (Ybf2), now Ssa3; Ssa2, both from yeast, and mammalian HIV Tat-interacting 60 kDa protein (TIP60) [188]. Recent studies have identified new KATs or have demonstrated that proteins with a known non-KAT catalytic activity are able to transfer an acetyl moiety to specific substrate lysines. Examples include GCN5L1 and the mitochondrial thiolase ACAT1 [189]. Most KATs belong to multiprotein complexes with various associated subunits, which define their catalytic activities and substrate specificities, especially in the case of histone acetylation [190]. The

Table 1
Members of the human HAT/KAT families (see Refs. [15,186,188,269]).

Family	HAT/KAT	New name	Subcellular localization	Representative substrates	Swiss-Prot accession no.
GNAT	HAT1	KAT1	Nucleus	H2A, H4	O14929
GNAT	GCN5 (GCN5L2)	KAT2A	Nucleus	H3, CEBPB	Q92830
GNAT	PCAF	KAT2B	Nucleus	H3, H4, ACLY	Q92831
p300/CBP	CBP	KAT3A	Nucleus/Cytoplasm	H2A, H2B, H3, H4, NCOA, FOXO1	Q92793
p300/CBP	P300	KAT3B	Nucleus/Cytoplasm	H3, FOXO1, HDAC1, SIRT2, ALX1	Q09472
	TAF1 (TAFII250)	KAT4	Nucleus	H3, H4	P21675
MYST	TIP60/PLIP	KAT5	Nucleus/Cytoplasm	H2A, H4, FOXP3	Q92993
MYST	MOZ/MYST3	KAT6A	Nucleus	H3, H4, p53, RUNX2	Q92794
MYST	MORF/MYST4	KAT6B	Nucleus	H3, RUNX2	Q8WYB5
MYST	HBO1/MYST2	KAT7	Nucleus	H4	O95251
MYST	MOF/MYST1	KAT8	Nucleus	H4, p53	Q9H7Z6
GNAT	ELP3	KAT9	Nucleus/Cytoplasm	H3, H4, α-tubulin	Q9H9T3
	TFIIIC90 (GTF3C4)	KAT12	Nucleus	H3	Q9UKN8
	SRC-1 (NCOA1)	KAT13A	Nucleus	H3, H4	Q15788
	SRC-3 (TRAM1, NCOA3, ACTR)	KAT13B	Nucleus/Cytoplasm	H3, H4	Q9Y6Q9
	SRC-2 (TIF2, GRIP1, bHLHe75, NCOA2, P160)	KAT13C	Nucleus	H3, H4	Q15596
	CLOCK	KAT13D	Nucleus/Cytoplasm	ARNTL/BMAL1, NR3C1/GR	O15516
	ATF-2 (CREB2, CREBP1)		Nucleus/Cytoplasm	H2B, H4	P15336
GNAT	ATAT1		Cytoplasm/Membrane	α-tubulin	Q5SQI0
	ACAT1		Mitochondria	PDP	P24752
	NAT10		Nucleus	Histones, α-tubulin	Q9H0A0
	GCN5L1 (BLOC1S1)		Mitochondria	ATP5A1, NDUFA9	P78537

associated complexes, which are able to bind to KATs and transport them to their appropriate localization, display different domains such as bromodomains (recognizing acetylated lysines), chromodomains, Tudor domains and WD40 repeats (recognizing chromatin structures and non-acetylated histone proteins). PHD finger domains are normally binding non-acetylated lysine. However, it was demonstrated that a tandem PHD finger domain of the human chromatin remodeling protein DPF3b is able to bind to acetylated K14 of H3 (H3K14ac) [191]. In addition to the enzymes belonging to the three major KAT families, KAT activity could be deciphered for several further proteins (for a detailed list of all human KATs and their associated complex subunits see Ref. [192]).

3.2.2. The manifold targets of KATs

Histone proteins are not the only known substrates of KAT complexes. Many different transcription factors and transcriptional co-regulators become modified by KATs. These are partly general transcription factors such as TFIIB or TFIIE, but also proteins of specific cellular signaling pathways like p53, β-catenin, NF-κB, MyoD or Rb [188]. Interestingly, RNA molecules also undergo post-transcriptional acetylation. Elp3 mediates this modification of nucleosides especially towards tRNA molecules [193]. Consequently, KATs are crucial modifiers for epigenetic and transcriptional regulation. Besides the nuclear substrates, cytosolic proteins also belong to the great substrate pool of KATs (see Sections 3.5 and 3.6). Recently, it was shown that NAT10 (not to be mistaken for the N-terminal acetyltransferase Naa10), which was first identified as a nucleolar KAT involved in H2B and H4 acetylation, is involved maintaining the structural integrity of the mitotic midbody organelle during the telophase [194]. Similar to Elp3, NAT10 is additionally able to facilitate acetylation of cytidine residues of rRNA and tRNA [195]. The proteins of the p300/CBP family were first identified as transcriptional co-activators and later as interaction partners of adenoviral-transforming protein E1A [196]. They are involved in the regulation of cell growth and development, including the NF-κB, Notch, TGF-β, p53 and Rb-cell signaling pathway [197,198]. These represent tumorigenic pathways, thus demonstrating a critical role of p300/CBP in cell transformation and oncogenesis (see Section 5.1) [198,199]. Interestingly, KAT autoacetylation is common and seems to play distinct roles for different KATs. The histone acetyltransferases p300 and CBP, acetylating histone and non-histone proteins alone or in the PCAF complex, can become autoacetylated at various lysine residues. p300 is autoacetylated at five lysine positions at the C-terminus resulting in an increased basal activity [200]. The conformational alterations induced by autoacetylation of CBP feature a crucial requirement for H3K53 binding and acetylation [201,202]. In both cases autoacetylation leads to an increased KAT activity. Autoacetylation of the MYST proteins Esa1 (yeast) and MOF (human) has a similar effect. Both enzymes become autoacetylated at lysine residues, which are part of their catalytic domain. These acetylation reactions are a precondition for substrate binding and subsequent acetylation [203].

3.3. Lysine deacetylases

3.3.1. The four classes of KDACs

Lysine deacetylases (KDACs) or histone deacetylases (HDACs) were first identified in 1995, acting on acetyl-lysines of histone proteins [204]. Later their function has also been dissected for several other proteins and cellular functions [205,206]. Although most of these deacetylases display activity towards multiple substrates, and except for the sirtuins (SIRT1–7), they are still known as HDACs (HDAC1–11). The KDAC family has phylogenetically been divided into four classes in higher eukaryotes. Class I, II and IV are Zn^{2+}-dependent amidohydrolases, whereas class III (also called sirtuins) uses NAD^{+} as co-substrate for its catalytic activity (Fig. 1C) [207]. Class IV has only one known representative, HDAC11, which differs phylogenetically from the Zn^{2+}-dependent yeast proteins Rpd3 (class I) and HDA1 (class II), as well as from the NAD^{+}-dependent Sir2 homolog, and therefore forms its own subclass [208]. Noteworthy, class I and II share a high homology in their catalytic domains [209]. The Zn^{2+}-dependent KDACs are mainly localized in the nucleus and cytoplasm, whereas sirtuins are additionally present in mitochondria (Table 2) [167,210]. Substrates of KDAC class I and II are in general histone molecules and various transcription factors. They are normally associated with transcriptional repressor complexes in the nucleus such as Sin3, NuRD/NRD/Mi2, CoREST, and SMRT/N-CoR. The only exception is HDAC8, which is active as a monomer. Nevertheless, the class II members HDAC6 and HDAC10 have various regulating roles in the cytoplasm. Tubulin, cortactin and Hsp90 are only some targets of HDAC6 (see Sections 3.5 and 3.6) [210–212]. HDAC11 (class IV), which is predominantly localized in the nucleus, triggers the decision between immune activation and immune tolerance by regulating the interleukin 10 expression in antigen-presenting cells. This is to date its only known physiological function [213].

Table 2
Members of the HDAC/KDAC family and their subcellular localization (see Refs. [215,455–457]).

Class	Member	Catalytic mechanism	Subcellular localization	Representative substrates	Swiss-Prot accession no.
I	HDAC 1	Zn^{2+} dependent	Nucleus	H2A, H2B, H3, H4, RelA, AR	Q13547
I	HDAC2	Zn^{2+} dependent	Nucleus	H2A, H2B, H3, H4, TSHZ3	Q92769
I	HDAC3	Zn^{2+} dependent	Nucleus	H2A, H2B, H3, H4, NF-κB, PCAF, STAT1, RelA	O15379
I	HDAC8	Zn^{2+} dependent	Nucleus/Cytoplasm	H2A, H2B, H3, H4, p53, ERRα	Q9BY41
II	HDAC4	Zn^{2+} dependent	Nucleus/Cytoplasm	H2A, H2B, H3, H4, HIF1α, p53, DNAJ88	P56524
II	HDAC5	Zn^{2+} dependent	Nucleus/Cytoplasm	GATA-2, GCMa	Q9UQL6
II	HDAC6	Zn^{2+} dependent	primarily Cytoplasm	Cortactin, α-tubulin, HSP90	Q9UBN7
II	HDAC7	Zn^{2+} dependent	Nucleus/Cytoplasm	PLAG1	Q8WUI4
II	HDAC9	Zn^{2+} dependent	Nucleus/Cytoplasm	ATDC	Q9UKV0
II	HDAC10	Zn^{2+} dependent	primarily Cytoplasm	HSP70, PP1	Q969S8
III	SIRT1	NAD^{+} dependent	Nucleus	P53, FOXO1, HSF1, KAT7, CBP	Q96EB6
III	SIRT2	NAD^{+} dependent	Cytoplasm	α-tubulin	Q8IXI6
III	SIRT3	NAD^{+} dependent	Mitochondria	GDH, Ku70, MRLP10, AceCS2	Q9NTG7
III	SIRT4	NAD^{+} dependent	Mitochondria	GLUD1	Q9Y6E7
III	SIRT5	NAD^{+} dependent	Mitochondria	CPS1, cytochrome c	Q9NXA8
III	SIRT6	NAD^{+} dependent	Nucleus	H3K56ac, RBBP8	Q8N6T7
III	SIRT7	NAD^{+} dependent	Nucleolus	H3K18ac, PAF53	Q9NRC8
IV	HDAC11	Zn^{2+} dependent	primarily Nucleus	H2A, H2B, H3, H4	Q96DB2

3.3.2. The class III KDACs: the sirtuins

The sirtuins need NAD^{+} as co-substrate for deacetylation, and it was shown *via* the use of various inhibitors that nicotinamide and 2′ or 3′-*O*-acetyl-ADP-ribose are formed as byproducts (Fig. 1C) [214]. The name sirtuins is derived from its first found representative sir2 (silent information regulator 2) in yeast. There, it is important for chromatin silencing in different loci and additionally plays a role in yeast longevity [215,216]. In mammals, seven different sirtuins (SIRT1–SIRT7) have been identified to date. They are localized in various cell compartments. SIRT1, SIRT6 and SIRT7 are localized in the nucleus, whereas SIRT2 is active in the cytoplasm. A special characteristic of SIRT3, SIRT4 and SIRT5, which distinguish them from other KDACs, is that they are acting in mitochondria and subsequently affecting metabolic processes (Table 3). Especially, SIRT3 displays a great influence on the intermediate metabolism by deacetylating several of its enzymes and regulating their activity (see Section 4) [217,218]. SIRT4 has a unique role in mammals because it displays an ADP-ribosyltransferase and lipoamidase activity in addition to its deacetylase activity. Thereby, its catalytic activity towards lipoyl- and biotinyl-lysine is higher than towards acetyl-lysine [219]. It transfers further ADP-ribose on glutamate dehydrogenase I (GLUD1), repressing its activity, and thus displaying an important role in caloric restriction [220]. The non-mitochondrial sirtuins are also involved in metabolic processes, especially glucose metabolism. This was demonstrated for SIRT1, SIRT6 and SIRT7 (see Section 4) [221–223]. Additionally, SIRT7, which is active in the nucleolus, was shown to specifically deacetylate the K18 on histone protein H3 (H3K18Ac), subsequently maintaining tumorigenicity of human cancer cells [224].

3.4. Role of histone acetylation in general epigenetic regulation

3.4.1. General aspects of histone modifications

The first proteins discovered to be acetylated were histones [225]. All four different histone proteins, H2A, H2B, H3 and H4 become acetylated by different HATs (Table 1). Together with DNA, histone proteins form the so called nucleosomes. One nucleosome consists of about 150–200 bps of DNA, which wraps itself almost two times around a protein core that is formed by two copies of each of the four histone molecules [226]. Chains of nucleosomes assemble to defined chromatin structures, which can be transcriptionally active or inactive. The histone molecules are modified by various PTMs, of which phosphorylation, methylation and acetylation play the most crucial roles for DNA accessibility and transcriptional regulation. The PTMs, and especially histone acetylation, determine the histone assembling as well as the folding and compactness of the DNA-histone interaction and therefore presenting a switch between permissive and repressive chromatin structure [227]. After synthesis, the histone proteins are transiently acetylated, determining their localization and deposition in the nucleus. This applies especially to K5 and K12 in newly synthesized H4 and is more species-dependent for histone H3 [190,228]. This specific acetylation pattern recruits chaperones, assisting in the formation of the nucleosome. After binding to the DNA, histones are deacetylated, and re-acetylated again in a different pattern, which is essential for chromatin functionality [190,229].

3.4.2. Histone acetylation leads in general to transcriptional activation

In general, a high degree of acetylation correlates with increased transcriptional activity. Histone acetylation destabilizes the

Table 3
Acetylation-modulated intermediary metabolic enzymes and the effect on their activity.

Enzyme	Process	Cellular compartment	Acetylation increases or decreases activity?	Reference[a]
Phosphoenol-pyruvate carboxykinase	Gluconeogenesis	Cytosol	Decrease	[166]
AceCS1	Acetyl CoA formation from acetate	Cytosol	Decrease	[321]
AceCS2	Acetyl CoA formation from acetate	Mitochondria	Decrease	[321]
LCAD	β-oxidation of fatty acids	Mitochondria	Decrease	[218]
EHHADH	β-oxidation of fatty acids	Mitochondria	Increase	[166]
MDH	Citric acid cycle/urea cycle	Mitochondria	Increase	[458]
SDH	Citric acid cycle	Mitochondria	Decrease	[459,460]
ASL	Urea cycle	Cytosol	Decrease	[166]
CPS1	Urea cycle	Mitochondria	Decrease	[461,462]
OTC	Urea cycle	Mitochondria	Decrease	[335]
PDHA1	Acetyl-CoA formation	Mitochondria	Decrease	[327]
Aconitase	CAC	Mitochondria	Increase	[463]

[a] In addition to listed references see reference [464].

DNA-histone interaction, because an acetylated lysine side chain loses its positive charge and thus the ability to form salt bridges with the negatively charged phosphate backbone of DNA [230]. This leads to an open, lightly packed chromatin structure (euchromatin), and consequently to an increase of gene transcription. The opposite, densely packed form of chromatin is called heterochromatin (Fig. 4A) [231,232]. This was shown for various acetylated lysines at different positions on different histone molecules. It was demonstrated that residues 14–23 of the tail of histone 4 are particularly important for fiber formation and dense chromatin structure. Acetylation of these residues, and especially acetylation of H4K16, disrupts the chromatin structure and results in transcription activation and maintains the euchromatin form [233]. Similar results were observed for acetylation of H3K56, H3K64 and H3K122 [230]. H3K56ac is specifically targeted by Sir2 in yeast, keeping H3K56 in a hypoacetylated state and maintaining heterochromatin structure near transcriptionally silent regions such as telomers [234]. In contrast to the abovementioned acetylated lysines, which disrupt histone-DNA interaction, H4K91 acetylation directly affects histone-histone interaction, in particular H2A-H2B-dimerization. Thus, H4K91ac, weakens the complete histone octamer and leads to alterations of the heterochromatin structure [235].

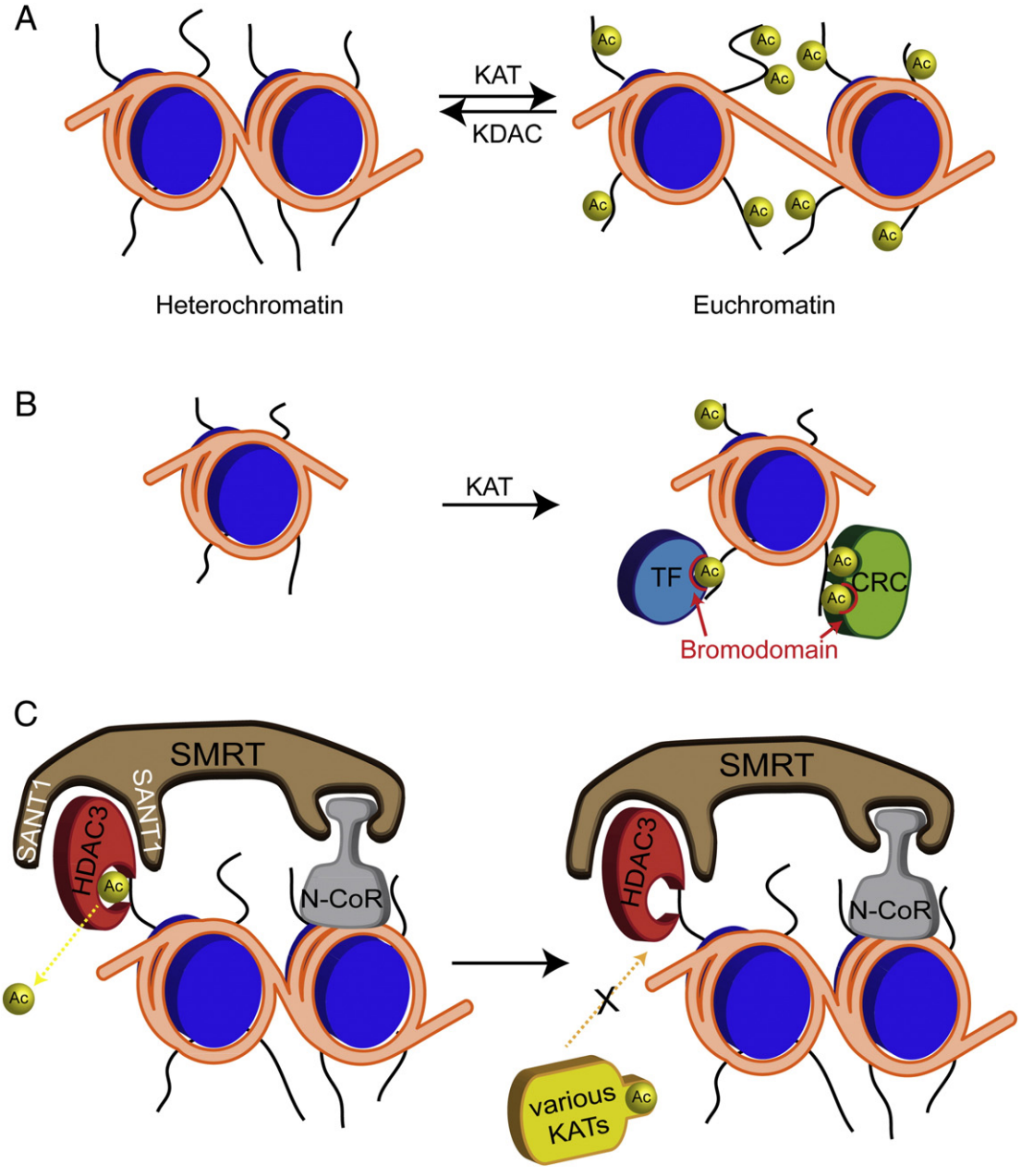


Fig. 4. Acetylation and regulation of histone acetylation. A) Reversible acetylation of histone tails by various histone acetyltransferases (HATs) weakens the DNA-histone interactions, and concomitantly loosens the compactness of the chromatin structure. This leads to conformational changes from heterochromatin to the more open euchromatin structure. A high histone acetylation rate is normally associated with an increased transcriptional activity. B) Histone tails containing acetylated lysine residues are recognized and bound by transcription factors (TFs) or chromatin remodeling complexes (CRCs) *via* bromodomains. Bromodomains consist of around 110 amino acids and form a four α-helices bundle. C) Transcriptional repression is regulated by specific repressors, recruiting histone deacetylases (HDACs). Shown here is the SANT-containing repressor SMRT and the corepressor N-CoR. Both recruit HDAC3 to specific genomic regions and activate the deacetylase activity of HDAC3. The two SANT-domains of SMRT are part of the functionality for HDAC3's deacetylase domain and act as histone binding domains with the preferentiality for unacetylated histone tails. Thereby, they block substantially acetylation sites for re-acetylation by HATs and maintain in this way the transcriptional repression.

3.4.3. Histone acetylation recruits additional gene regulatory proteins and chromatin-modifying enzymes

Histone acetylation enables the binding of bromodomain-containing proteins and transcription factors, expanding the number of regulatory factors. In humans, the bromodomain family consists in total of 46 different proteins (Fig. 4B) [236,237]. In contrast to gene transcription activation by KATs, KDACs repress transcription by histone deacetylation. A histone in a hypoacetylated state promotes binding of SANT-domain containing enzymes, mainly found in transcriptional co-repressors [238]. The SANT-domain enzymes, preferentially binding unacetylated histone tails, are part of the HDAC3 complex, which guarantees and maintains the recruitment of associated corepressors at specific genomic sites such as nuclear receptor corepressor (N-CoR) and silencing mediator of retinoid and thyroid receptors (SMRT) (Fig. 4C) [239]. Nevertheless, HDACs can also play a role in the proper transcription initiation at active gene sites as demonstrated for the Hos2 deacetylase in yeast [240]. For other active genes, HDACs repress the transcription initiation or are recruited to prepare for repression [190,241]. Altogether, the effects of KATs and KDACs on the nucleosome and concomitantly gene transcription depend on the genomic site they act on as well as the different complexes they form. Several transcription regulating complexes share the same KATs and KDACs but differ completely in their functions. To understand the regulation and specificity of these complexes is part of further investigations.

3.5. Acetylation of cytoskeletal proteins

Besides histones, cytoskeletal proteins are another crucial family which is targeted by KATs. Cytoskeletal complexes play an important role in cell shape, intracellular cargo transport, cell division and motility. The monomeric cytoskeletal G actin proteins can polymerize to filamentous F actin and form the versatile microfilaments in eukaryotic cells. Three different isoforms of G-actin exist, α-, β-, and γ-actin, and it was demonstrated that all three isoforms can be acetylated. Thereby, it was shown that lysine acetylation of γ-actin at position 61 increases the fiber stability (Fig. 5A) [242,243]. Not only actin or myosin proteins themselves are acetylated, but also proteins that interact and regulate these molecules such as cortactin. Cortactin binds to dynamic F-actin bundles promoting polymerization and branching [244]. When cortactin becomes acetylated by p300 or PCAF at nine different positions, its binding to actin is inhibited, provoking a direct effect on cell motility. This process is reversed by cortactin deacetylation *via* SIRT1 or HDAC6 (Fig. 5B) [245,246]. The regulation of the cytoskeleton by acetylation was further confirmed by studies which demonstrated that HDAC6 is a major effector of this system [211,247]. HDAC6 interacts with two actin polymerization controlling proteins, mDia1 and mDia2, and therefore directly interferes with actin stability [248]. Another group of important cytoskeletal filaments are microtubules, which are formed by repeating α- and β-tubulin heterodimers. α-tubulin was shown to

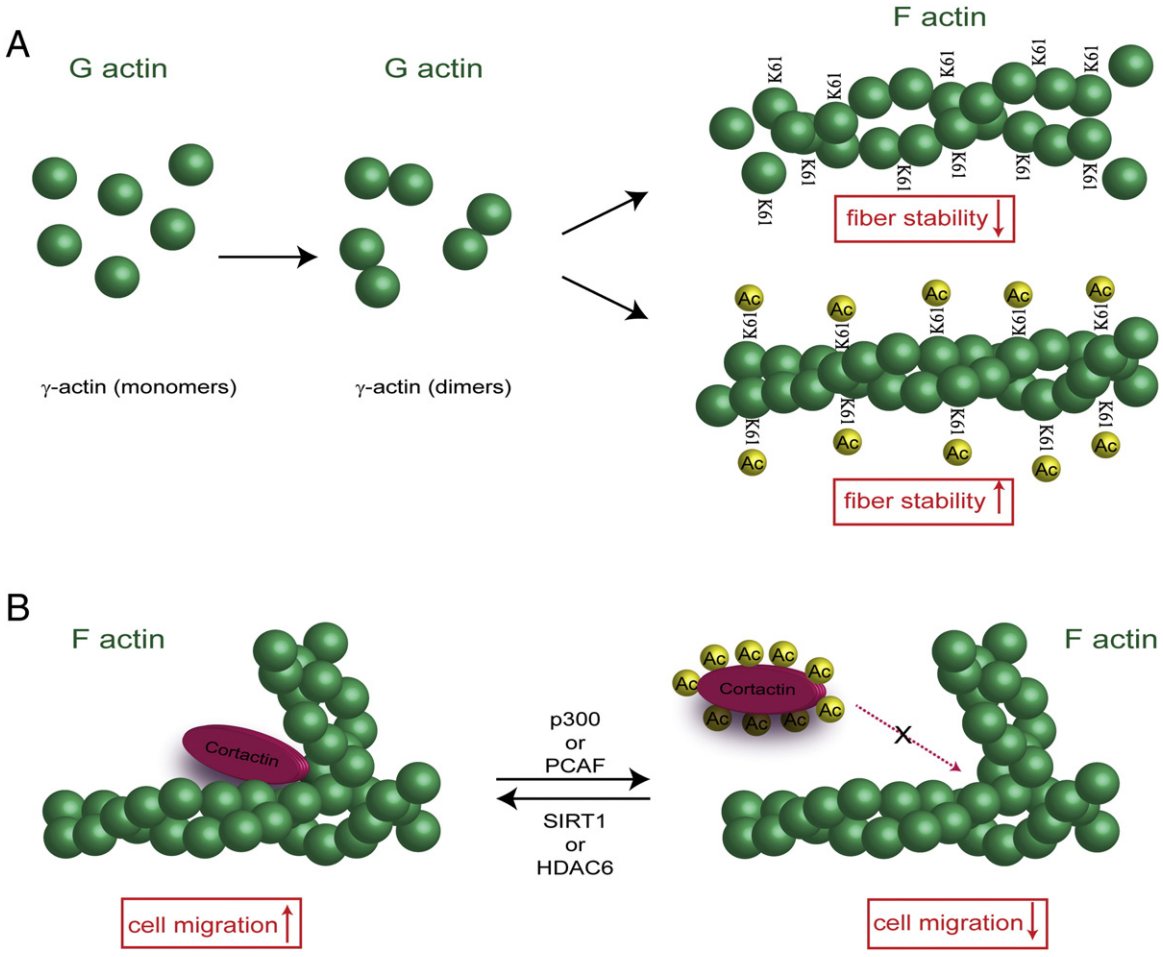


Fig. 5. Acetylation of cytoskeleton. Acetylation of cytoskeletal proteins (A) and (B) plays a crucial role in cell growth, stability and migration. A) Microfilamentous F-actin is formed by the dimeric isoforms of G-actin, α-, β-, and γ-actin. All three isoforms can be acetylated. It was shown that the acetylation of γ-actin at the position K61 results in an increased fiber stability and less restructuring. B) Additionally, proteins such as cortactin, which modulate actin polymerization and branching, are targets for acetylation. Cortactin itself can be acetylated at nine different lysine residues by p300/PCAF and be deacetylated again by SIRT1 or HDAC6. The acetylation abrogates the ability of cortactin to bind to F-actin, thus directly influencing cell motility.

be reversibly acetylated at position K40 and the acetylated α-tubulin is again targeted by HDAC6 [249,250]. Later it was shown that SIRT2 is also able to deacetylate α-tubulin acK40 [251]. Tubulins are one of many substrates HDAC6 and SIRT2 share. The acetylation of α-tubulin itself is catalyzed by several KATs, such as NAT10, ELP3, GCN5, and ATAT1 [252]. With advancements in mass spectrometry, additional acetylation sites came along [165]. The counterpart, β-tubulin, is also acetylated which affects the kinetics of tubulin polymerization [253]. Nevertheless, tubulin acetylation does not seem to directly affect architecture or tubulin conformation *per se*, but rather recruits tubulin binding proteins and affects their localization [254].

3.6. Further important non-histone substrates

The number of newly identified acetylation sites, belonging to proteins besides the well characterized histones and cytoskeletal proteins, is constantly increasing [167]. Several of these proteins have been studied in detail such as HMG proteins, c-Myc, estrogen and androgen receptors, E2F/Rb and many more [14]. The first recognized non-histone KAT substrate was the tumor suppressor p53 [14,255]. p53 is a key regulator of cellular processes and becomes enormously important under various types of stress. Although p53 is targeted by several different PTMs, acetylation seems to play a key role in activation. Three important acetylation sites, K120 (acetylated by TIP60/MOF), K164 and the C-

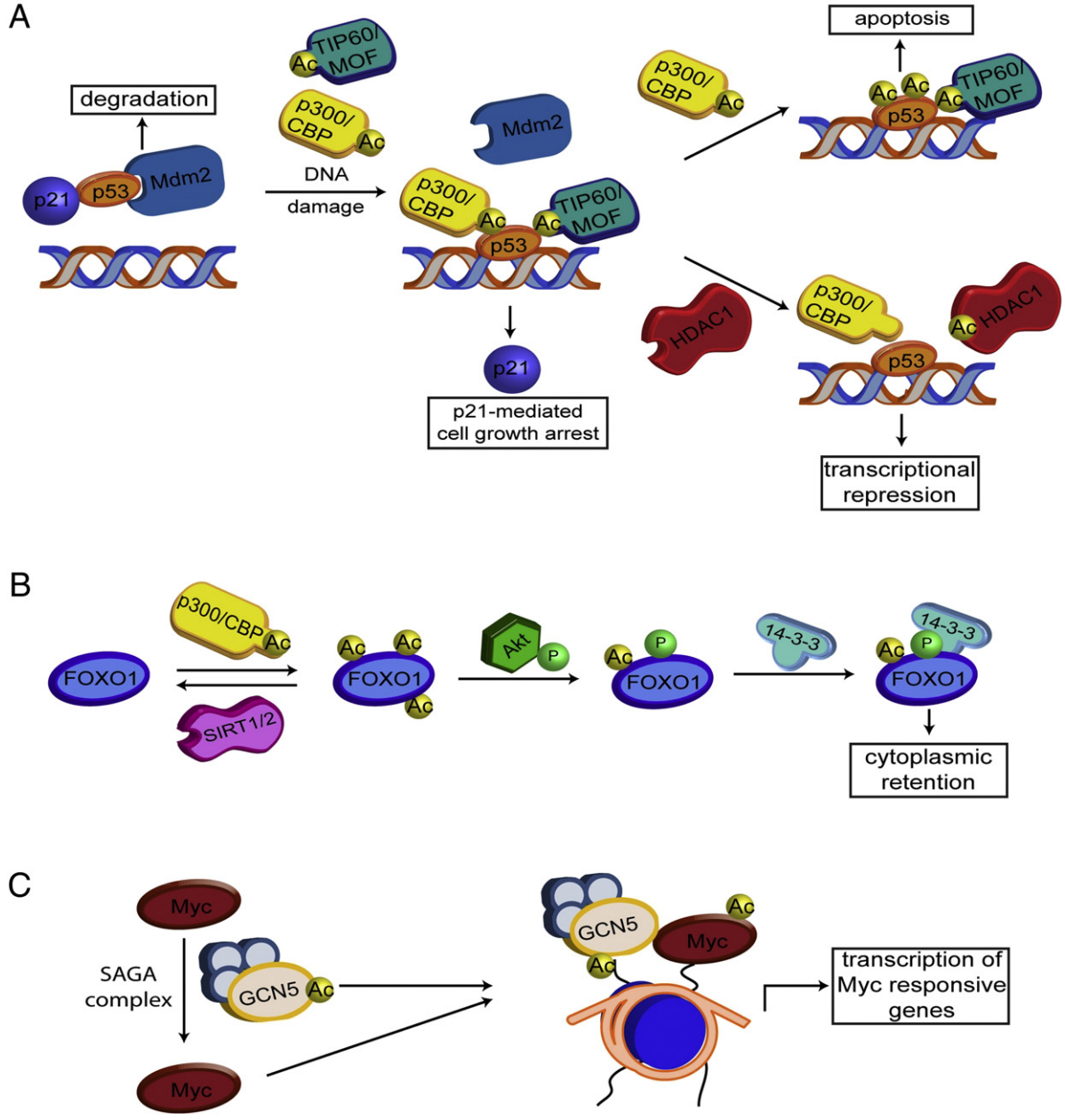


Fig. 6. Exemplary substrates regulated by lysine acetylation. A) Regulation of p53 activity by acetylation. Mdm2 binds to unacetylated p53 flagging it for degradation. When p53 becomes acetylated at position K120 and K164 by p300/CBP and TIP60/MOF, MDM2 and p21 binding are abolished, resulting in the activation of p53-responsive genes and concomitant cell cycle arrest. Two possible fates for p53 are now possible: further hyperacetylation of the C-terminus leading to the activation of apoptotic genes or deacetylation by HDAC1 resulting in transcriptional repression and subsequent cell survival. B) The transcription factor FOXO1 is acetylated by p300/CBP at multiple sites (deacetylation catalyzed by SIRT1 and SIRT2), which enables target genes discrimination, transcriptional activation and shuttling between cytoplasma and nucleus. FOXO1 acetylation recruits Akt kinase and results in subsequent FOXO1 phosphorylation. This enables the binding of the protein 14-3-3, and thus abrogating nuclear import. C) GCN5, the catalytic subunit of the SAGA complex, stabilizes MYC through acetylation. MYC recruits the SAGA complex to chromatin, where it acetylates histones and enables transcription of MYC response genes.

terminus, acetylated mainly by p300/CBP, are part of the activity mechanism [256]. p53 acetylation at these sites completely abolish the binding to p21 as well as the interaction with its repressor Mdm2, thus leading to transcriptional activation of p53-responsive genes and cell growth arrest [257]. Hyperacetylation of p53 results in an apoptosis and cell death. *Vice versa*, Mdm2 recruits HDAC1 and/or SIRT1 and concomitantly promotes the deacetylation of p53 again and thereby abolishing transcriptional activity (Fig. 6A) [257,258]. The small GTPase-binding protein Ran is also regulated by lysine acetylation. It is involved in many cellular processes such as actin cytoskeleton interactions, formation of the mitotic spindle, and nucleo-cytoplasmic transport [259]. Five distinguished acetylation sites in human have been identified, displaying various effects on the protein [165]. Acetylation of Ran determines its subcellular localization, its ability to bind to nuclear transport proteins as well as the GTP hydrolysis, and thus makes acetylation the tool of choice for Ran controlling [260]. Besides the transcriptional regulation by histone acetylation, a series of transcription factor families become lysine acetylated effecting their activity and DNA binding abilities. Two of these transcription factors are NF-κB (family of five proteins in mammalian cells) and FOXO (belongs to the major family of forkhead box O transcription factors) [261,262]. Both transcription factors regulate important subsets of cell functionality and become reversibly acetylated by p300/CBP at multiple sites (Fig. 6B) [263,264]. These acetylation events affect not only the transcriptional activity but also the selection of regulated genes [262,265]. In the case of FOXO1, acetylation also regulates the localization and shuttling between cytoplasm and nucleus by recruiting the kinase Akt. Akt phosphorylates acetylated FOXO1 concomitantly resulting in binding of the protein 14-3-3, and thus inhibiting nuclear import [167]. Chaperones recognize aggregation-prone proteins and assist their folding. Due to upregulated gene expression upon heat stress, many chaperones are called heat shock proteins (Hsps). The most abundant and complex Hsp in eukaryotic cells is the ATP-dependent Hsp90 [266]. It interacts with hundreds of different client proteins like AKT, c-Raf, c-Src, mineralocorticoid receptor and glucocorticoid receptor [266–268]. The activity of Hsp90 and the maturation of its substrates are also partly dependent on the acetylation status of Hsp90. It was demonstrated that Hsp90 can be acetylated at several lysine residues and that its activation is mediated by deacetylation *via* HDAC6 [269,270]. Thereby, K294 in Hsp90 stands out because its deacetylation is crucial for co-chaperone and client binding [271].

3.7. Physiological roles of ε-acetylation

3.7.1. Lysine acetylation and regulation of intracellular pH

Targeted acetylation of lysine residues of signaling proteins and in particular histone proteins at specific genomic loci is linked to a tight regulation of essential all types of DNA-templated processes as transcription, replication, recombination, repair, translation and formation of specialized chromatin structures [272]. As such, the consequences of protein lysine acetylation are tremendous and affect a range of cellular signaling pathways as well as metabolism, stress responses, apoptosis and membrane trafficking. Not surprisingly, histone acetylation is linked to regulation of intracellular pH (pHi) [273]. Histone acetylation and deacetylation occurs rapidly and continuously throughout the genome, thus consuming Ac-CoA and generating negatively charged acetate anions. As pHi decreases, histones become hypoacetylated in a HDAC-dependent manner and the released acetate anions are co-exported with protons out of the cell by the proton (H^+)-coupled monocarboxylate transporters (MCTs), preventing further reduction in the pHi. Conversely, histones become hyperacetylated as pHi increases, a typical mechanism in rapidly proliferating cells. Furthermore, different sites of histone acetylation respond differently to pH alterations as shown with H4K16ac and H3K18ac, where H3K18ac seems to be more unaffected by pH changes than H4K16ac [273].

3.7.2. Lysine acetylation and cognitive decline

Dysregulated acetylation is a common feature in neurodevelopmental disorders, neurodegeneration and aging. Histone acetylation is triggered by several forms of neuronal activity. Potassium chloride-mediated neuronal depolarization, and stimulation by dopaminergic, cholinergic and glutamatergic pathways all increase the acetylation of H2B, H3K14 and H3S10 [274,275].In these cases, all changes in histone acetylation occurred in parallel to phosphorylation events and direct activation of the MAPK-ERK-pathway [276,277], indicating a crosstalk between H3K14 acetylation and H3S10 phosphorylation events [272,277]. Neuronal activity also starts a positive-feedback loop of HDAC2 and brain-derived neurotropic factor (BDNF). Thus, a dissociation of HDAC2 from chromosomes leads to hyperacetylation of histones and subsequent neurotrophin-dependent gene expression [278]. Histone acetylation and deacetylation events and their implications in neuronal activity, synaptic plasticity and long and short-time memory promoting properties are reviewed in [279].

An aging brain is typically associated with cognitive decline. Hypoacetylation of neuroplasticity genes lead to transcriptional downregulation of genes essential for synaptic maintenance, function and neurotransmission. Studies from aging mice and rat brains have shown a reduced acetylation level of H3K9 and H4K12 as well as increased HDAC2 expression, the latter resulting in a hypoacetylated *BDNF* promoter-region [280–283]. In fact, a perturbed HDAC2-BDNF feedback loop has been suggested as a common feature of aging and neurodegeneration. A recent study additionally demonstrated in mid-life-aged flies that deregulation of the metabolism with elevated Ac-CoA levels and subsequent higher histone and protein acetylation levels result in a decreased life span. Reducing the Ac-CoA levels or inhibiting KAT7, which acetylates H4K12, promoted longevity in these flies [284]. Hypoacetylation of repeat-derived transcripts were also found in aging mice brains [285]. A reduced histone acetylation might help to silence these repeats and thereby protect against several brain disorders such as Huntington's disease and fragile X syndrome [286,287]. Furthermore, a reduced H3 and H4 acetylation and increased expression of several HDACs (HDAC1, 2, 3, 8 and 10) are associated with stress responses in animals [288]. Followed by increased DNA methylation of the promoter regions of the glucocorticoid receptor gene (GR; Nr3c1) and a reduced GR transcription, this leads to a heightened stress response in the animals [289].

3.7.3. Aberrant lysine acetylation causes developmental defects

The importance of a tight regulation of acetylation and deacetylation events is further highlighted by the histone deacetylases' many roles in early development. Deletion of each member of class I HDACs in mice is lethal. HDAC1-null mice display proliferation defects and growth retardation and die before embryonic day 10 [290,291]. HDAC1 regulate specific gene programs by activating or repressing certain promoters in embryonic cells. Modest hyperacetylation of H3 and H4 were found in embryonic HDAC1-deleted stem cells as well as upregulation of the cyclin dependent kinase inhibitors p21 and p27 [292]. Furthermore, deletion of *HDAC1* in zebrafish causes skeletal and neuronal defects that are lethal for the organism. The affected HDAC1-target genes were shown to belong to the Wnt signaling pathway [293–297]. HDAC2-null mice have severe cardiac malformations, bradycardia and die within the first 24 h of birth [290]. The excessive cardiac proliferation was linked to the missing HDAC2 inhibition of the homeodomain-only protein (HOP), however a complete mechanistic explanation for all transcriptional targets of HDAC2 remains unknown [298–300]. Importantly, HDAC1 and HDAC2 have redundant functions in cardiac growth and development, and regulate genes essential for Ca^{2+} flux and contractility [290]. HDAC3 mutant mice show gastrulation defects and die before embryonic day 9 [301–303]. Defects in DNA double-stranded break repair are associated with loss of *HDAC3* as well as a dysfunctional lipid- and cholesterol-homeostasis [302, 303]. All class II HDACs influence the expression and function of the

monocyte enhancer factor 2 (MEF2) transcription factor in different ways. HDAC4 has a central role in formation of the skeleton by regulating Runx2 and MEF2C transcription factor [304–306], while HDAC5 and 9 are essential for the control of cardiovascular growth and differentiation by regulating transcriptional factors such as the myocardin (MYCD) and calmodulin-binding transcriptional activator 2 (CAMTA2) as well as the serum response factor [307]. It is interesting to note that HDAC5 and 9 have redundant roles in regulating cardiac growth, as shown in response to cardiac stress that typically activates the calcineurin and calcium/calmodulin-dependent protein kinase (CaMK)-protein kinase D (PKD) pathways which results in phosphorylation of HDAC5 and 9, nuclear export and consequently activation of slow myofiber genes [308–310]. Importantly, HDAC1, 2 and 3 regulate cardiomyocyte differentiation and heart muscle lipid metabolism while HDAC5 and 9 are functional redundant and pivotal for vertebrate heart tube formation and growth by activation of the Wnt/β-catenin signaling pathway and following *bmp4* and *notch1b* expression [311]. HDAC6 is the main HDAC shown to deacetylate tubulin and has essential functions modulating the cytoskeletal dynamics and misfolded protein responses [312]. However, there exists some redundancy with HDAC10. HDAC7 is essential in endothelial cells and tightly controls the function of MEF2. Loss of HDAC7 is lethal and results in rupture of blood vessels, pericardial oedema and haemorrhaging, consequently due to lack of MEF2 repression and thereby upregulation of the matrix metalloproteinase 10 (MMP10) as well as a downregulation of the tissue inhibitor of metalloproteinase 1 (TIMP1) [313]. A dysregulated HDAC7 control of MMP10 is implicated in several human diseases such as atherosclerosis, aneurysm, myocardial infarction and tumor angiogenesis [314,315]. *Hdac8* knockouts die within 4–6 h after birth due to deficiency of cranial neural crest cells [316]. Interestingly, HDACs are important for both the glucose homeostasis and insulin resistance and as such shown to regulate diabetes as reviewed in [317] (Section 5.1).

The sirtuins are pivotal in maintaining the genomic integrity and target different histones as exemplified by H4K16ac, H3K9ac, K3K56ac and H3K18ac, but also target structural proteins, enzymes as well as non-histone components of the chromatin machinery [318]. They are involved in regulation of transcription, metabolism, cell cycle control, inflammation and found to suppress several age-associated diseases including cancer and metabolic pathologies [319,320]. The sirtuins functional mechanism and role for diseases are covered with more details in Sections 4 and 5.

4. Metabolic regulation of and by protein lysine acetylation and deacetylation

4.1. Protein acetylation depends on acetyl-CoA, the concentration of which fluctuates

Most cellular ATP is derived from Ac-CoA, which is produced by several sources: glycolysis from pyruvate by pyruvate dehydrogenase; β-oxidation of fatty acids; from citrate by Ac-CoA-citrate lyase (ACL); and from acetate, catalyzed by Ac-CoA synthetase. Pyruvate dehydrogenase, as well as the citric acid cycle components, and the machinery which catalyzes β-oxidation, are found in the mitochondria. ACL acts on cytosolic citrate which is shuttled out of the mitochondria. Ac-CoA synthetases are feedback-regulated by reversible inhibitory acetylation. Different isoforms of Ac-CoA synthetase (AceCS1 and AceCS2) exist. Respectively, they are found in the cytosol and in the mitochondria, and deacetylated by SIRT1 and SIRT3 [321]. This study did not identify the AceCS1/2 acetyltransferases and, to our knowledge, these have yet to be identified. The cytosolic and nuclear pools of Ac-CoA are free to exchange, and are used in acetylation of histones and non-histone proteins, as well as lipid, cholesterol and amino acid synthesis. Mitochondrial Ac-CoA, on the other hand, is principally involved in oxidation (reviewed in [322]).

In the nucleus, several enzymes are known to acetylate histones and non-histone proteins, using acetyl-CoA from the nuclear-cytosolic pool as the acetyl group donor. The concentration of acetyl-CoA fluctuates with the energy state of the cell (Fig. 7), and histone acetyltransferases appear to be dependent on donor concentration [283,323]. If so, they are regulated differently than most kinases, which have activities independent of the concentration of their cofactor ATP [324,325].

4.2. Effects of acetylation on intermediary metabolic enzymes

Given that most intermediary metabolic enzymes are located in the mitochondria, there is ample opportunity for regulation of metabolism through acetylation. In fact, proteins in mitochondria are extensively acetylated [165,166,243], and enzymes of the major metabolic pathways are also mainly found in acetylated forms. General levels of protein acetylation in the mitochondria increase with the concentration of Ac-CoA [326], which is itself dependent on its synthesis rate (reviewed in [322]). A non-exhaustive list of enzymes involved in intermediate metabolism which have been found to be modulated, with activity either increased or decreased, by acetylation, is found in Table 3. While there are examples of acetylation augmenting the activity of metabolic enzymes, the majority of the surveyed cases indicate that acetylation in general inhibits enzymatic activity.

4.3. The mitochondrial acetylation machinery

To our knowledge, only two putative mitochondrial acetyltransferases have been identified, which suggests that acetylation in the mitochondria is not universally non-enzymatic [327,328] (see Section 4.7). Mitochondrial acetylation of the pyruvate dehydrogenase complex subunit PDHA1 is catalyzed by the Ac-CoA acetyltransferase ACAT1, and leads to a loss of its PDH activity. Interestingly, ACAT1 was first identified as a thiolase catalyzing the reaction of two Ac-CoA into acetoacetyl-CoA in ketone body metabolism [329]. ACAT1 also acetylates pyruvate dehydrogenase phosphatase (PDP), an enzyme which normally dephosphorylates and activates PDHA1. Deacetylation and activation is performed by SIRT3 [189,327]. The first suggested mitochondrial KAT is GCN5-like 1 (GCN5L1). siRNA-mediated knockdown of GCN5L1 leads to a marked decrease in mitochondrial acetylation, and it directly opposes the action of SIRT3 by acetylating components of the electron transport chain [328].

4.4. The mitochondrial acetylome is influenced by energy availability

To demonstrate a general interplay between energy use and protein acetylation, studies have focused on the effect of feeding and fasting on the acetylome. A study on mouse tissues found that overall mitochondrial acetylation in calorie-restricted mice was elevated [330], while another group demonstrated that mice on a high-fat diet show increased mitochondrial protein acetylation [218]. This may be explained by the fact that while both fasted and fed mitochondria will have high Ac-CoA concentrations and consequently, concentration-dependent and non-enzymatic protein acetylation, during fasting, SIRT3 will be upregulated (Fig. 7) [218,326]. SIRT3 may also be regulated differently in different tissues. In response to fasting and calorie restriction, Sirt3 is upregulated in liver [218,326], but downregulated in muscle tissue [331]. Authors of the latter study suggest that the muscle-specific downregulation of Sirt3 by fasting is part of a shift away from carbohydrate utilization and towards fatty acid oxidation and lactate formation. SIRT3 may deacetylate and reactivate metabolic enzymes to cope with the need for increased ATP production through β-oxidation (Fig. 7B). (see also Section 4.2) Several studies have shown that non-enzymatic acetylation takes place in the mitochondrial matrix both *in vitro* and *in vivo*, meaning that the mitochondrial acetylation observed may not need an acetyltransferase to account for itself [169,332].

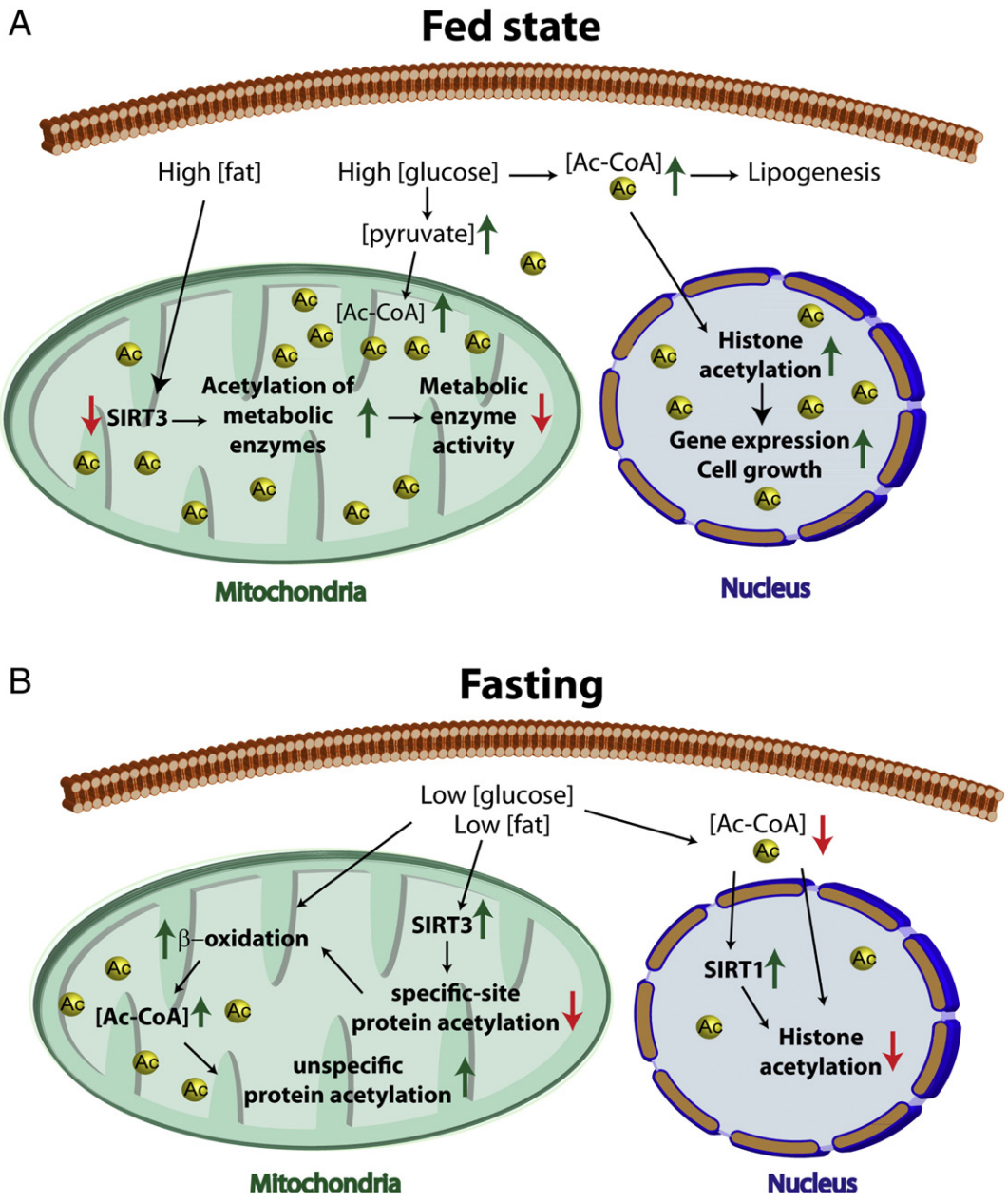


Fig. 7. Putative impact of energy homeostasis on the acetylome. Proposed model of how the fed (A) and fasted (B) acetylome is influenced by energy availability to control both gene transcription and mitochondrial homeostasis. A) In the fed state, high glucose concentrations will lead to high acetyl-CoA concentration in the cytosol and nucleus [323], increased histone acetylation, and active transcription. In liver mitochondria, high fat availability will give low expression and subsequent low levels of Sirt3, leading to increased acetylation of mitochondrial proteins, which may or may not be physiologically relevant as a metabolic inhibitory mechanism. B) During fasting, low nuclear-cytosolic acetyl-CoA levels will lead to low histone acetylation and gene expression. Increased β-oxidation of lipids will lead to elevated levels of acetyl-CoA in the mitochondria, with concomitant nonspecific and concentration-dependent protein acetylation in that organelle. However, SIRT3 is also activated in the liver under fasted conditions, and may selectively deacetylate and activate metabolic enzymes, increasing ATP production.

4.5. Sirt3 is the main mitochondrial deacetylase

Given the presence of mitochondrial non-enzymatic acetylation (see Section 4.7) and the low number of identified mitochondrial acetyltransferases, much research on the regulation of metabolism by acetylation has focused on the deacetylases. In mitochondria, SIRT3 is the major deacetylase. Knocking out *Sirt3* leads to hyperacetylation in the mitochondria, while no such hyperacetylation is seen in *Sirt4*- or *Sirt5*-deficient mice [333]. *In vivo* knockout mice have increased mitochondrial acetylation [333,334]. Phenotypically, *Sirt3* knockout mice are healthy under normal conditions, but show metabolic phenotypes during fasting, including low ATP levels and inability to cope with cold exposure [326]. Hirschey and colleagues linked this to the increased acetylation and subsequent inactivation of long-chain acyl-CoA dehydrogenase (LCAD), a key enzyme in β-oxidation located in the mitochondria. One study found that *Sirt3* KO mice had symptoms of metabolic syndrome, including insulin insensitivity, obesity, hyperlipidemia and steatohepatitis, when placed on a high-fat diet [218]. When fasted, *Sirt3* KO mice fail to deacetylate and activate OTC, and have altered amino acid profiles in the bloodstream [335]. However, knocking out *Sirt3* in mouse liver or skeletal muscle did not lead to any observable phenotypes [336], suggesting that the Sirt3 metabolic phenotype is not mediated through the liver or the skeletal muscle. Authors of the latter study suggested that loss of SIRT3 activity in

brown adipose tissue may be the reason for the phenotypes observed in the previous studies. One *in vivo* proteomics study, conducted on mouse liver mitochondria, found three distinct classes of mitochondrial acetylation sites [337]. These classes are defined by the residues flanking the acetylated lysine, and by what secondary structural elements they are part of. Those that have basic residues next to the acetylated lysine, and in addition are part of alpha helices, are most susceptible to deacetylation by SIRT3. Neutral or acidic residues next to the acetylated lysine make it less available to SIRT3, and as a result these sites were unaffected by *Sirt3* KO [337,338].

4.6. Feedback control of metabolism and gene regulation by acetylation

Since the acetyl donor, acetyl-CoA, is involved in various catabolic and anabolic pathways, it has been speculated that the availability of acetyl-CoA can influence the extent of protein acetylation. This is the case for mitochondrial acetylation (see Sections 4.3 and 4.4). However, chromatin-modifying KATs have also been shown to depend on the levels of nuclear acetyl-CoA for their activity. ACL is needed for the increased histone acetylation which occurs when cells are exposed to serum growth factors. This is catalyzed by GCN5, and mediated through glucose availability, with increased glucose concentrations giving increases in histone acetylation. Glucose availability was accompanied by increases in glycolytic gene expression [323]. This supports the idea that acetyl-CoA levels, which fluctuate based on the energy state of the cell, can directly influence the expression of growth genes.

Acetylation of DNA-binding factors can also influence metabolism at the transcriptional level. The peroxisome proliferator-activated receptor-coactivator 1-alpha (PGC-1-alpha) is an important transcription factor regulating gluconeogenesis in fasting and diabetes [339]. Acetylation by GCN5 renders this transcription factor inactive [340], while it is deacetylated by Sirt1 [341,342]. SIRT6 enhances the activity of GCN5 towards PGC-1, by deacetylating GCN5 at K549. PGC-1 is then acetylated, and thus deactivated [343]. Thus, this transcription factor controlling gluconeogenesis appears to be complementarily regulated through the opposing actions of two different KDACs and one KAT.

4.7. Non-enzymatic acetylation in the mitochondria and sirtuins as protein lesion repair enzymes

Because of the high pH and high concentration of Ac-CoA in the mitochondria, it has long been hypothesized that protein acetylation in mitochondria may occur non-enzymatically [344]. Indeed, enzyme-independent acetylation has since been demonstrated, and although two potential mitochondrial acetyltransferases have been identified, they cannot account for the observed levels of mitochondrial acetylation. Studies in *S. cerevisiae* [332] and in various mouse tissues [345] have shown that protein acetylation in mitochondria happens to a very low stoichiometry, in contrast to phosphorylation, a well-established posttranslational regulatory modification, [346] and Nt-acetylation [39]. This suggests that mitochondrial protein acetylation is mainly a non-enzymatic lesion caused by the high concentration of Ac-CoA and high pH in the mitochondria [169]. A function of SIRT3 would then be to repair these lesions [171,345]. However, it cannot be concluded that all of these acetylation events are protein lesions which the cell seeks to repair to retain its normal function. High concentrations of Ac-CoA could conceivably drive non-enzymatic acetylation and subsequent protein deactivation, acting as an Ac-CoA sensor and regulating the rate of Ac-CoA synthesis. In cases where low energy availability increases the need for ATP production through β-oxidation, the concentration-dependent, non-enzymatic protein acetylation of key metabolic enzymes may be counteracted by site-specific, SIRT3-catalyzed deacetylation. As an example, the acetylation of PDHA1 inhibits the enzyme, possibly slowing down the rate of Ac-CoA synthesis. These lysines are highly acetylated *in vitro*, with stoichiometries of 70% and 50% for PDHA1 and PDP1, respectively [327]. Although these measurements were not performed on *in vivo* PDHA1 and PDP1, and so should be interpreted with some caution, they do suggest a case where feedback-regulation of Ac-CoA formation may occur. In addition, while the impact of a single low-stoichiometry acetylation of a protein may not inhibit it to a large degree, the effect of several such modifications on multiple enzymes in a single pathway may, in sum, serve to feedback-regulate that pathway (see also review [347]).

5. Role of lysine acetylation in diseases

5.1. Aberrant lysine acetylation and its implications in disease

The tight balance between protein acetylation and deacetylation events play a critical role in the regulation of gene expression and signal pathways, affecting a range of cellular processes. Dysfunctions in the balance between KATs and KDACs are therefore associated with a variety of diseases such as cancer (see Section 5.2), diabetes, cardiac hypertrophy, neurodegenerative disorders (see Section 5.4), autoimmunity, asthma and retroviral pathogenesis [16,317,348–351].

5.1.1. Diabetes

Insulin and glucagon play essential roles in the regulation of the glucose level in blood. Several studies indicate that this aspect of glucose homeostasis is regulated by epigenetic mechanisms. In general, people with diabetes have an inability to utilize glucose efficiently due to insulin resistance. In a fed state, insulin promotes glucose uptake to peripheral tissues, decreases glucose production and stimulates glycogen synthesis in the liver [352,353]. Once insulin binds to its receptor, the insulin receptor substrate 1 (IRS-1) becomes phosphorylated and activates PI3K as well as AKT and eventually the glucose transporter 4 (GLUT4), which translocate from intracellular vesicles to the plasma membrane where it facilitates glucose uptake [317,354]. Several studies have shown KDACs to play a regulatory role in this insulin signaling. HDAC2 can bind to IRS-1 in liver cells, decrease the acetylation and thereby reduce insulin receptor-mediated tyrosine phosphorylation of IRS-1. The GLUT4 promoter is governed by the MEF2 binding domain and Domain I. Noteworthy, different class II HDACs regulate the expression and activity of GLUT4 and MEF2, in particular HDAC5 and HDAC6 are shown as essential regulators of insulin signaling [355,356]. SIRT1 on the other hand, improves glucose-induced pancreatic insulin secretion and is important in β-cell function. Therefore, it might be a potential target for diabetes type 2 treatment [357]. Furthermore, HDACs are also involved in signal transducers and activator of transcription 3 (STAT3)-mediated gluconeogenesis where STAT3 is acetylated by CBP proteins/p300 and deacetylated by an unknown KDAC(s). This underlines the importance of a tightly regulated acetylation/deacetylation pattern for diseases such as diabetes and obesity [317].

5.1.2. Chronic lung diseases

Chronic lung diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease, interstitial lung disease and acute respiratory distress syndrome are characterized by inflammation and coordinate expression of multiple inflammatory genes. Pro-inflammatory transcription factors such as NF-κB and activator protein 1 (AP-1) regulate many of these inflammatory/immune genes. Patients with these lung diseases typically have an increased KAT expression and increased acetylation level and a following decreased KDAC activity, favoring increased inflammatory gene expression [358]. Typically detected is the increased acetylation of H3 and H4, in particular H3K18, H4K8 and H4K12 as a consequence of oxidative stress [351,359].

5.1.3. HIV

Acetylation events are also important for retroviral pathogenesis as demonstrated with the human immunodeficiency virus (HIV-1) [360,361]. The viral IN protein integrate reverse transcribed HIV-1 DNA into the cellular genome, and is a substrate for p300-mediated

acetylation. Three lysine residues (K264, K266, and K273) in the C-terminal domain of IN were identified acetylation sites. Additionally, the HIV-1 protein Tat is acetylated at K28 by the p300/CBP-associated factor (PCAF), while K50 and K51 are substrates for p300/CBP and GCN5, thus further confirming the essential role of acetylation as a post-translational modification during Tat activation and viral integration [351,361].

5.1.4. The Rubinstein-Taybi syndrome

The Rubinstein-Taybi syndrome is a rare genetic neurodevelopmental disorder characterized by postnatal growth deficiency, skeletal abnormalities, dysmorphic features and mental retardation [362,363]. A certain level of CBP is essential for normal development as inactivation of one CBP allele cause this disease [363,364], but the syndrome is also caused by *de novo* mutations in p300 [365]. The mutations vary from relatively large deletions of exons which remove the entire gene, to point mutations, translocations or inversions disrupting the gene [366]. Both CBP and p300 regulate gene expression through their histone acetyltransferase activity and regulate multiple pathways involved in cell growth, control, DNA repair, differentiation, apoptosis and tumor suppression [367]. In 2004, Alarcon and colleagues found chromatin acetylation, memory and hippocampal long-term potential to be impaired in mice with only one CBP allele [368]. Studies by Wang et al. demonstrated that CBP is essential for differentiation of neurons and glial cells in the embryonic cortex [369]. Furthermore, they found this epigenetic switch regulated by aPKC ζ-directed phosphorylation of CBP S436. Typically, mouse models lacking CBP expression had a reduced acetylation-level of H2B and H2A, however by introducing HDAC inhibitors these histone acetylation deficits could be reduced [370]. A range of mutations and aberrations in CBP and p300 genes found in Rubinstein-Taybi syndrome are summarized [365,370,371]. Interestingly, Rubinstein-Taybi syndrome patients have an increased predisposition to cancer [372].

5.1.5. Pathogenic mutations in lysine acetyltransferases

Two *de novo* mutations c.3385C > T (p.R1129*) and c.3070C > T (p.R1024*) found in the lysine acetyltransferase gene *KAT6A* were identified in individuals with a dominant autosomal disease and further highlight lysine acetylation as essential for normal development [373]. The four probands with these nonsense mutations displayed developmental delays, speech delays, microcephaly, craniofacial dysmorphism, feeding difficulties, cardiac defects as well as ocular anomalies. The KAT6A mutations caused aberrant H3K9 and H3K18 acetylation as well as altered p53 signaling [373]. KAT6A acetylates K120 and K382 in p53, and both the HAT domain as well as the serine and methionine rich domain of KAT6A are required for p53 interaction [374]. Another five de novo mutations in the C-terminal transactivation domain of KAT6A were identified in six unrelated family members with intellectual disability and common phenotypes as already described in the study of Arboleda and colleagues [375]. These mutations included c3116_3117 delCT, p.S1039*; c.3830_3831insTT, p.R1278Sfs*17; c.3879 dupA, p.E1294Rfs*19; c.4108G > T p.E1370*; c.4292 dupT, p.L1431Ffs*8 in addition to a 0.23 MB microdeletion of the entire reading frame of KAT6A. Further demonstrating the importance of an intact C-terminal domain is the truncating mutations in *KAT6B*, a *KAT6A* paralogue [375]. These mutations are occurring with high frequency in genitopatellar syndrome and Ohdo/Say-Barber-Biesecker syndrome, and further complement previous studies of *KAT6A* knockout zebrafish and mice demonstrating similar developmental defects [375–378].

Grave's disease is a typical organ-specific autoimmune disease and the most common cause of hyperthyroidism [379]. Also here, a decreased H4 acetylation pattern was observed as well as increased HDAC1 and 2 expression levels [380]. However, no difference was observed in SIRT1 or the KATs p300 and CBP. As demonstrated by the different roles and regulations of histone deacetylases, their inhibitors are promising drug targets for a wide range of diseases including neurodegenerative and psychiatric disorders, cancer, cardiovascular dysfunction, autoimmunity and diabetes.

5.2. The impact of lysine acetylation on tumor biology and cancer

The global histone acetylation level in different tissues and cell types are heterogenic. However, several KDACs show aberrant expression in different tumor tissues and display a non-redundant function. Metabolic alterations and KDACs deregulation are therefore important hallmarks in cancer cells [381–384]. Immunohistochemical studies on a variety of cancer tissues have demonstrated a link between low cellular levels of histone acetylation and aggressive cancers with poorer clinical outcome such as decreased survival rate and increased risk of tumor recurrence [348,385–389]. Lysine acetylation of histone N-terminal tails is associated with chromatin opening and active transcription of genes in regions adjacent to the acetylated histones. In general, most KATs and KDACs may be both oncoproteins and tumor suppressors, depending on the cellular context. Since the many genes whose transcription they activate or repress may themselves either propagate or halt cancer progression, this is not surprising. In other words, the outcome for cancer progression of histone acetylation is dependent on whether it happens in the genomic region of a tumor suppressor or a tumor promoter.

5.2.1. CBP/p300

Small-cell lung cancer is an aggressive lung tumor with poor prognosis. Extensive global genome analyses revealed inactivating mutations in the genes of *CBP* and *p300*, both important histone modifiers, in small cell lung cancer [390]. The mutations in *CBP* and *p300* were clustered around the HAT domain and at the interface of substrate binding and thus possibly affecting the catalytic activity [390,391]. Indeed, D1399 (CBP) and D1435 (p300) mutations affected the acetylation activity *in vitro* [391–393]. The essential functions of CBP and p300 are further strengthened by identification of a range of other mutations in different tumors. The p.G1411E mutation in CBP was found in lung cancer [394] and follicular cancer [395] and p.G1411V and p.D1435G were found in relapsed acute lymphoblastic leukemia [396,397]. Furthermore, the p.R386fs alteration and the *CBP-RHBDF1* gene fusion results in a truncated protein and inactivation of the enzymatic activity [390,398]. The p.G114R, pE1435Y and pS1432P mutation in CBP, homologous to pG1375R, p.E1399Y and p.S1396P alterations in p300 all reduced the H3K19 acetylation in mice [399]. Somatic mutations in CBP and p300 genes also affect the response of HDAC inhibition in malignant B-cell lymphoma. This further demonstrates the implications of loss-of-acetylation on tumor development as this caused BCL6 overexpression and p53 inactivation [400–402]. Acetylation of p53 leads to its activation, while in contrast acetylation of BCL6 inhibits this oncoprotein. BCL6 inhibits the transcription of p53 and the p53-mediated apoptosis occurring in germinal centered B-cells. As such, DNA strand breaks and somatic mutations occurring in these cells escape from correction and the surviving cells eventually contribute to the development of B-cell lymphoma. Acetylation of BCL6 blocks the recruitment of HDACs to transcription start sites and thereby HDAC-mediated repression of target genes. The chromosomal loss or inactivating mutations of CBP and p300 in cancer tissue indicate a more tumor suppressive role of these proteins.

5.2.2. GCN5

GCN5 is the KAT subunit of the human SAGA complex (reviewed in [403]). It acetylates both histones and non-histone proteins. Its acetylation of H3 at K9 and K14 are general markers of active transcription (reviewed in [404]). The oncoprotein transcription factor Myc recruits the SAGA complex to chromatin, where it acetylates and activates transcription of Myc response genes (Fig. 6C) [405,406]. GCN5 acetylates the Myc protein itself, rendering it more stable than its unacetylated counterpart [407]. Disruption of Myc leads to large-scale hypoacetylation.

This is partly mediated through loss of activation of GCN5 [408]. Also, a conditional mouse *Gcn5* knockout in neural stem cells led to large-scale gene expression changes which partially overlapped with those seen in *Myc* knockouts [409]. Thus, Myc and GCN5 appear to cooperate in a feed-forward loop of activating transcription. Consistent with these experimental findings, GCN5 and the SAGA complex have been implicated in cancer development. For example, GCN5 was found to be highly expressed in non-small cell lung cancer. Its expression correlated with tumor size, and it was recruited by E2F1 to induce histone acetylation and subsequent activation of E2F1 and the mitotic genes cyclin D1 and cyclin E1 [410].

5.2.3. PCAF

In contrast to what appears to be a general tumor-promoting role of GCN5, its paralog, the acetyltransferase PCAF may be a tumor suppressor (see review [404]). PCAF and p300 both acetylate the tumor suppressor p53 *in vivo*, though at different lysine residues. The acetylation of p53 increases its DNA binding capacity [411,412]. In fact, acetylation appears to be essential for p53-mediated growth arrest and apoptosis [257]. Acetylation is also required for p53-mediated induction of apoptosis through HDAC-inhibitors [413] and through the microtubule inhibitor Taxol [414]. The acetylation of p53 by MOF or Tip60 on K120 is important for its activation of pro-apoptotic genes (reviewed in [415]). p53 is deacetylated by SIRT1 [416].

5.2.4. MOF

Loss of acetylation at K16 of H4 was found to be present in several human neoplasms, implicating it as a hallmark for cancer [386]. This histone modification is important for higher order chromatin structure [233]. The MOF acetyltransferase is very specific for H4K16 [417], and appears to be the main acetyltransferase of this site, as *Mof* knockout mice lack H4K16 [418]. *Mof* knockouts show cell cycle arrest, genome instability and defects in repair of DNA lesions [138].

5.2.5. HDACs

As seen with the KATs, KDACs have mutations or show aberrant expression in tumors. HDAC1 expression is elevated in gastric cancer and associated with nodal spread, and is as such a prognostic marker for survival [419]. However, both elevated HDAC1 and HIF1α expression in pancreatic cancers were associated with poor prognosis [420]. HDAC1 is implicated in the control of cell proliferation. Knockdown studies in breast cancer cells and osteosarcoma demonstrate G1 arrest or G2/M transition arrest and an increasing amount of apoptotic cells [421]. On the contrary, HDAC1 overexpression led to an increased proliferation as well as an undifferentiated phenotype in prostate cancer cells [422]. Somatic mutations found in *HDAC2* in human epithelial cancers conferred resistance towards anti-proliferative and anti-apoptotic HDAC inhibitors [423,424]. Furthermore, several *HDAC4* mutations were found in breast and colorectal cancer samples [425]. Similarly, ranges of other mutations or dysregulated expression levels exist for the different groups of HDACs and are reviewed in [348,426].

5.2.6. Sirtuins

The different sirtuins are essential for maintenance of the genomic integrity and reviewed in [318]. SIRT2 acts as a tumor suppressor and is involved in cell cycle progression, while SIRT3 on the other hand acts as both a tumor suppressor and promoter. The complexity and interplay between the sirtuins are further demonstrated by SIRT1, 2, 6 and 7 direct modulation of Myc function [427].

Depending on the tissue and cellular context, SIRT6 may function as an oncogene or as a tumor suppressor (reviewed in [427]). Normally, this cytosolic sirtuin will deacetylate H3K9ac [428] and H3K56ac [429,430], which normally contribute to telomere integrity and help avoid premature senescence [428]. Some studies find that SIRT6 is a tumor suppressor. For example, Sebastián et al. found that decreased levels of SIRT6 leads to upregulation of targets of its repressive activity, namely Myc and HIF1, leading to increased cell division and glycolysis, both hallmarks of cancer [431]. Other studies have for example found that SIRT6 increases the expression of cytokines which contribute to inflammation, and to enhance the migratory ability of pancreatic cancer cells [432].

5.3. The role of sirtuins in aging

The discovery that sirtuin overexpression appears to increase lifespan in several model animals has led to a great deal of research into their function and regulation (reviewed in [433]). Initially, yeast sir2 overexpression was discovered to give yeast cells increased lifespan [434]. Following this, *C. elegans* with an extra copy of the *sir-2.1* gene was found to have longer lifespan than wild type worm [435]. In *D. melanogaster*, increases in dSir2 expression leads to increase in lifespan in a dosage-dependent manner, nevertheless very high (>5 fold compared to normal expression) expression results in cytotoxicity and concomitantly decrease in lifespan [436].

SIRT6 has spectacular effects when misexpressed. *Sirt6* knockout mice develop normally, but are small and have reduced amounts of body fat, lymphopenia and osteopenia. They die before one month of age from low blood glucose [437]. *Sirt6* KO cells show telomere defects and early senescence [428]. Male mice who overexpress SIRT6, on the other hand, have increased lifespan [438]. This phenotype was connected to a decrease in the levels of circulating insulin-like growth factor 1 (IGF1) through the upregulation of IGF-binding protein 1, which is a modifier of IGF1 bioavailability [438]. Histone H1 is acetylated at K26, and deacetylation is catalyzed by SIRT1 [439]. SIRT1-mediated deacetylation of this residue and transcriptional repression was found to be lost in cells subjected to oxidative stress. Mice which overexpress SIRT1 or are treated with a sirtuin activator (resveratrol) have decreased mortality from radiation-induced cancer, suggesting that this protein may offer protection from the effects of DNA damage [440]. Increased ROS formation promotes lifespan and metabolic health reactions. Earlier studies indicate that nicotinamide (NAM) and its metabolite, 1-methylnicotinamide methyltransferase (MNA), promote this formation by inhibiting complex I in the respiratory chain. Interestingly, sirtuins contribute to these lifespan extensions in *C. elegans* by increasing the amount of the MNA precursor NAM through a deacetylation-independent mechanism, promoting the metabolic formation of the pro-oxidative substrate MNA. Instead, this sirtuin-mediated lifespan extension depends on methylation of NAM and provides a new mechanistic role for sirtuins beyond the classical histone deacetylation events [441].

5.4. Lysine acetylation in neurodegenerative disease

One of the hallmarks of Alzheimer's disease is tau protein hyperphosphorylation. Hyperphosphorylated tau aggregates into fibrils. This fibril formation and subsequent formation of insoluble plaques is a major factor in the etiology of Alzheimer's and related diseases, termed tauopathies [442]. Tau is also acetylated by p300, and deacetylated by SIRT1 [443]. SIRT1 levels correlate negatively with tau fibril accumulation and with Alzheimer's symptom duration [444]. Compared to its non-acetylated counterpart, acetylated tau is prone to accumulate. When tau is acetylated, lysines which could otherwise become ubiquitinated are blocked. Due to abrogation of this targeting for proteosomal degradation, tau accumulates and contributes to Alzheimer's progression [443]. When tau becomes acetylated it does not promote microtubule assembly, which is part of its normal function, and thus is prone to aggregate. This demonstrates how the mutual exclusion of two different lysine modifications can determine the fate of a protein, with physiologically crucial consequences. Acetylation of tau K280 was found in several human tauopathies [445]. A further study implicated K174 acetylation as a pathogenic event, rendering tau insoluble and more prone to aggregation. However, this specific acetylation

site appears to be unrelated to the blocking of ubiquitination and subsequent degradation, as the same pathogenic changes were seen with a K174Q mutant, which mimics acetylation [446]. Additionally, increased expression of HDAC2 and decreased histone acetylation are associated with the cognitive decline typical seen in Alzheimer's [447]. As reviewed in [279], HDAC2 binding to the promoters of genes involved in synaptic plasticity and learning such as synaptophysin and *BDNF* results in reduced expression as well as reduced histone acetylation. A negative-feedback loop on memory-sustained gene expression has been proposed. Interestingly, different HDAC inhibitors show promising results as treatments for age-related cognitive impairment [279].

6. Future perspectives

6.1. The manifold physiological roles of Nt-acetylation decipher hardly

Why does the cell Nt-acetylate proteins? Although several molecular consequences for Nt-acetylation have been described, an overall concept for its physiological role remains elusive. Especially the fact that around 80–90% of the human proteome is Nt-acetylated co- or post-translationally, makes the interpretation of data and the conclusion of a general rule difficult. Additionally, the different roles of NAT complexes in the tumorigenic process, and their involvement for different cancer tissues complicate the answer to the abovementioned question even more. Varshavsky and colleagues give a plausible explanation for Nt-acetylation as being part of a degradation signal in the N-end rule pathway, and therefore part of the proteasomal degradation system [90,448]. Nevertheless, more complexity is introduced by additional findings. The ubiquitin ligase Doa10 in yeast targets several proteins that are Nt-acetylated and non-acetylated [449]. Furthermore, ubiquitination which occurs at the N-terminus (*e.g.* catalyzed by the E2 enzyme Ube2w) can be prevented by Nt-acetylation, thus inhibiting degradation [450,451]. The exact contribution of Nt-acetylation in protein degradation will be part of upcoming studies.

Further, high expression levels of different NATs often correlate with low survival rates and aggressiveness of different types of tumors, while NAT depletion studies further demonstrate p53-mediated apoptosis as well as cancer cell sensitization for drug-induced cell death. As the NATs are essential for cell cycle progression and have several anti-apoptotic roles in cancer, they are potential therapeutic targets in cancer therapy. Indeed, NAT-inhibitors are under development with the ultimate goal of utilization in clinical treatment as well as further studying the cellular roles of NATs [452].

6.2. Do NATs have lysine acetyltransferase activity?

Is Naa10 a KAT *in vivo*? Several reports indicate that Naa10 is able to acetylate lysines, sometimes with physiologically important consequences. However, a recent follow-up study of these proteins as Naa10 substrates found that their acetylation was Naa10-independent, and that increasing concentrations of acetyl-CoA was sufficient to acetylate these proteins [453]. The structure of Naa10 also has an extended loop over the active site, which blocks lysines in sidechains from entering it. This same loop is found in all the solved NAT structures currently available; it is not found in the known KATs. This doesn't necessarily close the book on Naa10 as a KAT, but researchers studying it should keep it in mind.

6.3. New methods and approaches will shed light on lysine acetylation pathways

By the recently extensive use of mass spectrometry-based global analysis of lysine acetylation, many acetylation sites in proteins have been identified, nevertheless not all acetylation events are assigned to specific functional roles. The effects on metabolic enzymes have been investigated intensively, but neither the dynamic regulation nor the stoichiometry of acetylation events in these non-histone proteins is completely solved. In addition, several studies described important crosstalks between acetylation and various PTMs (including phosphorylation and methylation), such as it was shown for the histones H3 and H4 [272]. These crosstalks demonstrate that epigenetic gene regulation by PTMs is a very complex but fine-tuned mechanism. The further characterization of these mutual PTM interplays and their functional consequences as well as the characterization of lysine acetyltransferase pathways and the required quantitative analysis of lysine acetylation events are and will be under constant further investigations, especially by the development of new and more optimized MS-based approaches [454].

6.4. Is lysine acetylation of mitochondrial proteins enzymatically regulated?

It appears that most mitochondrial and cytosolic intermediary metabolic enzymes are acetylated, and that acetylation generally impairs the catalytic activity of the acetylated enzymes, although in some cases the opposite is true. Two likely mitochondrial acetyltransferases have been discovered, but it is probable that a large proportion of mitochondrial acetylation events are non-enzymatic, and that some should be regarded as a stress factor detrimental to protein function, rather than a regulatory mechanism. A function of SIRT3, the main mitochondrial deacetylase, would then be to repair these lesions [345]. Further research should explain how acetylation affects the relationship between metabolic regulation and carbon stress. The discovery of any novel mitochondrial acetyltransferases would be a major step forward in this respect. Clarifying the *in vivo* substrates of the two identified mitochondrial acetyltransferases should give clues about what metabolic processes are impacted by acetylation, in or out of a feedback loop. Whether N-terminal acetylation is governed by similar metabolic feedback loops to lysine acetylation is an open question.

7. Concluding remarks

While lysine acetylation definitely has gained and earned its position in the spotlight, Nt-acetylation is still lurking in the shadows. It is not a numbers game since Nt-acetylation modifies at least as many proteins in a eukaryotic cell as lysine acetylation does. The key word is biological impact. Reversible lysine acetylation acts as an essential regulatory modification in multiple cellular pathways. In contrast, the importance of the more static Nt-acetylation has only been shown in a couple of biological contexts. However, these fields are moving fast. While nothing may undermine the strong position of lysine acetylation, Nt-acetylation is trying to close the gap.

Transparency Document

The Transparency document associated with this article can be found in online version.

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