

Review Article

The Tale of Protein Lysine Acetylation in the Cytoplasm

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Reversible posttranslational modification of internal lysines in many cellular or viral proteins is now emerging as part of critical signalling processes controlling a variety of cellular functions beyond chromatin and transcription. This paper aims at demonstrating the role of lysine acetylation in the cytoplasm driving and coordinating key events such as cytoskeleton dynamics, intracellular trafficking, vesicle fusion, metabolism, and stress response.

1. Introduction

The story of cytoplasmic protein lysine acetylation begins long after the discovery of posttranslational acetylation of histones in the sixties [1]. In fact only in 1985 tubulin was described as the first acetylated cytoplasmic protein [2, 3]. Since then numerous other cytoplasmic proteins have been found acetylated. The first global proteomic study on acetylated proteins describes 37 acetylated proteins in the cytoplasmic fraction of Hela cells and 133 in mouse liver mitochondria [4]. In another study about 250 acetylated proteins, presumably localized in the cytoplasm, have been identified [5].

Lysine (K) acetylation is catalysed by a lysine acetyltransferase (KAT) formerly called histone acetyltransferase (HAT) (for new nomenclature see Allis et al. [6]), which transfers the acetyl-group of acetyl-CoA to the epsilon-amino group of an internal lysine residue. The reverse reaction is accomplished by deacetylases, which can be divided into several classes. The class I, IIa, IIb, and IV enzymes are zinc dependant, whereas members of the class III family (also called sirtuins) use NAD⁺ as a cofactor for the deacetylation reaction.

The high number of acetylated proteins present in the cytoplasm points to a critical role for this posttranslational modification in the regulation of cytoplasmic events. In this paper we will focus on selected examples illustrating the role of reversible acetylation in the cytoplasm and we will mention some proteins, identified by proteomic

approaches as being acetylated, when it could be important in the context of the discussed cellular processes. We will also provide an overview on what is known about the cytoplasmic localisation of the enzymes implicated in lysine (de)acetylation.

2. Cytoplasmic Localisation of KATs and HDACs

2.1. KATs. Most of the extensively characterised acetyltransferases are known as nuclear enzymes (see Table 1 for overview). Even Hat1, the first identified acetyltransferase, is predominantly localized in the nucleus, although it has been characterized as a type B acetyltransferase which refers to its role in the cytoplasm where it acetylates newly synthesised histones [7–9]. Under some circumstances, like early during development or in colorectal tumors, the cytoplasmic fraction of Hat1 increases [10, 11]. In addition, it has recently been shown that two different isoforms of Hat1 are expressed in keratinocytes, which differ in their cellular localisation [12].

Although acetyltransferases are considered mostly nuclear, an increasing number of studies reports on their nucleocytoplasmic transport. For instance PCAF and Gcn5 become phosphorylated following growth factor receptor signalling, which induces their translocation to the nucleus [13]. The cellular localisation of PCAF is not only regulated by phosphorylation. In fact PCAF can autoacetylate lysine

residues within its nuclear localisation signal (NLS) and deacetylation of these lysine residues leads to cytoplasmic accumulation of PCAF [14]. CBP and p300 behave almost like Hat1 since, during oocyte maturation, they are first found in the cytoplasm before being imported into the nucleus [15]. Furthermore, similar to Hat1, p300 is found in the cytoplasm in breast carcinomas but not in the adjacent normal mammary gland [16]. Both nuclear localisation and nuclear export signals have been found in Tip60, a member of the MYST family of acetyltransferases. Tip60 can be recruited to the plasma membrane by the amyloid precursor protein, which induces its phosphorylation and subsequent translocation to the nucleus [17]. In addition Tip60 appears in two splice variants. Whereas the longer isoform is essentially found in the nucleus, the shorter form, Tip60 beta (also called PLIP), missing exon 5, is located in both the cytoplasm and the nucleus and interacts with cytosolic phospholipase A2 [18, 19]. The acetyltransferase ATF2 also has nuclear localisation and export signals and is able to shuttle between the nucleus and the cytoplasm. Heterodimerisation with c-Jun in the nucleus is necessary to retain ATF2 in the nuclear compartment [20].

The most astonishing fact is that, although tubulin was the first acetylated protein described in the cytoplasm [2, 3] and a tubulin acetyltransferase activity had already been purified and characterised in 1986 [21], the scientific community had to wait until 2009 to put a name on an enzyme able to acetylate α -tubulin. In fact the acetyltransferase E1p3, which is the catalytic subunit of the transcriptional elongator complex, was found able to acetylate tubulin, which is essential for the maturation of cortical neurons [22]. The role of E1p3 as a tubulin acetyltransferase important for neuronal development has been confirmed in a genetic RNAi suppression screen for regulators of α -tubulin acetylation using the nematode *Caenorhabditis elegans* [23]. Besides its role in tubulin acetylation, E1p3 has been implicated in the regulation of other processes outside the nucleus such as stress signalling, tRNA modification, exocytosis and actin dynamics [24–28]. A study by Esberg et al., however, questions the role of E1p3 as an acetyltransferase since various effects observed in E1p3 deficient cells could be attributed to its role in tRNA modifications and more specifically to the absence of wobble uridine modified lysine and glutamine tRNA species [29, 30]. A recently published paper describes Gcn5 as another acetyltransferase, capable of acetylating α -tubulin after its recruitment to microtubules via a cytoplasmic proteolytic fragment of myc [31]. Importantly, another recent paper identifies Mec-17, a Gcn5-related protein, as a major α -tubulin acetyltransferase [32]. Finally, two reports suggest that enzymes having N-acetyltransferase activity could also acetylate internal lysine residues and contribute to tubulin acetylation [33, 34].

2.2. HDACs. Compared to the Hat families there are by far more examples of deacetylases located in the cytoplasm (see Table 2 for list of HDACs). Even members of the type I family of deacetylases, which in the past have been considered as strictly nuclear proteins, can be found in the

cytoplasm. For instance HDAC1 is a nuclear enzyme which, under pathological situations, is exported via CRM1 into the cytoplasm where it binds to kinesin motors, hindering cargo transport [35]. HDAC3, another type I deacetylase, is found in the nucleus and the cytoplasm and has both nuclear export as well as nuclear localisation signals [36]. It is retained in the cytoplasm via its interaction with I κ B α [37] until TNF- α signalling leads to the degradation of this binding partner [38]. Furthermore HDAC3 can associate with the plasma membrane where it is phosphorylated by src thereby increasing its activity [39]. Surprisingly, in contrast to the other class I enzymes which are more nuclear, HDAC8 is essentially in the cytoplasm where it associates with smooth muscle α actin to regulate cell contractility [40, 41].

Class IIa deacetylases (4, 5, 7 and 9) [42] are known to shuttle between the nucleus and the cytoplasm [43, 44]. HDAC7 is the only member of this family reported to be present also in mitochondria; it leaves mitochondria and the nucleus to accumulate in the cytoplasm after initiation of apoptosis [45]. All class IIa members have nuclear localisation signals and binding sites for proteins of the 14-3-3 family. An important regulatory mechanism relies on the phosphorylation of these 14-3-3 binding sites inducing the interaction with 14-3-3 proteins and subsequent accumulation in the cytoplasm. Cytoplasmic accumulation has been attributed to 14-3-3-mediated CRM1- dependant nuclear export but two publications have shown more recently that phosphorylation can target the NLS and that the deacetylases are retained in the cytoplasm after binding of 14-3-3 to the phosphorylated NLS and disruption of the nuclear import [46, 47]. Independent of its phosphorylation status, the nuclear export of HDAC4 is regulated by oxidation of two of its cysteine residues resulting in an intramolecular disulfide bridge, whose reduction inhibits nuclear export [48]. HDAC7 is another example of a class IIa enzyme, which can be exported from the nucleus independently of its phosphorylation status and 14-3-3 binding [49].

The translocation of type I and IIa HDACs into the cytoplasm in all the examples mentioned above (except HDAC8) is generally considered as a regulatory mechanism, which serves to reduce their action in the nucleus and so far cytoplasmic substrates have only been found for HDAC4 (as discussed below).

The most extensively studied cytoplasmic deacetylase is the type IIb enzyme HDAC6, which has several cytoplasmic substrates, including tubulin [50–52], cortactin [53], Hsp90 [54–57], β -catenin [58], and peroxiredoxin [59]. Although it bears intrinsic nuclear import and export signals, HDAC6 is almost exclusively localised in the cytoplasm [60, 61], where its actions underlie multiple regulatory processes. One way to regulate its action is to change its localisation within the cytoplasm. As mentioned below HDAC6 is translocated together with Hsp90 and Rac1 to membrane ruffles after PDGF stimulation where it influences actin dynamics [62]. Tubulin deacetylation by HDAC6 can be prevented by Cbl, due to competitive binding to β -tubulin [63]. Another way influencing its activity is the binding to various partner proteins either directly or indirectly. An example of an indirect interaction essential for HDAC6 activity is the formation

TABLE 1: Lysine (K) acetyltransferases.

New Name	Former name human	Former name D. melanogaster	Former name S. cerevisiae	Former name S. pombe	HAT complexes
GNAT family					
KAT1	HAT1	CG2051	Hat1	Hat1/Hag603	HAT-B
KAT2		dGCN5/PCAF	Gcn5	Gcn5	SAGA, ADA, ATAC
KAT2A	hGCN5				STAGA, TFTC
KAT2B	PCAF				PCAF complex
KAT9	ELP3	dELP3/CG15433	Elp3	Elp3	Elongator for RNA polymerase II
	HsMEC-17				
p300/CBP family					
KAT3		dCBP/NEJ			
KAT3A	CBP				
KAT3B	P300				
MYST family					
KAT5	TIP60/PLIP	dTIP60	Esa1	Mst1	NuA4
KAT6		(CG1894)	Sas3	(Mst2)	NuA3
KAT6A	MOZ/MYST3				
KAT6B	MORF/MYST4				
KAT7	HBO1/MYST2			(Mst2)	
KAT8	hMOF/MYST1	dMOF (CG1894)	Sas2	(Mst2)	MSL complex
nuclear receptor coactivators					
KAT13A	SRC-1				
KAT13B	ACTR				
	SRC-3				
	TIF-2				
	GRIP1				
	ATF-2				
Divers					
KAT4	TAF1 (TAFII250)	dTAF1	Taf1	Taf1	TFIID
KAT10			Hap2		
KAT11			Rtt109		
KAT12	TFIIIC90				
KAT13C	P160				
KAT13D	CLOCK				

of a tripartite complex composed of the farnesyltransferase, HDAC6, and microtubules. Disruption of the complex by KO of the alpha subunit of the farnesyltransferase or by an inhibitor of this enzyme leads to enhanced tubulin acetylation [64]. BBIP10, a protein essential for primary cilia formation also binds to and inhibits HDAC6, but so far it is not clear whether this interaction is direct or not [65]. An example of a direct interaction is the binding of Dia2 to one of the two deacetylase domains of HDAC6, which leads to activation of HDAC6 in osteoclasts [66]. Two other examples are the microtubule-associated protein tau and the tubulin polymerisation promoting protein TPPP/p25, which can bind to HDAC6 and inhibit its activity leading

to a subsequent increase in microtubule acetylation [67–69]. Ilp45 (a newly discovered protein) as well as CYLD, a deubiquitinating enzyme, can both inhibit HDAC6 by direct binding to the deacetylase domains of HDAC6, which in the case of Ilp45 will also lead to HDAC6 degradation [70, 71]. A third way to regulate HDAC6's activity is by its posttranslational modification. It has been shown for instance that HDAC6 interacts with EGFR and is phosphorylated by EGFR at Tyr570 after ligand-induced receptor activation [72]. This reduces HDAC6 activity leading to tubulin acetylation and accelerated delivery of endocytosed EGFR to lysosomes. In contrast Aurora A, a mitotic ser/thr kinase, phosphorylates HDAC6 leading to its activation

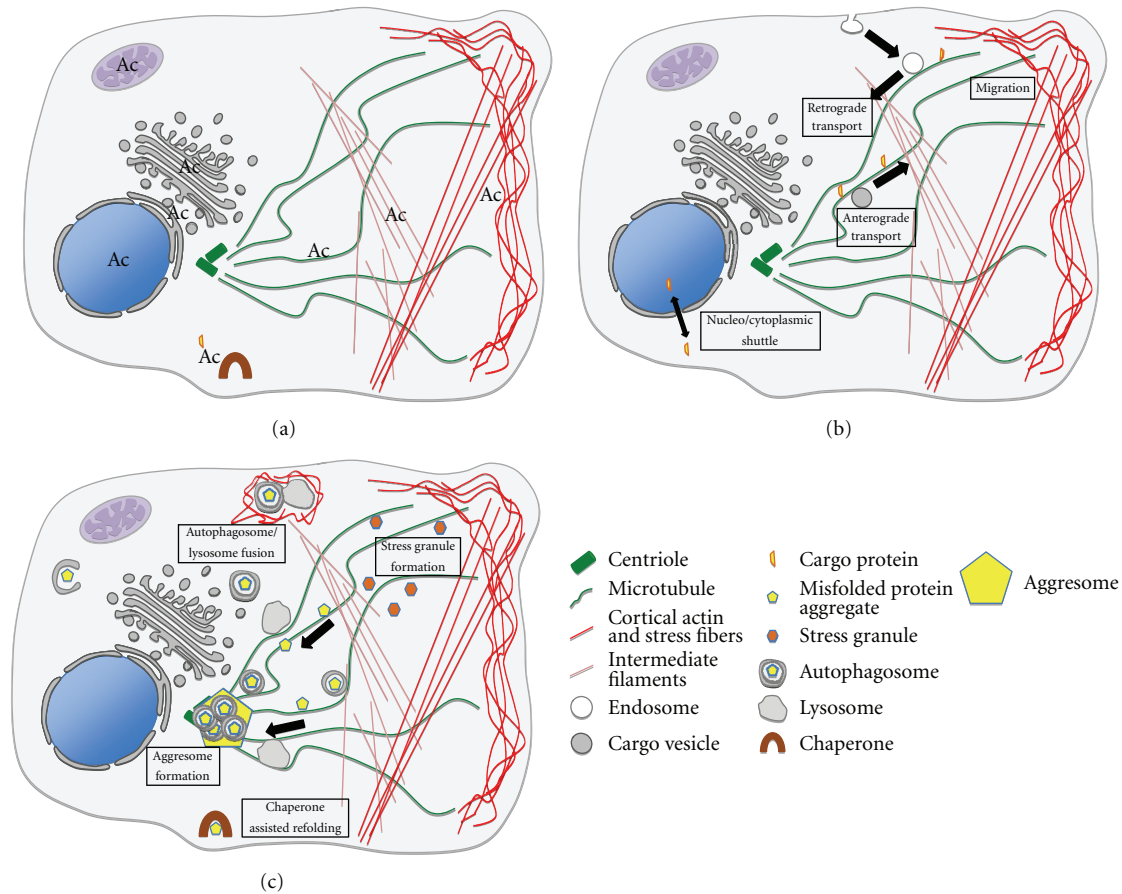


FIGURE 1: Schematic overview of cytoplasmic mechanisms regulated by acetylation. (a) Localisation of acetylation events within a cell. Indicated are individual acetylated proteins and cytoskeletal structures (cortical actin and actin stress fibers, microtubules, intermediate filaments) as well as organelles (nucleus, mitochondria, ER, ERGIC, golgi) in which acetylation and deacetylation events take place. (b) Involvement of reversible acetylation in the regulation of various cytoplasmic processes, including cell migration following cytoskeleton remodelling, individual protein transport as well as vesicular transport and nucleocytoplasmic shuttling of proteins. (c) Regulation of stress response and cytoplasmic cleanup systems by various acetylation/deacetylation events.

resulting in tubulin deacetylation and resorption of primary cilia in human retinal cells [73]. In this context it is worth mentioning that HDAC6 (as well as other HDACs) can be found in complexes together with phosphatases and both enzymes are active under these conditions [74]. HDAC6 activity, besides being regulated by phosphorylation, can also be reduced by p300-mediated acetylation [75]. In addition to its deacetylase function, HDAC6 has other important cellular tasks, such as cargo transport by binding to the dynein and kinesin motor complexes, or binding to mono and polyubiquitin, which is necessary for aggresome formation and induction of quality control autophagy (QC-autophagy) (for review see [76, 77]).

HDAC10, the other class IIb enzyme, is present in the cytoplasm and the nucleus and, in contrast to the class IIa family members, is not exported through a CRM1-mediated transport mechanism [78–81]. Finally HDAC11, the only type IV deacetylase, is essentially a nuclear enzyme but can be found in the cytoplasm in latent HIV infected cells [82, 83].

The sirtuin or class III family of deacetylases are a functionally distinct family for two reasons. First they

depend on the cofactor NAD^+ for their activity, and second they do not release free acetate after hydrolyses of the acetyl group but rather transfer it onto ADP-ribose. In mammals, seven sirtuins have been described (Sirt1-7) [84]. Only Sirt1, Sirt2, and Sirt3 have a true deacetylase activity all the others have only ADP-ribosyltransferase activity. At least, this was considered the truth until it was observed that Sirt6 could deacetylate lysine 9 of histone H3 [85]. No cytoplasmic localisation, however, has been observed for Sirt6; we will therefore focus only on Sirt1-3 [86].

Sirt1 has both a nuclear localisation and a CRM1-dependent export signal and, in most cells, it is present both in the nucleus and the cytoplasm [87]. Upon induction of neural differentiation it is transiently transported into the nucleus but for NGF-induced neurite outgrowth it has to be present in the cytoplasm [88, 89]. As discussed below, Sirt1 has important roles in the cytoplasm linked to autophagy and cell migration via deacetylation of cortactin [90, 91].

Sirt2 is almost only localised in the cytoplasm due to an active CRM1-dependent export mechanism [92]. It has been implicated in tubulin deacetylation [93] and seems to

TABLE 2: Lysine (K) deacetylases.

Name	Localisation	Cytoplasmic substrates
Class I		
HDAC1	mainly nucleus	
HDAC2	nucleus	
HDAC3	mainly nucleus/cytoplasm	
HDAC8	mainly cytoplasm	
class IIa		
HDAC4	cytoplasm/nucleus	MLP, DNAJB8
HDAC5	cytoplasm/nucleus	
HDAC7	cytoplasm/mitochondria/nucleus	
HDAC9	cytoplasm/nucleus	
Class IIb		
HDAC6	cytoplasm	tubulin, cortactin, Hsp90, β -catenin, peroxiredoxin
HDAC10	cytoplasm/nucleus	
Class IV		
HDAC11	mainly nucleus	
Class III(sirtuins)		
sirt1	cytoplasm/nucleus	cortactin, Atg5, Atg7, Atg8
sirt2	cytoplasm	tubulin, cortactin?
sirt3	mitochondria/long form cytoplasm	
sirt4	mitochondria	
sirt5	mitochondria	
sirt6	nucleus	
sirt7	nucleus	

deacetylate tubulin especially under certain circumstances, for instance during mitosis to regulate mitotic microtubule dynamics [94] or during oligodendrocyte differentiation [95]. It was suggested that Sirt2 inhibition could reduce alpha synuclein toxicity in Parkinson disease, but the molecular interplay has not been identified [96, 97].

Finally, Sirt3 is known as a mitochondrial enzyme (for a detailed review see [84]), but a long form of Sirt3 partially localised in the cytoplasm has been recently described [98].

At last, it is worth mentioning that quite a few nuclear and cytoplasmic acetylated proteins are targeted by both, class I/II as well as class III, deacetylases as for instance histones [99], tubulin [50–52, 93], Ku70 [98, 100], p53 [101, 102], and cortactin [53, 91]. For most of these examples it is not clear whether HDACs of different classes show a preference for particular acetylated lysine residues in these proteins. Actually, motif preferences for lysine acetylation only start to emerge. The local sequence context around

acetylated lysine residues in cytoplasmic proteins appears to be different from that of histones but similar to that of other nuclear proteins. Furthermore mitochondrial acetylation motifs differ from acetylation sites found in both histones and other nuclear/cytoplasmic proteins [4, 5]. In spite of these advances a precise consensus sequence for the substrate specificity of different Kats or HDACs has yet to be defined.

3. Functional Implications of Cytoplasmic Lysine Acetylation

3.1. Regulation of the Cytoskeleton. Since the cytoskeleton is involved in many cytoplasmic processes, we will start by describing what is known about the regulatory effect of acetylation on the three main types of cytoskeletal components, namely, actin filaments, microtubules, and intermediate filaments (Figures 1(a) and 1(b)).

3.1.1. Actin Filaments. The globular monomeric form of actin (G-actin) polymerises to form a double helix (filamentous or F-actin), which can then be bundled into stress fibers. There are three major isoforms of actin. Beta and gamma actin form the stress fibers are important for cell shape and cell movement. Alpha actin constitutes the microfilaments in muscle cells, which together with myosin assures the traction forces necessary not only for muscle contraction but also for cytoplasmic streaming in nonmuscle cells. Using proteomic approaches it has been shown that all three actin isoforms can be acetylated [4, 5] and acetylation of lysine 61 in gamma actin may result in stabilisation of actin stress fibers [4]. Not only actin itself but also several regulatory proteins of the actin cytoskeleton are modified by acetylation. For instance six out of the seven subunits of the Arp2/3 complex, which is important for actin nucleation, are acetylated [5]. Cortactin binds to F-actin in the cell cortex and can recruit the Arp2/3 complex to the cortical actin cytoskeleton when it has been activated by phosphorylation. But phosphorylation is not the only regulatory modification of cortactin. It has been shown that cortactin can be acetylated by p300 or PCAF on nine different lysine residues present in its central repeat domain [53, 91]. When acetylated its translocation to the cell periphery is inhibited and its actin binding capacity reduced. This leads to diminished actin dynamics at the cell periphery and thus to altered cell motility. Deacetylation of cortactin is mediated via HDAC6 and Sirt1 (maybe also Sirt2), which may act in cooperation to induce cell migration [53, 91]. In fact the actin cytoskeleton is essential for cell migration since it is necessary for the formation of membrane ruffles or lamellipodia, filopodia, and actin stress fibers, which reflect different dynamic states of the actin cytoskeleton. Actin dynamics is also regulated by small GTPases of the Rho family. A simplified general scheme implicates RhoA in stress fiber formation, Rac1 in lamellipodia and cdc42 in filopodia formation. The activation of these G-proteins in turn depends on the action of GDIs (GDP dissociation inhibitors), GAPs (GTPase-activating proteins), and GEFs (GDP/GTP exchange factors). It has been shown that acetylation of RhoGDI alpha prevents its inhibitory action

on Rho family members leading to enhanced stress fiber and filopodia formation [4]. RhoA can also be inhibited by the E-cadherin-binding protein p120 catenin. Acetylation of p120 changes its subcellular localisation thereby relieving its inhibitory action on RhoA [4]. Rac1 activation, leading to membrane ruffle formation, associated macropinocytosis, and cell migration, depends on deacetylation of the chaperon Hsp90 by HDAC6, but the precise sequence of events has not been elucidated [62].

Muscle contraction can also be regulated by acetylation as observed for actomyosin filament activity in cardiac muscle cells. In fact the muscle LIM protein (MLP), which colocalizes with myofilaments at the Z-disc of sarcomeres, is a mechanical stretch sensor. Acetylation of MLP by PCAF enhances the calcium sensitivity of myofilaments. HDAC4 seems to be the deacetylase responsible for MLP deacetylation [103].

3.1.2. Microtubules. As already mentioned, α -tubulin, which together with β -tubulin forms the heterodimeric building block of microtubules, was the first cytoplasmic protein described to be acetylated [2, 3]. α -tubulin is acetylated on lysine 40 which, until recently, was considered to be the only acetylated lysine residue in tubulin isoforms. Interestingly, in a recent systematic proteomic identification approach for acetylated proteins, lysine 40 of α -tubulin was not identified. This is most probably due to the fact that an immunoprecipitation step using a pan acetylated lysine antibody has been used in this approach, which most probably has a low affinity for this particular residue. However, several other acetylated lysine residues in different tubulin isoforms (α as well as β subunits) were detected, but their role and significance have still to be elucidated [5]. Even our understanding of the functional role of the acetylation at lysine 40 of α -tubulin is not clear cut. The reason for this may come from the fact that the expression of nonacetylatable α -tubulin does not result in any obvious phenotype [104–106], nor does hyperacetylation following KO of HDAC6 [107]. In general, acetylated microtubules are considered to represent the subpopulation of more stable microtubules in the cell. There has been however a long debate in the literature as to whether acetylation is the cause or a consequence of microtubule stabilisation. While it has been suggested that acetylation just accumulates with time in microtubules with a long half-life [108], others have proposed that acetylation could directly stabilise microtubules [50, 51]. Yet, hyperacetylation in neuronal cells does not lead to microtubule stabilisation [109]. Also, in cells KO for the tubulin deacetylase HDAC6, hyperacetylation of microtubules is not accompanied by detyrosination, which is the other hallmark of stable microtubules [62]. Thus we are proposing an alternative hypothesis for the role of tubulin acetylation. In fact, acetylated microtubules are not very abundant in most of the cells cultured in vitro. There are, however, a few exceptions. At least three cell types have heavily acetylated microtubules in their cytoplasm; these are neurons, platelets, and megacaryocytes, the platelet progenitors. In addition there are cellular substructures

formed by microtubules, which are also heavily acetylated like primary cilia, flagella, mitotic spindles and midbodies. What all these structures and cell types have in common is the need of microtubule bundles. Thus acetylation may allow for more efficient bundling of microtubules, which in turn may lead to enhanced stability of these microtubule bundles. In support of this hypothesis are several observations described in the literature. Naranatt et al. have shown that, 30 min after infection of cells by HHV-8, a transient increase of microtubule acetylation is seen which is accompanied by a thickening of microtubule bundles. Both, acetylation as well as the thickening of microtubules, come back to basal levels about 2-3 hours after infection [110]. Similarly, pneumolysin, a virulence factor of streptococcus pneumoniae, can induce microtubule acetylation and concomitant microtubule bundling [111]. Also, overexpression of calpain 6, a catalytically inactive calpain isoform, induces hyperacetylation and bundling of microtubules [112]. Another example is the tubulin polymerisation promoting protein TPPP/p25, which induces not only tubulin polymerisation but also acetylation and subsequent bundling and stabilisation of microtubules [68]. Microtubule bundles are also promoted by p180, a rough ER associated protein, after induction of tubulin acetylation [113]. In addition, early during neuronal commitment an acetylated array of microtubules is formed which is arranged in a bundle of parallel microtubules [114].

Besides its contribution in stabilisation and/or bundling of microtubules, tubulin acetylation plays an important role in cellular transport events as discussed below. It should be mentioned here that there is a coordinated interplay between the actin cytoskeleton and the microtubular network of which one coordinator is the RhoA effector Dia [115, 116], which can bind to microtubules and, as mentioned above, also binds to actin filaments. In fact Dia has been shown to influence microtubule orientation, stability and acetylation states. Some of the studies conducted so far describe enhanced microtubule acetylation following RhoA and Dia activation [110, 117–119]. It is not known, however, whether in these cases enhanced acetylation is due to direct Dia mediated HDAC6 inhibition or to activation of a tubulin acetyltransferase. In another study using osteoclasts, Dia activation leads to the opposite effect namely deacetylation of microtubules due to the interaction of Dia with, and concomitant activation of, HDAC6 [66]. The outcome of Dia activation on microtubule acetylation/stabilisation may thus be cell type dependent. Further complexity might be added to the finetuning of these regulatory events by the fact that a Dia-related isoform seems to be acetylated itself [5].

3.1.3. Intermediate Filaments. At least some of the constituents of the third class of cytoskeletal elements, the intermediate filaments, have also been found acetylated. One example is vimentin, which is acetylated on several lysine residues [5], another is cytokeratin 8, which is acetylated on three lysine residues. In contrast to tubulin and actin however, in this case, acetylation seems to destabilize the polymer [120, 121].

3.2. Transport. Cellular transport along microtubule tracks is particularly important in cells, which have long extensions like axons and dendrites of neuronal cells. This may be the reason why the important role of microtubule acetylation for cargo transport has first been observed in neurons. The microtubule motor kinesin is implicated in anterograde transport, whereas dynein motors are involved in retrograde transfer of cellular materials (Figure 1(b)). It has been shown that binding of kinesin-1 to and mobility on microtubules is enhanced by tubulin acetylation and thus delivery of Jip-1 (a cargo protein of kinesin-1) to neurite tips is accelerated [122]. Another example of more efficient kinesin-1-mediated transport along acetylated microtubules is the vesicular transport of the neurotrophic factor BDNF. In neurons of Huntington disease patients, BDNF is not transported and secreted efficiently due to a polyglutamine expansion in the htt protein, which is unable to stimulate microtubule-based transport. Hyperacetylation of microtubules can rescue this deficiency. In addition the authors show that both kinesin as well as dynein-dependent microtubular transport is enhanced by tubulin acetylation [109]. Regulation of receptor trafficking by enhancing the speed of endosome transport is also augmented by microtubule acetylation [72, 123]. EGFR vesicle recycling however is not influenced under these conditions [123]. Collectively, these observations indicate that the transport of individual cargo proteins, as well as some but not all vesicular transport processes, are regulated by microtubule acetylation (Figure 1(b)).

Viruses have developed strategies to profit from the host cellular transport machinery for efficient infection. The herpes virus HHV-8 for instance is able to enhance microtubule acetylation by activation of RhoA and its effector Dia2, which speeds the dynein dependent delivery of viral DNA to the nucleus [110]. The adenovirus acts in a similar way [119]. The vaccinia virus instead inhibits RhoA and, in turn, Dia2 leading to diminished tubulin acetylation but increased tubulin dynamics in the cell periphery, which in this case could help viral release [117]. Efficient invasion of bladder cells by uropathogenic *E. coli* bacteria also requires HDAC6-mediated deacetylation of microtubules [124].

In the context of cellular transport mechanisms it is worth mentioning that several motor proteins have themselves been identified as being acetylated and future studies will have to tell whether transport regulation attributed to microtubule acetylation could have been influenced also by motor protein acetylation [5].

3.3. Translation, Quality Control, and Cytoplasmic Cleanup. Acetylation has been widely studied for its role in transcriptional regulation in the nucleus and it is almost astonishing that, to our knowledge, no observation on translational regulation by acetylation has been described so far. It is worth mentioning, however, that in global proteomic studies a huge number of translation initiation factors or ribosomal proteins have been found acetylated [4, 5]. Thus a possible role of acetylation in translational control mechanisms remains to be discovered. The amount of expressed proteins is not only controlled at the transcriptional and translational

levels but also by regulation of their half-life. Acetylation is widely used to influence protein stability in both directions but, since this topic has been reviewed recently [125], it will not be discussed here.

Besides quantity control, the cell is also equipped with quality control and cleanup systems for cellular proteins to avoid the accumulation of misfolded, aggregated proteins in the cytoplasm, which would have a deleterious effect on coordinated normal cellular functions (Figure 1(c)). Following translation many newly synthesised proteins have to be assisted for correct folding or assembly into multi-subunit complexes. This is ensured by chaperones. Chaperones are also implicated in the management of misfolded proteins which arise following different environmental stress conditions like heat shock, oxidative stress and aging, or pathological expression of proteins due to mutations or over-expression. In case of an unsuccessful management by chaperones, misfolded proteins are ubiquitinated and degraded by the proteasome. After a prolonged or extensive stress period or under experimental overexpression of proteins, the chaperone/proteasome pathway cannot cope anymore with the massive conformational defects of proteins, which accumulate and aggregate in the cytoplasm. This gives rise to a more global stress response, leading to stress granules and aggresome formation and induction of QC-autophagy. The important role of HDAC6 in all of these different cellular defence mechanisms has been well described (for review see [76, 77]) and will not be discussed in detail in this paper. We will rather emphasize the critical importance of some acetylated lysine residues within other key actors involved in these processes.

3.3.1. Chaperones/Proteasome. Chaperones are well known as proteins assisting nucleosome formation. There are however also several chaperones important for the folding or assembly of cytoplasmic protein complexes and many chaperones have been discovered following heat shock treatment, which leads not only to their transcriptional induction but also to their immediate activation. Hsp90 can be acetylated on several lysine residues and its activation state depends on its acetylation status. Its immediate activation is mediated by HDAC6-dependent deacetylation, which is essential for ATP binding of Hsp90 [54] and for its binding to its cochaperone p23 as well as to various client proteins like AhR (aryl hydrocarbon receptor) [126], Bcr-Abl, AKT, c-Raf [54], or the glucocorticoid receptor [57, 127]. Besides other acetylated lysine residues deacetylation of lysine 294 in Hsp90 is particularly important for cochaperone and client binding [56] but, as mentioned above, HDAC6 mediated deacetylation of this site is also responsible for Hsp90 mediated Rac1 activation resulting in actin reorganisation and cell migration [62]. The different functional roles of Hsp90 could be dictated by its cellular localisation since Hsp90 is translocated to membrane ruffles to mediate its role in actin remodelling [62]. By deacetylation of Hsp90, HDAC6 may regulate its own survival since HDAC6 has been shown to be itself an Hsp90 client protein [128].

Alpha A-crystallin, a chaperone in the soluble fraction of eye lenses, becomes acetylated on lysine 70, a region supposed to be important for its activity, and alphaB-crystallin appears to be acetylated on lysine 92 [129, 130]. Crystallins may thus be another example of chaperones whose activity is regulated by acetylation. The chaperone DNAJB8 can be acetylated on two conserved lysine residues situated in its carboxyterminal part. Although these lysine residues are not implicated in substrate binding, deacetylation mediated by HDAC4 activates the chaperone and suppresses cytotoxic protein aggregation [131].

As mentioned above, in case chaperones are unable to assist correct folding of their client proteins, these misfolded proteins are eliminated by proteasomal degradation. One example is again Hsp90. In its inactive ADP-bound state it associates with the cochaperone Hsp70, which prepares the misfolded client protein for degradation by its association with a ubiquitin ligase. Hsp70 is also hyperacetylated following either class I HDAC or HDAC6 inhibition. In contrast to Hsp90, hyperacetylation of Hsp70 promotes its interaction with client proteins leading to their ubiquitination and degradation by the proteasome [132].

3.3.2. Stress Granules/Aggresome/Autophagy. When the load of misfolded proteins is too high the cells suspend their normal function and respond with an immediate block of mRNA translation (except for stress response factors like heat shock proteins/chaperones). Accumulation of the halted transcripts gives rise to the appearance of stress granules. In parallel, the accumulating misfolded proteins become ubiquitinated and transported along microtubules to the centrosome where they form the so-called aggresome. HDAC6 is essential for both stress granule and aggresome formation [133, 134]. It has been suggested that HDAC6 could act in the transport process as an adaptor by binding to the dynein motor complex on the one hand and binding via its ubiquitin binding domain to ubiquitinated proteins on the other [133]. Parkin, a ubiquitin E3 ligase (often mutated in Parkinson disease), tightly binds to HDAC6 and is also transported by HDAC6 in a microtubule motor dependent manner to the forming aggresome. There may be ongoing parkin-mediated ubiquitination of misfolded proteins during transport along the microtubules [135, 136]. Given that microtubule motor-dependent transport is enhanced when microtubules are acetylated one would expect that the deacetylase activity of HDAC6 is inhibited during these transport processes and that deacetylase deficient forms of HDAC6 should be able to rescue stress granule and aggresome formation in HDAC6 KO cells. Since this is not the case and in addition, HDAC6 and parkin are both active during the transport to the aggresome, it seems that a deacetylation event is essential for aggresome and stress granule formation. Whether tubulin is the relevant substrate or not remains to be determined.

Aggresomes or smaller ubiquitinated misfolded protein aggregates are cleared by basal or QC-autophagy. Double membranous vesicular compartments called autophagosomes are formed in order to isolate the cytoplasm containing the material to be eliminated. These vesicles then

fuse with lysosomes, and the lysosomal enzymes ensure the proteolytic digestion of their content. HDAC6 is essential for the delivery of autophagosomal constituents and lysosomes to the pericentriolar localised aggresome by transport along microtubule tracts, as observed for the clearing of aggregated huntington [137]. HDAC6 then plays a second role in the fusion between autophagosomes and lysosomes by recruiting and deacetylating cortactin which in turn recruits actin filaments to tether the two vesicle populations [138, 139]. QC-autophagy can be distinguished from starvation-induced autophagy since the latter does not depend on HDAC6. Both, however, depend on the same autophagy-related genes (Atg). Recent studies have shown that starvation-induced autophagy is regulated by the acetylation status of Atg5, Atg7, and Atg8, which are proteins required for the formation of the autophagosome. They are acetylated by p300, which prevents autophagosome formation [140]. Deacetylation is accomplished by Sirt1 and is essential for the induction of autophagy following nutrient deprivation [90]. This observation correlates with the fact that Sirt1 is implicated in metabolic processes and upregulated during fasting conditions [141]. Stimulation of starvation-induced autophagy requires also hyperacetylation of tubulin, which could explain why the absence of HDAC6 does not prevent this type of autophagy [142].

3.4. Plasma Membrane and Organelles. Several ion pumps of the plasma membrane, like the Na^+/K^+ -ATPase and the Ca^{2+} -ATPase can associate with acetylated microtubules or acetylated tubulin dimers but not with unacetylated tubulin. Association with acetylated tubulin inhibits the pumps and may serve at the same time as an anchorage site for the microtubular network to the plasma membrane [143]. Acetylated tubulin at the plasma membrane is also found in another context. The viral protein gp120 of HIV binds to its receptor CD4 in the plasma membrane of T cells and induces tubulin acetylation and accumulation at contact sites. These plasma membrane domains rich in acetylated tubulin could be entry sites for HIV, since active HDAC6 diminishes HIV infection [144].

Mitochondria harbour an enormous amount of acetylated proteins, and there are several publications on the important role of acetylation for the regulation of metabolic and age-related processes, which could not be included in this paper.

Interestingly, recent studies describe acetylation and deacetylation events occurring in the lumen of the ER and Golgi apparatus, respectively. Bace1, the protease responsible for amyloid precursor protein cleavage, and the LDL receptor become acetylated in the ERGIC [145, 146]. Acetylation is essential for their stabilisation and progression along the secretory pathway. Both proteins are deacetylated in the Golgi apparatus. This implies not only the presence of Hats and HDACs in these cellular compartments but also an ER import system for acetyl-CoA. While the responsible Hat enzymes have been identified and appear to be type II membrane proteins, the HDACs still remain to be discovered and

the acetyl-CoA transporter is currently under investigation [147].

3.5. Nuclear-Cytoplasmic Shuttle. Besides the regulation of protein stability, activity and interactions, acetylation is widely used for regulating the cellular localization of proteins, especially for nuclear import and export (Figure 1(b)). Most proteins, which shuttle between the nucleus and the cytoplasm, are acetylated by p300/CBP, including HNF-4, CIITA, PCNA, SRY, cAbl, CtBP2, p53, PAP, and β -catenin, RECQL4 [148–157]. Two out of those can also be acetylated by PCAF [154, 155], and there is only one report published so far where Gcn5-mediated acetylation plays a role, concerning CDC6 [158]. Until now no general rule for the localisation of the acetylated subpopulation of proteins has been deciphered. For some proteins, acetylation enhances localisation in the cytoplasm [149, 151, 153, 154, 158, 159], whereas for others acetylation will preferentially favour a nuclear localization [148, 150, 152, 155, 156, 160, 161]. The mechanism by which acetylation influences cellular localisation can be either the modification of an interaction with a binding partner leading to retention in a particular compartment, or an altered interaction with nuclear import/export factors. For poly(A) polymerase (PAP) and the DNA helicase RECQL4 it was shown that acetylation disrupts their interaction with the nuclear import factors leading to their accumulation in the cytoplasm [149, 153]. In contrast, SRY acetylation provokes its nuclear import, which also depends on its interaction with a nuclear import factor, but in this case acetylation induces an increased interaction of the acetylated form with importin beta [148]. Interestingly, in order to stay in the nucleus HNF-4 has to be kept in an acetylated state at its NLS. Deacetylation leads to CRM1-dependent export most probably after a conformational change liberating its nuclear export signal [156]. Similarly, cytoplasmic localisation of acetylated p53 depends on CRM1 binding to its nuclear export signal which is accessible only when p53 oligomerization is prevented by lysine acetylation [151]. Another example of CRM1-dependent export regulated by acetylation is NF-kappaB. When present in the nucleus the RelA subunit of NF-kappaB can be acetylated on several lysine residues, which differentially influence its nuclear export mediated by the NF-kappaB inhibitor Ikbalpha [161, 162].

Interestingly, the nuclear import factor importin alpha is itself targeted by reversible acetylation by p300/CBP, which stimulates heterodimer formation with importin beta [163, 164]. In addition, several other transport factors are among the acetylated proteins identified by Choudhary et al. These include importin beta as well as CAS, the exportin responsible for recycling importin alpha to the cytoplasm, and the more general export receptor CRM1 [5].

4. Concluding Remarks

The overwhelming amount of published work on important aspects of cytoplasmic acetylation precludes an exhaustive overview covering the current knowledge (for additional

aspects see [165]). We have therefore focused on selected examples illustrating some important points and wish to apologize for other interesting observations, which have not been included.

Having discussed the importance of acetylation in the cytoplasm, it may be worth insisting on the fact that cells should be considered as entities which cannot be strictly divided into two different compartments. The interpretation of some of the results might have been biased by indirect effects due to transcriptional regulation or leakage of nuclear proteins during biochemical purification steps. Also proteins generally considered as typical cytoplasmic residents do play important roles in the nucleus. Actin, for instance, known as a major cytoskeletal and thus cytoplasmic constituent, also plays important roles in the nucleus as a part of transcription or DNA remodelling complexes. Even tubulin was recently found translocating between the nucleus and the cytoplasm [166]. To circumvent problems related to the presence of the nucleus for the characterisation of cytoplasmic acetylation events, we propose platelets as a good model system. Platelets are devoid of a nucleus but are equipped with all the important players to execute known cytoplasmic processes like exocytosis, adhesion, aggregation, shape change, remodelling of the cytoskeleton, and even apoptosis-related events. Furthermore all these processes have to be tightly regulated and induction has to be extremely rapid to ensure hemostasis and prevent thrombosis.

We would like to conclude with the prediction that, although numerous acetylated proteins have been already identified in the cytoplasm, there are likely more to be discovered. This idea is supported by the fact that acetylation of lysine 40 of alpha tubulin has not been detected in the proteomic survey of acetylated proteins by Choudhary et al. [5] and other acetylation sites may have been missed for the same technical reasons (see above). New strategies including bioinformatic prediction approaches [167, 168] may lead us to new candidates for reversible acetylation. We therefore believe that the story will not end here and future will tell us more about acetylated proteins and exciting new regulatory mechanisms. Finally this paper highlights the importance of reversible cytoplasmic protein acetylation in a wide range of cellular functions and regulatory mechanisms. The functional significance of this modification has been largely recognized in the past for transcriptional control mechanisms in the nucleus and at present, as summarized here, also for cytoplasmic events. Thus the functional role of reversible protein lysine acetylation now definitely approaches the regulatory power of protein phosphorylation as rightly predicted by Kouzarides [169].

Abbreviations

ADP:	Adenosine diphosphate
AhR:	Aryl hydrocarbon Receptor
Arp:	Actin-related protein
ATAC:	Ada Two-A Containing
ATF2:	Activating Transcription Factor 2

ATP:	Adenosine triphosphate
BBIP10:	BBSome Interacting Protein 10
BDNF:	Brain Derived Neurotrophic Factor
Cbl:	Casitas B-lineage lymphoma
CBP:	CREB Binding Protein
CD:	Cluster of Differentiation
CDC6:	Cell Division Cycle 6
CRM1:	Chromosome Region Maintenance 1
EGFR:	Epidermal Growth Factor Receptor
Elp3:	Elongator complex protein 3
ER:	Endoplasmic Reticulum
ERGIC:	Endoplasmic Reticulum—Golgi Intermediate Compartment
Gcn5:	General control of amino acid synthesis 5
Hat:	Histone acetyltransferase
HDAC:	Histone deacetylase
HHV-8:	Human Herpes Virus 8
HIV:	Human Immunodeficiency Virus
HNF-4:	Hepatocyte Nuclear Factor 4
HSP90:	Heat Shock Protein 90
KAT:	lysine (K) acetyltransferase
LDL:	Low-density Lipoprotein
MYST:	MOZ, Ybf2/Sas3, Sas2, Tip60
NAD:	Nicotinamide Adenine Dinucleotide
NF-kappaB:	Nuclear Factor-kappaB
NGF:	Nerve Growth Factor
NLS:	Nuclear Localization Signal
PAP:	Poly A Polymerase
PCAF:	p300/CBP-associated Factor
PCNA:	Proliferating Cell Nuclear Antigen
PDGF:	Platelet-derived Growth Factor
QC-autophagy:	Quality Control-autophagy
Rac1:	Ras-related C3 botulinum toxin substrate 1
RECQL4:	RecQ protein-like 4
Rho:	Ras homolog gene
RNAi:	RNA interference
SAGA:	Spt-Ada-Gcn5 Acetyltransferase
Sirt:	Sirtuin
SRY:	Sex-determining Region Y
STAGA:	SPT3-TAF9-GCN5/PCAF acetylase
TFTC:	TBP-free TAF-containing Complex
Tip60:	Tat interacting protein 60
TNF:	Tumor Necrosis Factor

TPPP:	Tubulin Polymerization-Promoting Protein
tRNA:	transfer RNA.

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