Review

HDAC6: a key regulator of cytoskeleton, cell migration and cell–cell interactions

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Histone deacetylase 6 (HDAC6) is a cytoplasmic enzyme that regulates many important biological processes, including cell migration, immune synapse formation, viral infection, and the degradation of misfolded proteins. HDAC6 deacetylates tubulin, Hsp90 and cortactin, and forms complexes with other partner proteins. Although HDAC6 enzymatic activity seems to be required for the regulation of cell morphology, the role of HDAC6 in lymphocyte chemotaxis is independent of its tubulin deacetylase activity. The diverse functions of HDAC6 suggest that it is a potential therapeutic target for the treatment of a range of diseases. This review examines the biological actions of HDAC6, focusing on its deacetylase activity and its potential scaffold functions in the regulation of cell migration and other key biological processes in which the cytoskeleton plays an important role.

Introduction

The cytoskeleton is an essential structural and functional component of the cell. It is composed of dynamic arrays of actin microfilaments, intermediate filaments and microtubules, all of which are physically and functionally linked [1]. The regulation of cytoskeletal filaments and their interconnection is essential for diverse functions, including cell transport, mitosis, adhesion and migration, and it continues to be a matter of intense study.

Microtubules are polarized filaments composed of polymerized α-tubulin–β-tubulin heterodimers. Microtubules flux between polymerization and catastrophe (depolymerization), and the rates of growth and shortening are regulated by post-translational modifications of tubulin and by a plethora of microtubule associated proteins (MAPs) and cytosolic signaling molecules [2]. These proteins include stabilizing factors [e.g. MAP2, Tau (also known as MAP4), EMAP and XMAP215] and destabilizing factors (e.g. stathmin), certain kinesin-like proteins [e.g. XKCM1 (Xenopus Kinesin Catastrophe Modulator-1)], and the microtubule-severing protein katanin [2]. The importance of accessory proteins in the regulation of microtubule dynamics is emphasized by the observation that, *in vitro*, purified tubulin polymerizes approximately five-fold to ten-fold more slowly than in intact cells [3]. Stable microtubules are enriched with post-translational modifications, such as tubulin detyrosination and acetylation of α-tubulin at lysine 40. However, it is still a matter of debate whether tubulin acetylation *per se* mediates microtubule stabilization [4–7].

The histone deacetylase HDAC6 has recently emerged as a tubulin deacetylase [8,9] that has effects on microtubule-mediated processes through both deacetylase-dependent and -independent mechanisms. In this review, we describe the role of HDAC6 during the regulation of cell migration, immune synapse formation, viral infection and microtubule-mediated intracellular transport.

HDAC6 tubulin deacetylase

Histone acetylation generally induces chromatin relaxation and gene transcription, whereas deacetylation favors chromatin condensation and transcriptional quiescence. Histones are acetylated on specific lysine residues through the action of histone acetyltransferases (HATs). HDACs catalyze the reverse reaction. Several mammalian HDACs have been identified. Class I HDACs are 400–500 amino acids long, and include HDAC1, HDAC2, HDAC3 and HDAC8. Class II HDACs are ~1000 amino acids long; class IIa comprises HDAC4, HDAC5, HDAC7 and HDAC9, and class IIb comprises HDAC6 and HDAC10 [10–12]. Class III comprises the Sir2-like deacetylases Silent Information Regulator (SIRT1)–SIRT7, ranging in size from 310–757 amino acids [13]. HDAC11 shares conserved residues in its catalytic core regions with HDACs from classes I and II [13], and is considered to be an independent enzyme, representing a potential new class of HDACS, class IV. Recent studies have identified an expanded substrate repertoire for HDACs and have shown that the function of these molecules is not limited to histone deacetylation and the regulation of gene transcription.

The HDAC classes show distinct subcellular localizations: class I HDACs are mainly localized to the cell nucleus, whereas the class II molecules HDAC4, HDAC5

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0962-8924/$ – see front matter © 2008 Elsevier Ltd. All rights reserved. doi:10.1016/j.tcb.2008.04.003 Available online 9 May 2008

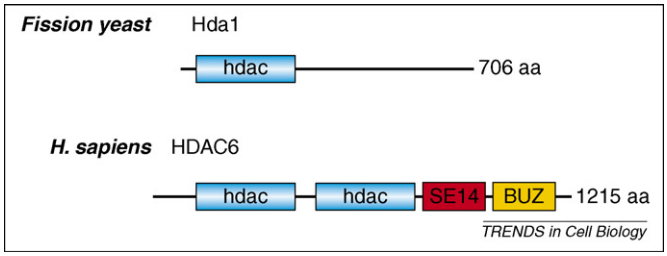

Figure 1. HDAC6 structure. Blue boxes indicate the deacetylase (HDAC) domain. The numbers of amino acids (aa) are indicated at the right of each structure. SE14, SerGlu-containing tetradecapeptide repeats. BUZ is a ZnF domain. The related HDAC domain of the fission yeast Hda1 enzyme is also illustrated.

and HDAC7 are able to shuttle between the nucleus and the cytoplasm – a phenomenon controlled by calmodulin-dependent kinase-mediated phosphorylation [14]. By contrast, human HDAC6 contains a Ser Glu-repeat domain (SE14), which acts as a cytoplasmic retention signal and mediates its stable anchorage in the cytoplasm [15].

HDAC6 is the only HDAC that possesses two functional deacetylase domains and a zinc finger (ZnF) motif (Figure 1) [16–18]. *In vivo*, the enzymatic activity of HDAC6 is exerted on tubulin, heat shock protein 90 (Hsp90) and cortactin substrates; however, *in vitro*, HDAC6 is also able to deacetylate histones [4,17,18]. The Zn^{2+} chelator trichostatin A (TSA) reversibly inhibits HDAC6 deacetylase activity [4,8,9,19]. In addition to the identification of its enzymatic substrates, several HDAC6-interacting proteins have since been identified (Table 1); these include the AAA-ATPase chaperone p97 (also known as VCP) [20], mDia2 [21], the $p150^{glued}$ component of the dynein–dynactin microtubule motor complex [8], and the catalytic subunit of protein phosphatase 1 (PP1) [22,23]. Interestingly, HDAC6 also interacts with SIRT2 [24], a structurally unrelated cytoplasmic class III HDAC that also deacetylates α-tubulin. HDAC6 is thus a cytoplasmically localized protein that potentially regulates several cellular functions through deacetylase-dependent and/or -independent mechanisms (Table 1 and Figure 2). The following sections focus on the roles of HDAC6 in cellular processes in which the cytoskeleton plays an important part.

Cell morphology, adhesion and migration

Cell migration is necessary for developmental morphogenesis, immune surveillance, tissue repair and regeneration, and tumor metastasis. Although there is no single mechanism used by all cell types, most migrating cells are polarized through directed membrane-trafficking, and asymmetrical redistribution of the cytoskeleton and signaling molecules. Polarized cells show a 'leading edge' or frontal flat lamella, which is the site of protrusive activity and retrograde flow coupled to adhesion. Protrusive activity is largely dependent on directed actin polymerization and myosin activity, whereas the dependence of cell polarity on microtubule dynamics is seen only in some cell types. For example, fibroblasts and epithelial cells require an intact microtubule cytoskeleton so that they can migrate during wound healing; however, the intact microtubule cytoskeleton is not required for the motility and maintenance of directionality of faster cells, such as keratocytes or leukocytes.

A polarized migrating fibroblast has filopodia and a single leading edge at the advancing front. The microtubule-organizing center (MTOC) and the Golgi apparatus are oriented towards the direction of migration, and there is some capture and stabilization of microtubule plus-ends near the leading edge. This organization is thought principally to enable directed molecule and membrane vesicular transport, which is necessary for migration [25]. By contrast, leukocytes migrating along a chemotactic gradient show two clearly distinct morphological and functional poles: the leading edge, where chemokine receptors are concentrated and actin is actively polymerized; and the

Table 1. HDAC6 substrates, interacting proteins and related biological functions

Substrates	HDAC6-related function	Potential therapeutic target diseases
α-tubulin	Tubulin deacetylation	Antigen presentation deficiencies
	Regulation of immune synapse formation, HIV-1 viral infection	HIV-1 viral infection (AIDS)
	Cell migration and chemotaxis	Tumor cell metastasis (cancer)
Cortactin	Cortactin deacetylation	Biological disorders associated with actin-based cell migration
	Regulation of cellular migration and F-actin binding	
Hsp90	Hsp90 deacetylation	Neurodegenerative disorders
	Governs misfolded protein degradation and clearance, and regulates GR (Glucocorticoid Receptor) and gene transcription activation	
Interacting proteins		
p97 (VCP,Cdc48p)	AAA-ATPase in endoplasmic reticulum-associated proteosomal degradation	Neurodegenerative disorders
$p150^{glued}$ (dynactin)	Adaptor protein for the molecular motors dyneins and kinesins	
mDia2	Osteoclast maturation	Diseases related to deficiencies in bone formation, resorption and regeneration
Ubiquitin	Signal for cellular processes, such as protein degradation and endocytosis	Neurodegenerative disorders
PLAP	Phospholipase A2 activation protein controlling prostaglandin levels and phospholipase activity	
NF-κB (p50,65)	Transcription factor in inflammation and cell growth control	Gene expression-related deficiencies
Runx2	Transcription factor essential for skeletal development	
Sumoylated p300	Transcriptional co-regulator with lysine acetyltransferase activity	Gene expression-related deficiencies
PP1	Phosphatase, regulation of the interaction between PP1 and Akt	Deficiencies in cell migration and survival

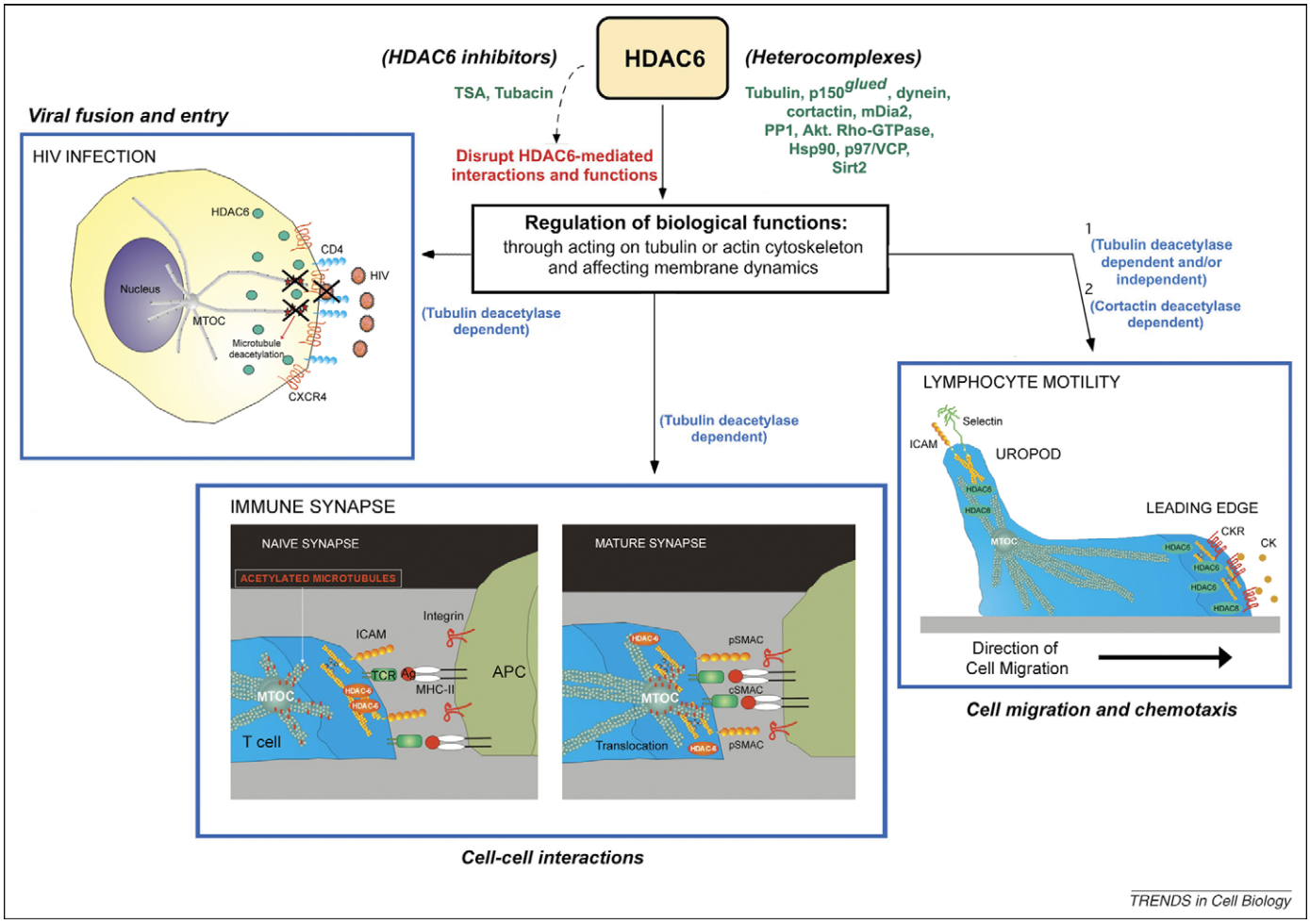

Figure 2. HDAC6 substrates, interacting proteins and biological functions. The scheme shows HDAC6 substrates and interacting proteins (indicated as heterocomplexes), such as tubulin, p120^{glued}, dynein, cortactin, mDia2, PP1, Akt, Rho-GTPase, Hsp90, p97 or VCP and Sirt2, and summarizes the most important immune functions regulated by HDAC6, such as HIV-1 viral fusion and infection, immune synapse formation, and lymphocyte chemotaxis. Dependence or independence on HDAC6-deacetylase activity is indicated. The figure also shows specific or broad-spectrum inhibitors (e.g. tubacin or trichostatin A [TSA], respectively) that prevent HDAC6 deacetylase activity, disrupt the interaction of HDAC6 with its substrates and interacting proteins, and impair its related biological functions. **(a)** HDAC6 is recruited to the HIV-1–cell contact areas and impairs viral-induced tubulin acetylation, which is required for efficient HIV-1 entry and infection. This impairment occurs without affecting distribution and expression of the CD4, CCR5 and CXCR4 viral receptors. **(b)** HDAC6-tubulin deacetylase activity regulates immune synapse formation and the associated intracellular signaling. HDAC6 translocates and concentrates at the contact site between the T cell and the antigen-presenting cell (APC). Overexpression of HDAC6 in T cells disorganizes the clusters of CD3 and the integrin LFA-1 (Lymphocyte function associated molecule-1) at the immune synapse. Inhibition by TSA reverts this effect. IL-2 production and the antigen-specific translocation of the microtubule organizing center (MTOC) were also severely compromised by overexpression of HDAC6. **(c)** HDAC6 relocates to the leading edge of migrating cells regulating cell motility in a tubulin-deacetylase- and/or cortactin-deacetylase-dependent manner, in the case of the non-chemotactic migration of fibroblasts, and independently of its deacetylase activity for chemokine-induced lymphocyte migration (i.e. chemotaxis). The effect of HDAC6 on cell migration does not appear to be related to an abnormal organization and function of the cell-surface molecules located at the leading edge or at the uropod of the migrating cell. Abbreviations: Ag, antigen; APC, antigen presenting cell; CK, chemokine; CKR, chemokine receptor; cSMAC, central supramolecular activation clusters; ICAM, intercellular adhesion molecule; MHC-II, major histocompatibility complex II; MTOC, microtubule organizing center; pSMAC, peripheral supramolecular activation clusters; TCR, T-cell receptor.

uropod, an actin-supported appendage at the trailing edge. The uropod contains the Golgi apparatus and is enriched both with actin-binding proteins belonging to the ezrin–radixin–moesin (ERM) family of proteins and with the adhesion receptors ICAM-1 (Intercellular Adhesion Molecule-1), ICAM-2, ICAM-3, PSGL-1 (P-selectin Glycoprotein ligand-1), CD43 and CD44 [26]. During cell migration, T lymphocytes retract their MTOCs to the uropod, where microtubules are packed in close bundles. Despite the fact that microtubules have been implicated in maintaining cell shape in other cell types [27,28], in T lymphocytes, the retraction of microtubules to the uropod neither confers structural support to this structure nor contributes actively to cell locomotion. However, the elongated uropod-bearing morphology seems to facilitate the cell plasticity required for transmigration through constricted spaces, such as those found in endothelial monolayers [29].

HDAC6 localizes to the motile, protrusive structures of polarized cells, including the leading edge and the uropod [30], and it participates in the formation of actin-dependent membrane structures such as ruffles and macropinosomes [31]. Moreover, activated T-cells show increased levels of acetylated microtubules around the MTOC, partially co-localizing with HDAC6. Whether this increased acetylation is required for microtubule retraction to the uropod or whether it occurs after this process is still an open question.

HDAC6 deacetylase activity-dependent and -independent functions in cell migration and morphology

Although the importance of microtubules for the establishment and maintenance of cell polarity is well established

[28,32,33], there are conflicting studies regarding the importance of HDAC6 deacetylase activity in cell migration [6,30,31]. In support of a role for deacetylase activity in this process, expression of *HDAC6*, but not a deacetylase-deficient mutant, increases migration of NIH 3T3 mouse fibroblasts, and selective inhibition of HDAC6 with TSA and/or tubacin inhibits fibroblast motility [4,8]. HDAC6 directly deacetylates cortactin, favoring its binding to F-actin and suggesting that HDAC6 additionally modulates NIH 3T3 motility through cortactin deacetylation [34].

In osteoclasts, HDAC6 acts as a component of the signaling pathway that regulates cell morphology and maturation [21]. The formation and stabilization of the podosome belt, a specialized structure involved in bone matrix resorption, requires microtubule acetylation, stimulated by RhoA-mediated inhibition of mDia, and the inhibition of HDAC6. The RhoA-effector mDia2 co-precipitates with HDAC6 and is able to activate its tubulin deacetylase activity in COS cells [21].

Interestingly, actin has recently been identified as a lysine-acetylated protein [35]; the identification of actin as a substrate of HDAC6 would open new avenues for understanding how this enzyme regulates cell morphology and migration.

Countering a role for the deacetylase activity of HDAC6, studies have shown that HDAC6 exerts several functional roles independently of its enzymatic activity, the promotion of lymphocyte migration and chemotaxis being a notable example [30]. In T cells, overexpression of a deacetylase-deficient HDAC6 mutant increases migration to the same extent as its wild type counterpart [30]. And, although the inactive tubacin analog niltubacin does not inhibit migration of NIH 3T3 fibroblasts [4], in T cells, niltubacin and another inactive analog, MAZ-1391, are as effective as the tubacin parent compound [30]. This effect is probably due to inhibition by these inactive compounds, of HDAC6-protein interactions, as has been suggested with other inhibitors [22,23].

The regulation of cell migration by HDAC6 thus appears to be cell type-specific and to involve cytoskeletal-related molecular interactions and intracellular signaling pathways dependent on, and distinct from, those mediated through tubulin deacetylation. One possible explanation is that HDAC6 functions as a scaffold in the rapid formation of molecular complexes required for lymphocyte chemotaxis, whereas fibroblast migration requires both this scaffold function and the deacetylase activity [30,31]. In support of this, a deacetylase-active HDAC6 mutant that is deficient in binding to ubiquitinylated proteins decreases mouse fibroblast migration to a similar extent as the deacetylase-deficient form does [31]. Expression of this HDAC6 molecule, which has a deleted BUZ (Binder of Ubiquitin Zn Finger) domain, might result in the loss of HDAC6 protein–protein interactions, and these observations suggest that deacetylase-independent and -dependent functions of HDAC6 are required for fibroblast migration.

Tumor cell invasion and metastasis

HDAC6 activity is associated with malignant transformation [36]. HDAC6 interacts with breast cancer metastasis suppressor 1 (BRMS1) [37], a molecule stabilized by Hsp90, which is itself regulated by HDAC6-mediated deacetylation. Hsp90 deacetylation destabilizes BRMS1 and decreases its metastasis suppressor activity as yet unknown mechanisms. Additionally, HDAC6 together with HDAC4 and HDAC8 act as essential epigenetic regulators of transforming growth factor (TGF)-β1-mediated neo-expression of smooth muscle α-actin (α-SMA), a cytoskeletal protein that enhances contractile activity and promotes fibrosis, tumor cell morphology, tissue healing and cancer development. The absence of HDAC4, HDAC6 or HDAC8 results in the synthesis of the TGF-interacting factor and TGFB-induced factor homeobox 2 proteins, which are repressors of TGF-β1 signaling during myofibroblastic differentiation [38].

HDCA6 might also be involved in angiogenesis. Chemical inhibition of this enzyme blocks endothelial cell growth and diminishes the expression of angiogenesis-related genes, such as *VEGF* (Vascular Endothelial Growth Factor) and *HIF-1α* (Hypoxia-Inducible Factor) [39]. Depletion of HDAC6 has a similar effect, and these findings thus point to the possible development of antitumoral therapies based on the specific inhibition of HDAC6 [39,40].

Immune- and pathogen-mediated cell–cell interactions

Besides being involved in cell adhesion and migration, the regulatory role of HDAC6 on tubulin cytoskeleton also appears to be involved in other important cell functions, such as intercellular interactions, and intracellular transport and trafficking.

Immune synapse

Upon interaction with an antigen-presenting cell (APC), T cells reorganize adhesion and signaling receptors in a highly segregated structure called the immune synapse [41]. In the immune synapse, the TCR (T Cell Receptor) and associated molecules congregate in the central area (i.e. the central supramolecular activation cluster [cSMAC]), whereas adhesion receptors reorganize in a surrounding external ring called the peripheral SMAC [41,42]. It has been proposed that the immune synapse regulates the balance between signal attenuation and T-cell activation [43,44]; and it has been suggested that, reciprocally, sustained T-cell activation is required for immune synapse organization and maintenance [43]. HDAC6 is important for the early and late events of T-cell activation. The profile of HDAC6 localization and activity during antigen-specific T-cell interactions with APC clearly indicates that the establishment of initial contacts activates HDAC6 and redistributes it from the cytosol to actin-rich membrane protrusions, with concentration of HDAC6 moving progressively from the central to the peripheral region of contact. The coincidence of early TCR-triggered signals and α-tubulin deacetylation at T cell–APC contacts strongly suggests a causal relationship between these phenomena and immune synapse formation. Chemical inhibition of HDAC6 facilitates the initial phase of synapse formation, without affecting receptor phosphorylation. Nevertheless, HDAC6 tubulin deacetylase activity favors the recruitment and retention of

phosphorylated CD3ζ at the microtubule cytoskeleton, which might negatively regulate T-cell activation by impairing both the redistribution of CD3 towards the cSMAC and the formation of a functional immune synapse in which the reorientation of the MTOC is defective [45]. A potential negative regulatory role for the cytoskeleton-associated TCR in T-cell activation has been proposed before [46]. The cytoskeletal anchorage of phosphorylated CD3ζ would uncouple the receptor from plasma membrane-associated signaling pathways required for full T-cell activation. In this regard, interleukin-2 (IL-2) secretion and synthesis is diminished in T cells overexpressing HDAC6 [45]. Although this effect seems to be mainly due to HDAC6 tubulin deacetylase activity and the inhibition of MTOC translocation, an effect on IL-2 gene transcription cannot be excluded. In addition, it is feasible that HDAC6 also regulates immune synapse by modulation of actin dynamic processes.

An additional role proposed for HDAC6 in the immune synapse involves association with the microtubule motor protein dynein. Concerted action of acetylated microtubules and motor proteins in T cells at the immune synapse area might generate sliding forces that move the MTOC towards the site of contact with the APC. Dynein, which is involved in the reorientation of the MTOC in fibroblasts [47], is localized at the cell–cell contact area of cognate T-cell–APC conjugates [48]. It is feasible that interaction between acetylated microtubules and dynein is required to translocate the MTOC and to organize CD3 in the immune synapse, and that this interaction is regulated by HDAC6. In support of this, it has been shown that, during microtubule-mediated transport, dynein associates with HDAC6 in other systems, such as the movement of ubiquitinated proteins along microtubule tracks towards aggresomes (see below) [49–51].

A recent study with *Hdac6* deficient mice reveals that they are viable, fertile and contain hyperacetylated tubulin and Hsp90. However, under homeostatic conditions, the absence of Hdac6 only moderately affected the immune response and bone development [52]. Further studies in *Hdac6* knockout mice of different disease models are required to understand the pathophysiologic role of HDAC6.

Viral infection

Several viruses, such as HIV-1 [53], induce acetylation of tubulin to enable efficient infection and spreading [54,55]. The molecular events underlying HIV-mediated target-cell fusion and entry require that each HIV-1-envelope viral (Env)–(gp120–gp41) interacts with multiple CD4 and CXCR4 or CCR5 cell-surface viral receptors and co-receptors [56]. This fusogenic activity of the Env–gp41 viral protein mediates lipid exchange between the HIV and plasma membrane lipid bilayers, producing a fusion pore at the viral–cell contact region. This pore enables entry of the viral genome into target cells [56,57]. However, it is only poorly understood how the dynamic state of the host plasma membrane regulates HIV-1 infection. Experimental evidence indicates that short cortical microtubules directly control membrane dynamics [58], and we have recently found that HDAC6 regulates HIV-1 infection [53]. By altering the acetylation status of cortical tubulin, HDAC6 overexpression inhibits, and HDAC6 silencing increases, HIV-1 viral infection. In addition, HDAC6 redistributes to the HIV-1-induced CXCR4-CD4 clustering areas at the cell surface of target cells during the first virus–cell interaction. This results in a reduction of the levels of acetylated α-tubulin at the HIV-1–cell contact regions [53]. It is therefore conceivable that the localization of acetylated microtubules at the plasma membrane, directed by HIV-1, enhances linkage between the plasma membrane and the cell cortex, thereby favoring the fusogenic activity of the Env–gp41 viral protein during pore fusion formation. This would also support a role for HDAC6 tubulin deacetylase activity in the regulation of plasma membrane dynamics.

Other studies support a role for HDAC6 in other viral infections. Pan-HDAC inhibitors enhance HTLV-1 (Human T cell Leukemia Virus Type 1)-*tax* gene expression in infected cells [59]. In addition, human herpes virus 8 (HHV-8) and herpes simplex virus 1 (HSV-1) are able to facilitate infection by stabilizing microtubules and inducing hyperacetylation [54,55]. Microtubules are also clearly implicated in the transport of HSV-1 capsids at the initial stage of infection [60,61]. Authors propose that the HSV-1 tegument protein VP22, a structural component that anchors to the viral capsid, mediates the association between the capsids and the tubulin cytoskeleton. They also suggest that VP22 further facilitates the trafficking of viral capsids inside target cells during HSV-1 viral entry, perhaps by stabilizing microtubule bundles, which are subsequently acetylated.

Misfolded-protein degradation and stress response

The main pathway for protein degradation is the ubiquitin proteasome system (UPS), a multiproteic proteolytic complex that degrades short-lived ubiquitin-marked proteins[0]. Other important degradation pathways include the aggresome and the macroautophagy–lysosome systems [62]. Accumulation of misfolded proteins, a consequence of UPS impairment, is cytotoxic and degenerative. In a *Drosophila* proteasome-inhibited model, overexpression of wild type HDAC6, but not deacetylase-deficient HDAC6, strongly suppresses the degenerative phenotype, indicating that HDAC6 deacetylase activity is required to suppress cytotoxicity. Accordingly, knockdown of endogenous HDAC6 increases tissue degeneration. When the UPS is overwhelmed, HADC6 can regulate toxicity by enhancing the macroautophagic system through microtubule- and dynein-mediated transport, ensuring delivery of autophagosomes to lysosomes [63].

The aggresome, a juxtanuclear inclusion body in which misfolded proteins are processed, is formed in conditions of proteasome deficiency. The ubiquitin-binding–ZnF (ZnF–UBP) of HDAC6 plays a crucial role in the clearance of cytotoxic aggregates of misfolded proteins [50]. Dynein motors carry and remove HDAC6-associated polyubiquitinated aggregates from the cytoplasm and relocate them in the aggresome. HADC6 thus acts as a linker between polyubiquitinated proteins and dynein motors. The deacetylase and ZnF–UBP domains of HDAC6 are both required for aggresome formation. In HDAC6-silenced cells, the

accumulation of ubiquitin-misfolded proteins leads to a two-fold higher level of apoptosis. The ability of HADC6 to promote accumulation of polyubiquitinated proteins is counteracted by the chaperone p97 (also known as VCP), which also binds to HDAC6 [51]. Binding by p97 controls the release of polyubiquitinated chains from HADC6 and thus regulates their turnover [20]. HADC6 is also concentrated in Lewy bodies in both Parkinson's disease and dementia with Lewy bodies [50].

In addition to enhancing dynein-mediated processes, microtubule acetylation also promotes motor kinesin-1 binding and transport to microtubules [64]. Augmented tubulin acetylation, which results from inhibition of HDAC6 with TSA, increases dynein and kinesin-1 binding to microtubules *in vivo* and enhances the intracellular transport of proteins such as BDNF (Brain-Derived Neurotrophic Factor). Conversely, impairment of α-tubulin lysine acetylation decreases recruitment of motor complexes and BDNF transport [65]. In Huntington's disease, microtubule-dependent transport is altered [66], and microtubule acetylation is reduced. Here, the different role of HDAC6 might be due to the polarized transport along microtubules – in this case kinesin-1 directs HDAC6 to the plus ends of acetylated microtubules [63–66]. It would be interesting to analyze the function of HDAC6 in this condition.

Beside its role in the degradation of misfolded protein, HDAC6 and dynein-microtubule-dependent transport also has an important function in cell protection. This is mediated through the formation of other highly dynamic cytoplasmic structures termed stress granules, in which protein translation is reversibly suppressed in response to environmental stress.

The ability to form stress granules is impaired in HADC6-deficient or TSA-inhibited cells. Nocodazole and the dynein ATPase inhibitors EHNA (Erythro-Hydroxynonyl-Adenine) and vanadate also inhibit stress granule formation, demonstrating that assembly and transport of stress granule components requires an intact microtubule network and dynein. Thus, HDAC6 unites acetylation, the microtubule network and the motor proteins, thereby providing the machinery for stress granule formation [67].

Conclusions

HDAC6, through its direct deacetylation of tubulin, cortactin and Hsp90, and also through its association with interacting partner proteins, modulates cellular response in several important phenomena, including immune synapse organization, viral infection, cell migration, and the transformation and degradation of misfolded proteins. Through its participation in the transport and clearance of misfolded proteins, HDAC6 activity is also associated with neurodegenerative disorders. HDAC6 is additionally involved in fibroblast migration, lymphocyte chemotaxis and transendothelial migration, which appear to be independent of the deacetylase activity of the enzyme. HDAC6 is thus a pivotal regulatory molecule in many key biological processes, and as such it makes an attractive target for the development of treatments for many diseases.

Acknowledgements

F.S.-M. is supported by grants BFU2005–08435/BMC, FIPSE (Fundación para la Investigación y Prevención del SIDA en España) 36289/02, Ayuda a la Investigación Básica 2002 (Fundación Juan March) and Fundación Lilly. A.V.-F. is supported by grants FIS-PI050995 (Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo, Spain), FIPSE 24661/07, FMM and IDT-TF-06/066 (Consejería de Industria, Comercio y Nuevas Tecnologías del Gobierno Autónomo de Canarias, Spain). J.M.S. is supported by grant PI070356 and a Contrato-Investigador FIS (Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo, Spain). The authors have no conflicting financial interests. Editorial support was provided by Simon Bartlett. Authors thank Dr M. Vicente-Manzanares for the original design of drawings in Figure 2. The CNIC is supported by the Spanish Ministry of Health and Consumer Affairs and the Pro-CNIC Foundation.

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