MOLECULAR ONCOLOGY 3 (2009) 321–338

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Review

Endocytic proteins in the regulation of nuclear signaling, transcription and tumorigenesis

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ARTICLE INFO

Article history:
Received 21 April 2009
Received in revised form
1 June 2009
Accepted 2 June 2009
Available online 11 June 2009

Keywords:
Endocytosis
Transcription
Tumorigenesis

ABSTRACT

Accumulating evidence argues that many proteins governing membrane sorting during endocytosis participate also in nuclear signaling and transcriptional regulation, mostly by modulating the activity of various nuclear factors. Some adaptors and accessory proteins acting in clathrin-mediated internalization, as well as endosomal sorting proteins can undergo nuclear translocation and affect gene expression directly, while for others the effects may be more indirect. Although it is often unclear to what extent the endocytic and nuclear functions are interrelated, several of such proteins are implicated in the regulation of cell proliferation and tumorigenesis, arguing that their dual-function nature may be of physiological importance.

1. Introduction

It is becoming widely accepted that endocytic internalization and trafficking can affect the intracellular signal transduction at various levels. As recognized early on, many plasma membrane receptors upon binding of their signaling ligands are internalized and targeted for lysosomal degradation, with endocytosis acting as one of signal-terminating factors. More recent studies demonstrated that in several cases signaling continues intracellularly after the internalization of ligand–receptor complexes into endosomal compartments and requires an active participation of the endocytic machinery for signal propagation. The proposal of endosomes as signaling compartments, initially postulated in the mid-nineties, has gained increasing experimental support in the last few years, and several examples of signaling originating from endosomes have been reviewed by Disanza et al. (2009). Finally, the least known and perhaps the most intriguing phenomenon linking endocytosis and signal transduction is the fact that a growing number of proteins involved in endocytosis are reported to undergo nucleocytoplasmic shuttling and/or interact with nuclear molecules involved in transcription or chromatin remodeling (Pilecka et al., 2007). It appears that certain endocytic proteins translocate to the nucleus in response to extracellular signals in order to exert a specific biological effect, thus serving as a vehicle of molecular communication between intracellular organelles. Still, in many cases it is, however, unclear to what extent the endocytic and nuclear functions are related or represent disparate tasks, so called moonlighting. It seems also that some endocytic proteins may affect transcription indirectly, by modulating certain signaling events in the cytoplasm. While

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doi:10.1016/j.molonc.2009.06.001

no comprehensive studies have been undertaken to investigate this phenomenon, available literature reports allow drafting an emerging picture of how endocytic proteins may be involved in various aspects of nuclear signaling.

In this review we will summarize the data describing alternative nuclear functions of proteins primarily involved in the process of clathrin-mediated endocytosis. With respect to their endocytic functions, these proteins can be divided into three subgroups:

(1) clathrin and clathrin adaptors that link cargo to the clathrin lattice (β-arrestin 1 and 2, Dab2, epsin 1, EPS15, Numb);
(2) accessory proteins required for clathrin coat assembly and formation of coated vesicles at the plasma membrane (Bin1/amphiphysin II, CALM, dynamin, endophilin, HIP1, intersectin, Nm23 proteins);
(3) endosomal proteins that reside on early and late endosomes and direct cargo traffic through endocytic compartments (APPL proteins, sorting nexins, members of ESCRT-0, -I, -II, -III complexes).

The main sites of action of these proteins within the endocytic pathway are depicted in Figure 1, while their endocytic and nuclear functions are summarized in Table 1. The details of their roles in endocytosis can be found elsewhere (Schmid and McMahon, 2007; Tanaka et al., 2008). Below we will review the known mechanisms of nuclear localization of selected endocytic proteins, followed by the description of their involvement in transcriptional regulation and chromatin remodeling processes. Finally, since many aspects of nuclear signaling by endocytic proteins are required for maintaining physiological homeostasis, we will focus on the examples of their aberrant functions that are connected to tumorigenesis.

2. Nuclear localization of endocytic proteins

An increasing number of proteins typically present on clathrin-coated vesicles and endosomes display the ability to relocalize to the cell nucleus. Importantly, these proteins associate with cellular membranes only peripherally and are essentially soluble, thus potentially able to act in various intracellular compartments, including the nucleus. Several examples of mechanisms whereby endocytic proteins enter and exit the nucleus were reviewed previously (Pilecka et al., 2007). These mechanisms are based on the presence of nuclear localization signal (NLS) and/or nuclear export signals (NES), or interaction with carrier proteins. The nuclear localization of endocytic proteins may be constitutive or induced, dependent on cell cycle or can represent a feature of certain splice variants or modified forms of a given protein.

2.1. *NLS-mediated nuclear import*

Active nuclear import through the nuclear pore complex is mediated by members of the importin family, which recognize different types of NLS within the sequence of a target protein. HIP1 is an example of endocytic protein with a classical NLS; ESCRT-III component CHMP1 contains bipartite nuclear localization signals; Dab2 and APPL2 contain potential NLSs (Pilecka et al., 2007). Bin1 has an NLS adjacent to its BAR domain, which is absent in the related molecule amphiphysin I.

2.2. *NES-mediated nuclear export*

Several endocytic proteins are actively exported from the nucleus with the help of exportin CRM1 (chromosomal region maintenance 1) that recognizes a leucine-rich NES within transported molecules. The action of CRM1 is blocked by an antifungal antibiotic leptomycin B (LMB), which causes nuclear accumulation of target proteins. Classical NES is present in the sequence of only few endocytic proteins, e.g. EPS15 or β-arrestin 2. Even though most of proteins associated with clathrin-coated pits appear to be excluded from the nucleus at steady-state, EPS15, epsin 1 and CALM become accumulated in the nucleus upon treatment with LMB (Hyman et al., 2000; Vecchi et al., 2001). However, LMB has little effect on the nuclear accumulation of APPL1 (our unpublished data).

2.3. *Nuclear localization dependent on carrier proteins*

There are known interactions between endocytic proteins and certain carrier proteins that deliver them to the cell nucleus. For example, sorting nexin 6 (SNX-6) is a vesicle trafficking protein that interacts with transforming growth factor-β (TGFβ) receptors and is delivered to the nucleus by Pim oncoproteins that are required for Abl-mediated cell transformation (Ishibashi et al., 2001). Binding to nuclear proteins AATF (Burgdorf et al., 2004), Daxx (Muromoto et al., 2004) and Rta (Chua et al., 2007) increases nuclear localization of TSG101, an ESCRT-I component. CALM directly interacts with a nuclear protein CATS (CALM interacting protein expressed in thymus and spleen), which increases the nuclear localization of CALM and of the leukemogenic fusion protein CALM/AF10 (Archangelo et al., 2006). Also, Numb becomes recruited to the nucleus by overexpressed HDM2 (mouse double minute 2 homolog) (Juven-Gershon et al., 1998).

2.4. *Inducible versus constitutive nuclear accumulation*

Interestingly, the shuttling of endocytic proteins may be either induced upon specific stimulation of the cell (e.g. β-arrestins, HIP1, APPL1, Nm23-H1) or constitutive (e.g. EPS15). β-Arrestin 1 translocates to the nucleus upon stimulation of κ- and δ-opioid receptors (Kang et al., 2005), while β-arrestin 2 translocates to the nucleus upon stimulation of hOR17-4 (Neuhaus et al., 2006). Nm23-H1, among different functions, appears also to act as a granzyme A-activated DNase translocating from the cytoplasm to the nucleus of a target cell soon after attack by cytotoxic T lymphocytes, in order to nick chromosomal DNA (Fan et al., 2003). HIP1 accumulates in the nucleus upon androgen stimulation (Mills et al., 2005). Translocation of APPL1 to the nucleus is induced in HeLa cells upon short treatment with epidermal growth factor (EGF) (Miaczynska et al., 2004) or in cultured adipocytes upon longer

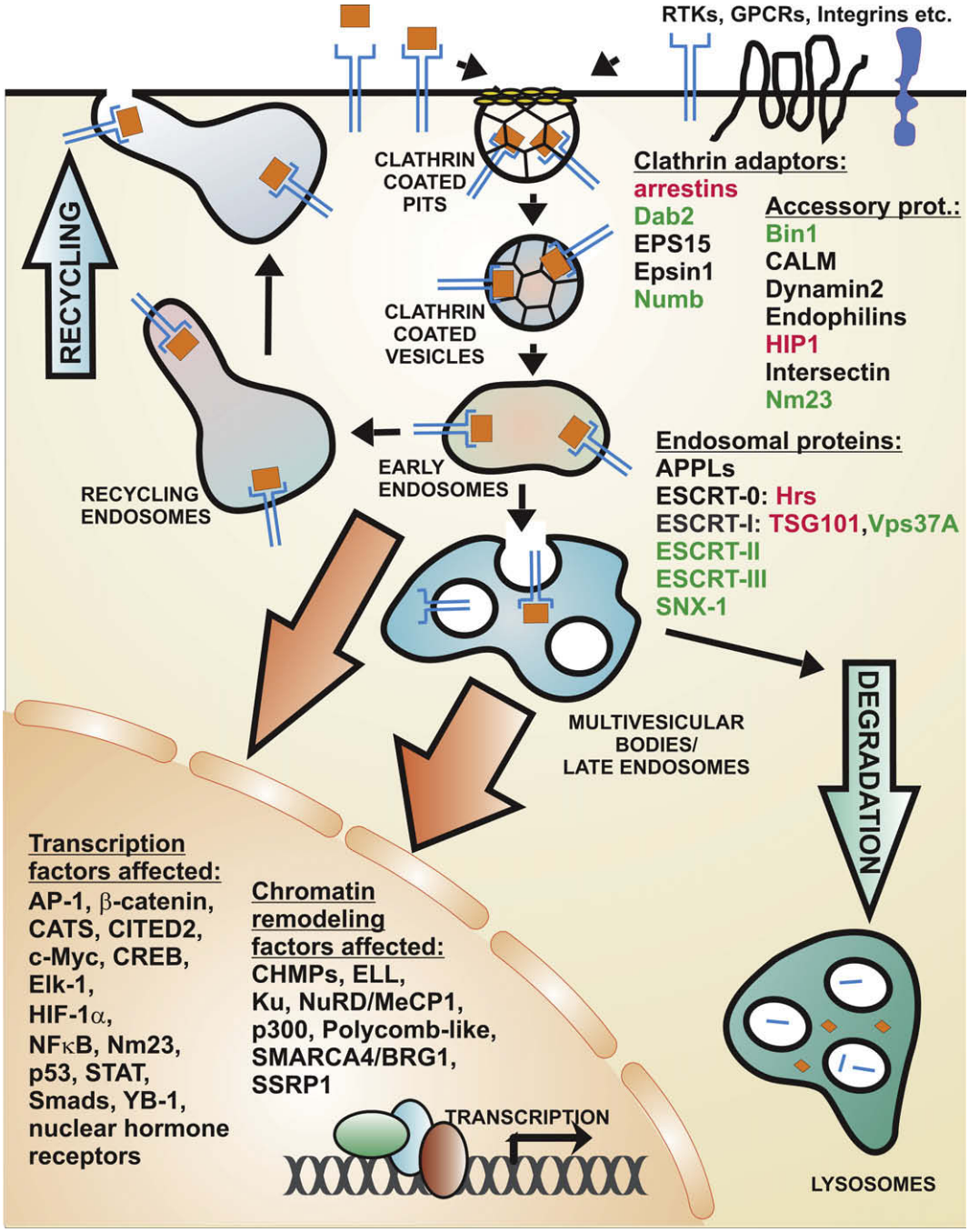

Figure 1 – The scheme depicting the major compartments of the endocytic pathway and selected endocytic proteins participating in the transmission of signaling to the nucleus, by affecting the transcription machinery and/or the chromatin-remodeling factors. Proteins with some oncogenic activities are shown in red, while proteins with known tumor-suppressive functions are marked in green. See text and Table 1 for detailed description. RTKs, receptor tyrosine kinases; GPCRs, G protein-coupled receptors.

treatment with insulin (Saito et al., 2007). However, these and other stimuli (UV, H_2O_2, heat shock) do not increase nuclear localization of EPS15 (Vecchi et al., 2001).

2.5. *Cell cycle-dependent nuclear translocation*

In some cases, the nuclear distribution is visible mainly during a particular stage of cell cycle. The cell cycle-dependent nuclear translocation was observed in the case of endocytic proteins regulating cell proliferation such as Dab2 or TSG101. Dab2 localizes to the nucleus of pre/postmitotic cells, while during interphase it is found in the cytoplasm (Mishra et al., 2002). TSG101 localizes on endosomes, in the cytoplasm and in the nucleus during interphase, and colocalizes with the mitotic apparatus during mitosis (Xie et al., 1998). It accumulates in the nucleus in G1 and S phases, while its expression level remains constant throughout the cell cycle (Zhong et al., 1998).

Table 1 – Functions of selected endocytic proteins in the cell nucleus and in cancer development and progression. See text for detailed description and references.

Protein	Endocytic function	Nuclear process affected	Role in cancer
β-Arrestins	Clathrin adaptors that modulate the desensitization and trafficking of GPCRs (G protein-coupled receptors).	• Inhibition of AP-1 and NF-κB transcriptional activity; • Inhibition of Elk-1-driven transcription due to impaired translocation of ERK2 to the nucleus.	• See below
β-Arrestin 1	Clathrin adaptor for GPCRs; see above.	• Recruitment of histone acetyltransferase p300 to CREB at the promoters of *c-fos* and *p27*, followed by an increase in acetylation of histone H4; • Negative regulation of STAT1 activation induced by interferon-γ.	• Induction of metastasis by overexpression of β-arrestin 1 in cells injected into nude mice.
β-Arrestin 2	Clathrin adaptor for GPCRs; see above.	• Regulation of gene expression after fertilization; • Negative regulation of NF-κB activation upon treatment with TNF-α, IL-1β or UV irradiation; • Stabilization of p53 by relocation of its negative regulator HDM2 from the nucleus to the cytoplasm; • Stimulation of activity of retinoic acid receptors.	• Enhanced migration of some types of cells *in vivo* in *β-arrestin* 2-deficient mice.
Bin1/amphiphysin II	A related amphiphysin I is an accessory protein in clathrin- and dynamin-dependent internalization. Both Bin1 and amhiphysin I contain BAR domains which participate in the generation and stabilization of membrane curvature.	• Inhibition of c-Myc-driven transcription; • Possible role in DNA repair and expression of telomeric heterochromatin by interaction with Ku proteins.	• Attenuation of wild-type Bin1 expression in many types of cancer; • Presence of tumor-specific splice variants with deficiencies in tumor suppressor activity in many types of cancer; • Bin1 loss-of-function causes lung and liver cancer formation and drives colon cancer progression in mouse models; • General cancer suppression due to inhibition of c-Myc oncogene activity; • Support of immune surveillance.
CALM (Clathrin Assembly Lymphoid Myeloid Leukemia Protein)	Accessory protein that promotes the formation of clathrin-coated vesicles by binding to both membrane lipids and endocytic components such as clathrin.	• Unknown - possibly related to CATS-dependent transcription.	• Chromosomal rearrangements in leukemias of various types, leading to fusion of *CALM* and transcription factor *AF10* gene.
Clathrin heavy chain (CHC)	Subunit of clathrin, a structural component of the clathrin coat formed on the plasma membrane pits containing internalized cargo.	• Recruitment of histone acetyltransferase p300 to *p53* and enhancement of p53-dependent transcription.	• Chromosomal rearrangements in anaplastic large-cell lymphoma and in inflammatory myofibroblastic tumor leading to fusion of *CHC* and *ALK* genes; • Chromosomal rearrangements in pediatric renal carcinoma leading to fusion of *CHC* and transcription factor *TFE3* gene.
Dab2 (Disabled homolog 2, also known as DOC-2)	Clathrin adaptor that links cargo (mainly receptors of low-density lipoproteins) with clathrin, AP2 complex and accessory proteins.	• Inhibition of AP-1 activation induced by TPA due to interaction with DIP1/2; • Enhancement of Smad-dependent transcription upon TGFβ treatment; • Negative regulation of the canonical Wnt pathway due to the stabilization of the β-catenin destruction complex; • Enhancement of the non-canonical Wnt pathway stimulated by Wnt-5A.	• Attenuation of Dab2 expression in many types of cancer as an early event in tumorigenesis; • Putative function of a tumor suppressor.

Table 1 (*continued*)

Protein	Endocytic function	Nuclear process affected	Role in cancer
Endophilins	Accessory proteins binding different endocytic proteins including dynamin; contain BAR domain.	• Interaction of endophilin 3 with MTA1 (component of the NuRD complex).	• Gene fusion resulting in a chimeric protein MLL-endophilin 2 with transforming activity, found in acute myeloid leukemia.
EPS15 (EGFR pathway substrate 15)	Clathrin adaptor stably associated with AP2 complex.	• Unknown - transcriptional activity detected in GAL4 reporter assays is dependent on DPF motifs of EPS15.	• Chromosomal rearrangements in leukemias of various types leading to fusion of *EPS15* and *MLL* genes and oncogenic conversion of MLL; • Increased expression of a closely related protein EPS15R in hepatocellular carcinoma.
ESCRT-0 (endosomal complex required for transport-0) composed of Hrs and STAM	Endosomal sorting proteins involved in biogenesis of multivesicular bodies; participate in sorting of ubiquitinated cargo proteins for degradation.	• Inhibition of STATs-dependent transcription by Hrs; • Enhancement of transcription induced by activin during embryonic development; • Negative regulation of cytokine-induced DNA synthesis by Hrs.	• Upregulation of Hrs expression in many types of cancer; • Positive regulation of cell proliferation, transformation and metastatic potential.
ESCRT-I, composed of TSG101, Vps28, Vps37 and Mvb12	Endosomal sorting proteins; as above under ESCRT-0.	• See: TSG101 below	• See: TSG101 below; • Downregulation of Vps37A in hepatocellular carcinoma; • Negative regulation of cell proliferation, transformation and invasion by Vps37A.
ESCRT-II, composed of EAPs (ELL-associated proteins) EAP20, EAP30 and EAP45	Endosomal sorting proteins; as above under ESCRT-0.	• Regulation of the inhibitory activity of the RNA polymerase II elongation factor ELL.	• Putative cancer suppression function attributed to the ability of ESCRT-II to mediate degradation of tumor-related receptors.
ESCRT-III, composed mainly of CHMPs 1-7 (chromatin-modifying proteins 1–7)	Endosomal sorting proteins; as above under ESCRT-0.	• Chromatin remodeling; • Stable gene silencing during development; • Stabilization of p53 transcription factor; • Potential function in the nuclear sumoylation machinery.	• Putative cancer suppression function; • Expression of CHMP1A reduced in pancreatic tumors.
HIP1 (Huntingtin Interacting Protein 1)	Accessory protein that binds to phosphatidylinositol lipids and to different endocytic proteins including clathrin and AP2 complex; regulates cytoskeletal dynamics by binding to actin.	• Activation of androgen receptor-driven transcription; • Enhancement of estrogen- and glucocorticoid receptors-driven transcription.	• Chromosomal rearrangements in chronic myelomonocytic leukemia leading to fusion of *HIP1* and *PDGFRβ* genes, with a fusion protein exhibiting transforming activity; • Upregulation of HIP1 expression in many types of cancer.
Nm23 (nonmetastatic cell proteins 23)	Accessory proteins, act as nucleoside diphosphate kinases (NDPKs) promoting GTP loading of dynamin; inhibit Rac1 signaling.	• Binding to *PDGF-A* gene promoter; • Positive regulation of expression of c-Myc and genes involved in myeloid-specific differentiation by Nm23-H2; • Association with estrogen receptors and modulation of estrogen-regulated gene transcription.	• Metastasis suppressor proteins; • Expression of Nm23-H1 lost in many tumors in advanced stages, however overexpression observed in early stages of cancer; • Inhibition of metastatic potential in xenografts of cells upon re-expression of Nm23-H1; • Higher incidence of metastasis of hepatocellular carcinoma cells to lung in knockout mice.
Numb	Clathrin adaptor that is trafficked with internalized receptors; interacts with EPS15 and α-Adaptin (component of AP2 complex).	• Inhibition of Notch-dependent signaling; • Stabilization of p53 transcription factor by binding to HDM2.	• Loss of Numb protein in breast cancer due to its extensive ubiquitination and proteasomal degradation; • Poor patient prognosis in case of Numb-negative breast tumors.

(*continued on next page*)

Table 1 (continued)

Protein	Endocytic function	Nuclear process affected	Role in cancer
Sorting nexins (SNX)	Endosomal sorting proteins containing a phospholipid-binding domain PX.	• Unknown – SNX-6 interacting with Pim oncoproteins in the nucleus.	• Attenuation of SNX-1 expression in colon cancer; • Possible role of SNX-6 in the regulation of hematopoietic cell transformation.
TSG101 (tumor susceptibility gene 101)	Endosomal protein, component of ESCRT-I complex.	• General transcriptional suppression in GAL4 assays; • Inhibition of the transcriptional activity of nuclear hormone receptor superfamily: estrogen, glucocorticoid, retinoic acid and thyroid hormone receptors; • Stabilization of the androgen receptor by preventing its polyubiquitination and enhancement of AR-driven transcription; • Positive regulation of the level of transcription factors: CITED2 and HIF-1α; • Negative regulation of p53 level by stabilization of HDM2; • Increases transactivating activity of Rta (transactivator of viral lytic genes).	• Upregulation of TSG101 expression in invasive breast cancer and ovarian cancer, correlating with poor patient prognosis; • Upregulation of TSG101 in papillary thyroid carcinomas and gastrointestinal stromal tumors; • Induction of malignant transformation by overexpression of TSG101 in mammary gland in transgenic mouse model; • Defective cell proliferation in knockout mice, leading to embryonic lethality.

2.6. *Nuclear localization of splicing variants or modified forms*

Several variants of a protein can originate from alternative splicing, some of which may be preferentially located in the nucleus or at the endosomal membranes, as demonstrated for Dab2 and Bin1. Alternative splicing generates three different Dab2 isoforms in humans: p96, p93 and p67. While p96 is localized to the plasma membrane, p67 localizes to the cytosol and nucleus and is proposed to function as a transcriptional activator (Cho et al., 2000). Normal and tumor cells vary with respect to the localization of different isoforms or conformations of Bin1 (Wechsler-Reya et al., 1997). In normal cells, Bin1 is predominantly nucleoplasmic but also present in punctate subnuclear domains. Conversely, in a panel of tumor cells expressing Bin1, it is mainly localized to the subnuclear compartment, and it is likely that only the nuclear isoforms of Bin1 have a function in tumor suppression (DuHadaway et al., 2003). Bin1 also plays a role in the differentiation process, as its overexpression accelerates, while antisense cDNA impairs differentiation of muscle cells (Wechsler-Reya et al., 1998). In undifferentiated C2C12 myoblasts Bin1 is localized exclusively in the nucleus, and the differentiation was correlated with the appearance of cytoplasmic isoforms (Wechsler-Reya et al., 1998). Finally, distinct forms of mammalian CHMP1 protein are found in the cytoplasmic and nuclear compartments. These are likely to represent differential post-translational modifications of CHMP1 (Stauffer et al., 2001).

3. Regulation of gene transcription by endocytic proteins

The most common nuclear function ascribed to endocytic proteins is their involvement in the regulation of gene expression. They may serve as transcriptional coactivators and corepressors, binding and/or regulating the activity of known transcription factors. Multiple protein–protein interaction domains present in many endocytic proteins can facilitate their incorporation into several multimolecular assemblies, including the transcriptional complexes built around DNA. Some endocytic proteins (EPS15, CALM (Vecchi et al., 2001), TSG101 (Sun et al., 1999) and Dab2 (Cho et al., 2000)) exhibit transcriptional activity in a GAL4-based transactivation assay. Most endocytic proteins appear to act at the regulatory step of transcription initiation, where transcription factors facilitate recognition of promoter-specific DNA sequences by RNA polymerases. The association of an endocytic protein with a transcription factor can affect the activity, stability, or localization of the latter. In rare cases endocytic proteins can bind to DNA and act themselves as transcription factors (e.g. Nm23 proteins, see below). In several instances, the observed transcriptional regulation exerted by endocytic proteins can also be attributed to more indirect mechanisms resulting from the fact that these proteins often modulate the activities of signaling cascade at various levels. Below we will describe the examples of clathrin adaptors, endocytic accessory proteins and endosomal proteins, which act as transcriptional regulators via direct or indirect mechanisms.

3.1. *Clathrin and clathrin adaptors*

Clathrin and adaptor protein complex AP2 are key components and main ‘‘pathway hubs’’ for clathrin-mediated internalization, exhibiting a large number of interactions with other cargo-specific adaptors and accessory proteins (Schmid and McMahon, 2007). These interactions are highly dynamic and coordinated in time to drive cargo recruitment, clathrin polymerization and vesicle formation. At many

stages of these processes multiple low affinity associations have to take place concomitantly. Their occurrence is facilitated by increased local concentrations of interacting partners due to the localized membrane recruitment and/or oligomerization of proteins. It is likely that the scaffolding abilities of clathrin and adaptors are exploited not only for building clathrin-coated vesicles but also for the formation of transcriptional complexes in the nucleus.

Approximately 5% of *clathrin heavy chain* (CHC) is present in the nuclei, but upon deletion of the trimerization domain of CHC its monomeric form accumulates predominantly in the nucleus (Ohmori et al., 2008). Nuclear fraction of CHC binds to the p53-responsive promoter and specifically enhances p53-dependent transactivation (Enari et al., 2006). Intriguingly, it is the monomeric clathrin that is sufficient for this activity, as it is able to recruit histone acetyltransferase p300 to p53 (Ohmori et al., 2008). Since the trimerization domain of CHC is not necessary for the transactivation of p53 target genes, and as CHC can either bind p53 or clathrin light chain, the transcriptional and endocytic functions of clathrin are mutually exclusive.

Several examples of *β-arrestins* acting as nuclear messengers influencing gene transcription have been recently reviewed (Ma and Pei, 2007). Upon stimulation of δ- and κ-opioid receptors (belonging to the family of seven-membrane-spanning G protein-coupled receptors; GPCRs), β-arrestin 1 binds to the promoter regions of the *c-fos* and *p27* genes, recruiting histone acetyltransferase p300 to the transcription factor CREB (Kang et al., 2005). This enhances specific acetylation of histone H4, leading to chromatin reorganization and increased gene expression. β-Arrestin 2 is translocated to the nucleus upon GPCR stimulation and is involved in the regulation of the early transcriptional events during fertilization (Neuhaus et al., 2006).

Several cases of more indirect involvement of β-arrestins in transcriptional regulation and/or nuclear signaling were also reported. One mechanism of action employed by β-arrestins is related to their ability to shuttle to and from the nucleus, typically resulting in redirection of their binding partners out of the nucleus. β-Arrestin 2 (but not β-arrestin 1) redistributes the pro-oncogenic ubiquitin ligase HDM2 and JNK3 (Jun N-terminal kinase 3) from the nucleus to the cytoplasm (Wang et al., 2003). While β-arrestins negatively regulate lipopolysaccharide-induced NF-κB activation, they positively affect ERK1/2 (extracellular signal-regulated kinase 1/2) activity and specific pro-inflammatory gene expression (Fan et al., 2007). β-Arrestin 2-dependent production of interleukin 6 (IL-6) has been associated with forming of a complex between β-arrestin 2, adaptor protein CARMA3, and lysophosphatidic acid receptors (Sun and Lin, 2008). β-Arrestin 1 promotes dephosphorylation of STAT1 (signal transducer and activator of transcription 1) by the phosphatase TC45, thus reducing gene transcription and antiviral responses induced by interferon-γ (Mo et al., 2008). Transcription factor STAT1 has been identified as one of many proteins binding β-arrestin 2 (Xiao et al., 2007). About 1/3 of the β-arrestin interactome consists of nucleic acid-binding proteins generally involved in transcription, translation and RNA processing (Xiao et al., 2007). Among others, these include histones, histone deacetylase 2 (HDAC2), transcription factors YB-1 and myocardin, and transcription regulatory proteins such as TIF 1B, Tho4, and BACH2. Such a large set of nuclear and cytoplasmic proteins interacting with β-arrestins argues for their broad and diverse roles in cell physiology.

With respect to transcription, the fusion of GAL4 DNA-binding domain with a *Dab2* short splice variant p67, and to a lesser extent with p96, displays intrinsic transcriptional activity. It is the proline-rich C-terminal region of Dab2, which plays an essential role in the transcriptional activation (Cho et al., 2000). Via its interactions with different signaling mediators, Dab2 participates in several pathways converging at the activation of specific transcription factors. It serves as a negative regulator of transcriptional complex AP-1, formed by c-Fos and c-Jun and associated with cell proliferation and tumorigenicity. In this case, both p96 and p67 forms of Dab2 can inhibit the AP-1 activity induced by TPA (12-O-tetradecanoylphorbol-13-acetate, activator of protein kinase C) measured in a luciferase reporter gene assay (Tseng et al., 1999). Stimulation by TPA results in a specific serine phosphorylation of the N-terminal domain of Dab2. Recruitment of DAB2IP (also known as DIP1/2, Ras GTPase-activating protein and putative prostate tumor suppressor) to phosphorylated Dab2 results in the suppression of protein kinase C-elicited Ras activation, block of mitogen-induced gene expression and growth inhibition of prostate cancer (Wang et al., 2002). The functional interaction between DIP1/2 and Dab2 is required for inhibition of AP-1-mediated gene transcription induced by TPA (Wang et al., 2002). Similarly, overexpression of DIP1/2 inhibits the serum response element (SRE) reporter gene activity downstream the Raf/MEK/ERK axis (Wang et al., 2002).

Dab2 also acts as a scaffolding adaptor affecting gene transcription downstream of a variety of cellular stimuli. It is implicated in the regulation of TGFβ and Wnt signaling pathways. Dab2 associates with the type I and type II TGFβ receptors and signal transducers Smad2 and Smad3 in a ligand-dependent manner (Hocevar et al., 2001). It is required for TGFβ-mediated Smad2 phosphorylation, Smad translocation to the nucleus and Smad-dependent transcriptional responses. In addition, Dab2 is involved in TGFβ-mediated activation of JNK kinase, which leads to the expression of fibronectin and increased cell motility (Hocevar et al., 2005). In the context of the Wnt pathway, overexpression of Dab2 increases JNK activation in a non-canonical pathway stimulated by Wnt-5A, while it negatively regulates a canonical Wnt signaling. Dab2 was found to stabilize the β-catenin destruction complex upon Wnt-3A stimulation through the interactions with Dvl-3 and Axin (Hocevar et al., 2003). Dab2 increases the half-life of Axin as it interferes with Axin binding to LRP5/6 co-receptor, thus preventing dephosphorylation and degradation of Axin (Jiang et al., 2008). Mouse embryonic fibroblasts deprived of Dab2 exhibit increased nuclear levels of β-catenin, and a higher basal and Wnt-induced reporter activity (Hocevar et al., 2003). In addition, Dab2 antagonizes androgen receptor-mediated cell growth in both normal and malignant prostatic epithelial cells. Via interaction with c-Src and suppression of its kinase activity, Dab2 causes inactivation of ERK and AKT proteins critical for proliferation and survival (Zhoul et al., 2005). Consistent with its putative role as an inhibitor of cell proliferation, knockdown of Dab2 results in increase in phosphorylated ERK1/2 (Diwakar et al., 2008). However, in cells treated with

albumin, which induces the MAP kinase pathway, Dab2 is required for activation of ERK1/2, and it is dispensable for secretion of TGFβ-1 (Diwakar et al., 2008).

EPS15 exhibits transcriptional activity in GAL4 reporter assays, which suggests a possible function as a direct transcriptional modulator. Using truncation mutants of EPS15, it was determined that the region containing DPF motifs is required for transactivation of the GAL4 promoter, and deletion of the C-terminal NES further increases the transcriptional activity (Vecchi et al., 2001).

Epsin 1 (EPS15 interactor) is involved in clathrin-mediated endocytosis via direct interactions with clathrin, the clathrin adaptor AP2 and EPS15. Epsin 1 binds the transcription factor promyelocytic leukemia zinc-finger protein (PLZF) (Hyman et al., 2000). PLZF is a transcriptional repressor and negative regulator of cell proliferation, implicated in the development and pathogenesis of acute promyelocytic leukemia. Epsin 1 itself is not active in GAL4-based transactivation assay (Vecchi et al., 2001).

It has been suggested that the well-known role of *Numb* as an inhibitor of Notch signaling, determining cell fate by asymmetrically partitioning at mitosis, is based on its endocytic activity (for further details, see the review by Fuerthauer and Gonzalez-Gaitan, 2009). An alternative function of Numb related to transcription regulation depends on its ability to prevent ubiquitination and degradation of p53 (Juven-Gershon et al., 1998). In this way Numb controls the p53 stability and enhances the p53-dependent transcriptional activity.

3.2. *Accessory proteins acting in clathrin-mediated endocytosis*

Accessory proteins, by their dynamically regulated interactions with clathrin, adaptors and/or between themselves, contribute to the formation of clathrin-coated vesicles at different stages (Schmid and McMahon, 2007). Their involvement in the transcriptional regulation can be direct by binding to DNA (Nm23 proteins) or indirect, resulting from associations with other molecules.

While the function of amphiphysin I in endocytosis has been extensively studied, such role for a related *Bin1/amphiphysin II* is not well characterized, although some Bin1 splice isoforms associate with endocytic complexes. Instead, this protein appears to participate in various aspects of nuclear physiology. Bin1 binds c-Myc oncogene, inhibiting Myc-mediated cell transformation and promoting apoptosis (DuHadaway et al., 2001; Sakamuro et al., 1996). Bin1 blocks Myc-dependent transcription of several genes and selectively suppresses transactivation of artificial promoters responsive to Myc/Max or GAL4-Myc. In addition, the GAL4-Bin1 fusion displays repressive function unrelated to histone deacetylases in a manner independent of the c-Myc binding domain (MBD) (Elliott et al., 1999). The BAR domain of Bin1 physically binds to Ku, a DNA end-binding protein that promotes telomere homeostasis and functions in apoptosis and DNA repair (Ramalingam et al., 2007). Studies on the yeast homologs of these proteins showed that Bin1 restricts the activity of Ku70 and Ku80 and suggested a possible participation of Bin1 in the processes of DNA repair and expression of telomeric heterochromatin (Ramalingam et al., 2007). The endocytic and nuclear functions of Bin1 are likely separated, as the ubiquitous nuclear isoforms lack sequences needed for targeting to clathrin-coated vesicles and do not affect endocytosis.

CALM protein is a ubiquitously expressed paralog of the neuronal clathrin assembly protein AP180. Besides its role in endocytosis, the transcriptional activity of CALM in a GAL4 reporter assay (Vecchi et al., 2001) has been discovered and attributed to the presence of a transcriptional activator domain (TAD) (Archangelo et al., 2006).

Dynamins are members of the GTPase family, required for coated vesicle formation. They assemble around the necks of clathrin-coated pits and participate in pinching off vesicles from the plasma membrane. Dynamins interact with multiple signaling molecules such as Grb2, c-Src, and ERK kinases. Overexpression of dynamin 2 (but not dynamin 1) activates the transcription factor p53 and induces apoptosis, leading to reduced cell proliferation, DNA fragmentation, and caspase-3 activation (Fish et al., 2000).

Intersectin is an accessory protein that interacts with dynamin through SH3 domains and with epsins through EH motifs. Overexpression of intersectin activates the transcription factor Elk-1 in the MAPK-independent manner (Adams et al., 2000). Moreover, intersectin stimulates the JNK-dependent pathway through its EH motifs (Mohney et al., 2003) and interacts with Ras exchange factor Sos via the SH3 domains (Tong et al., 2000). Interestingly, overexpression of a full-length intersectin is sufficient for the activation of Ras in the absence of added growth factors or serum. However, the SH3 domains of intersectin, when expressed alone, function in a dominant-negative manner, inhibiting Ras and decreasing activation of MAPK (Tong et al., 2000). Intersectin associates with an isoform of phosphatidylinositol 3-kinase, PI3 K-C2β, and enhances its basal and growth factor-stimulated activity, resulting in AKT activation (Das et al., 2007). Inducible expression of either full-length intersectin or the EH domain region is sufficient to induce transformation of NIH 3T3 fibroblasts (Adams et al., 2000). Conversely, a decreased expression of intersectin stimulates apoptosis in neuroblastoma cells and primary cortical neurons (Das et al., 2007).

It has been observed that upon androgen stimulation *HIP1* associates with androgen receptor (AR) and translocates to the nucleus where it binds to the promoters of androgen-responsive genes and coactivates their expression (Mills et al., 2005; Vecchi and Di Fiore, 2005). Interestingly, a mutation impairing binding of HIP1 to lipids and clathrin-coated pits appears to increase its cytosolic pool available for nuclear import and thus enhances its coregulatory effect on AR-dependent transcription. HIP1 stimulates transcription in a GAL4-based reporter assay and induces expression of luciferase from a promoter containing androgen-responsive elements (ARE) (Mills et al., 2005). In addition, HIP1 reduces the rate of AR degradation, which can potentially prolong the cellular responses to androgen. HIP1 also enhances transcriptional activity of other nuclear hormone receptors, such as estrogen and glucocorticoid receptors (Mills et al., 2005). The role of HIP1 in gene transcription and apoptosis has been summarized in a recent review (Bhattacharyya et al., 2008). Of interest, the interacting partner of HIP1, HIPPI, binds to specific upstream sequences of several caspase genes (caspase-1, -8 and -10) and induces their expression (Majumder et al., 2007). Several lines of evidence

demonstrate that HIP1 and HIPPI adaptor proteins mediate pro-apoptotic signaling (Bhattacharyya et al., 2008).

Members of a multifunctional *Nm23* family have not been typically considered as endocytic proteins; however, they are able to regulate a variety of cellular processes, including endocytosis, transcription and tumor metastasis. Nm23-H1 facilitates synaptic vesicle internalization occurring at nerve terminals (Krishnan et al., 2001), as well as endocytosis of E-cadherin and transferrin receptor during disassembly of adherens junctions in epithelial cells (Palacios et al., 2002). Meanwhile, Nm23-H2 was shown to translocate to the plasma membrane, colocalize with the agonist-stimulated thromboxane A2 receptor (a member of GPCR family) and regulate its internalization by promoting the inactivation of Rac1 signaling (Rochdi et al., 2004). With respect to the roles in transcription, Nm23-H2 has been reported to act as a transcription factor capable of regulating expression of c-Myc and other genes involved in myeloid-specific differentiation. Additionally, both Nm23-H1 and Nm23-H2 bind to nuclease-hypersensitive elements in the *platelet-derived growth factor A* (*PDGF-A*) gene promoter, correlating with either positive or negative transcriptional regulation (for more details see review by Postel et al., 2000). Recently, Nm23-H1 and Nm23-H2 have also been shown to alter the estrogen-induced gene transcription due to the interactions with estrogen receptors α and β, respectively (Curtis et al., 2007; Rayner et al., 2008). Nm23-H2 translocates to the nucleus upon treatment with estrogen, while Nm23-H1 was even demonstrated to associate with the promoter region of an estrogen-responsive *progesterone receptor* gene. Additionally, overexpression of Nm23-H2 protein exhibited a synergistic effect with estrogen treatment on the reduction of cell migration (Rayner et al., 2008).

3.3. *Endosomal proteins*

Four multiprotein complexes designed ESCRT-0, -I, -II and -III act sequentially in the process of sorting of ubiquitinated cargo proteins for degradation. Strikingly, the subunits of each ESCRT complex appear to have functions reaching beyond cargo sorting, including activities in the cell nucleus. The roles in transcriptional regulation were described for selected components of ESCRT-0 (Hrs, STAM), ESCRT-I (TSG101) and multiple ESCRT-II subunits (EAPs). In addition, the subunits of ESCRT-III (CHMPs) are implicated in chromatin remodeling processes. Of interest, mammalian ESCRT-II and -III components were identified first as nuclear proteins, before their role in endocytosis has been characterized based on the homology to the yeast counterparts.

Within *ESCRT-0* complex, a scaffold protein *Hrs* (hepatocyte growth factor-regulated tyrosine kinase substrate) interacts with *STAM* (signal-transducing adaptor molecule), which binds JAK2/3 kinases involved in the induction of c-Myc, c-Fos, and DNA synthesis upon stimulation with interleukin 2 and granulocyte–macrophage colony-stimulating factor (Asao et al., 1997). Hrs counteracts the activity of STAM, as it negatively regulates DNA synthesis mediated by the cytokines. Hrs interacts also with the neurofibromatosis-2 tumor suppressor protein schwannomin/merlin, and both proteins can inhibit activation of STATs (Scoles et al., 2000). Hrs reduces the activation of STAT1- and STAT3-responsive luciferase reporters in a dosage-dependent manner (Scoles et al., 2002). Overexpression of Hrs reduces cell proliferation and anchorage-independent growth (Gutmann et al., 2001). In addition, Hrs plays a critical role in the efficient association of Smad2 to the activin receptor through cooperation with an FYVE domain-containing protein SARA (Smad anchor for receptor activation). Transfection of Hrs induces luciferase reporter gene activity in assays performed with activin-responsive p3TP-Lux and pARE-Lux plasmids (Miura et al., 2000). Mutant Hrs lacking the C-terminal half causes decreased responses to stimulation by activin and TGFβ, leading to defective embryonic development (Miura et al., 2000).

ESCRT-I component *TSG101* is a transcriptional inhibitor in the GAL4 assay, and it suppresses the basal activity of several tested promoters: thymidine kinase, rabbit β-globin, and large T antigen of simian virus 40 (SV40) promoters (Watanabe et al., 1998). It also inhibits the transcriptional activity of nuclear hormone receptor superfamily, including receptors for estrogen, androgen, glucocorticoid, vitamin D, retinoic acid, and thyroid hormone (Hittelman et al., 1999; Sun et al., 1999; Watanabe et al., 1998). Structurally, it is the leucine-zipper motif in the coiled–coil region within the C-terminal part of TSG101 which is required for its activity as a general transcriptional suppressor (Li and Cohen, 1996). Conversely, the N-terminal part fused to GAL4 DNA-binding domain activates transcription (Sun et al., 1999). This region of TSG101 contains UEV domain (homologous to the ubiquitin-conjugating enzyme domain) and is required for efficient activation of androgen receptor-mediated transcription (Burgdorf et al., 2004). In addition, TSG101 interacts with apoptosis-antagonizing transcription factor (AATF, also termed Che-1), which is transcriptional coactivator of steroid hormone receptors involved also in DNA damage response, cell-cycle checkpoint control and growth arrest (Passananti et al., 2007). Overexpressed AATF is able to recruit TSG101 to the nucleus, and both proteins cooperatively enhance androgen receptor-mediated transcription. The mechanism of observed activation is indirect, as TSG101 seems to prevent polyubiquitination of the receptor, thereby locking it in the monoubiquitinated form that is transcriptionally active (Burgdorf et al., 2004). Interestingly, TSG101 knockdown suppresses the expression of two transcription factors regulating cell growth and survival: CITED2 (CBP/p300-interacting transactivator with ED-rich tail 2) and HIF-1α (hypoxia-inducible factor). Accordingly, TSG101 is important for transcriptional activation of HIF-1α (Young et al., 2007a).

Homozygous *TSG101*$^{-/-}$ mouse embryos die at day E6.5 and display decreased proliferation, elevated p53 protein level and increased transcription of a p53 effector, the cyclin-dependent kinase inhibitor p21 (Ruland et al., 2001). The downregulation of p53 and stimulation of cell cycle by TSG101 can be explained by its ability to stabilize HDM2, the negative regulator of p53 (Li et al., 2001). Interactions between TSG101 and HDM2 represent a feedback control loop, since elevation of HDM2 promotes proteolysis of TSG101 (Li et al., 2001). However, other studies showed that the deletion of TSG101 had no effect on HDM2 steady-state levels and function, thus the activation of a p21-mediated G1 arrest might be an indirect effect of TSG101 deficiency on other cellular processes that subsequently trigger stress response pathways (Carstens et al., 2004).

The components of *ESCRT-II* complex can affect expression of certain genes by controlling the rate of promoter-specific initiation of transcription. Subunits of mammalian ESCRT-II have been initially referred to as the ELL-associated proteins (*EAPs*). ELL binds to RNA polymerase II (Pol II) and increases the rate of the transcriptional elongation by suppressing transient pausing at multiple sites along the DNA. It also acts as a negative regulator of polymerase activity by inhibiting promoter-specific initiation of transcription by Pol II. ELL forms a stable complex with three subunits of ESCRT-II: EAP20/hVps25, EAP30/hVps22/hSnf8, and EAP45/hVps36/hVac3 (Shilatifard, 1998). Such heterotetramer increases the catalytic rate of transcription elongation *in vitro*, since binding of EAPs suppresses the transcriptional inhibitory activity of ELL (Kamura et al., 2001; Shilatifard, 1998).

4. Regulation of chromatin remodeling by endocytic proteins

Endocytic proteins may regulate chromatin remodeling, which allows initiation of transcription by ''loosening'' nucleosomes, permitting the entry of DNA-binding transactivators, RNA polymerase II and the basal transcription machinery to the regulatory regions of the promoters. The examples of proteins, which bind to chromatin remodeling complexes are: ESCRT-III complex, APPL1/2 proteins and potentially endophilin 3.

The name of mammalian *ESCRT-III subunits* (*CHMPs*) can interchangeably stand for charged multivesicular body proteins or chromatin-modifying proteins. In a systematic screen for human CHMP protein partners, 19 out of 45 novel interactions involved nucleus-related proteins (Tsang et al., 2006). CHMP1 (mammalian Vps46) controls chromatin structure and cell-cycle progression (Stauffer et al., 2001). It is distributed both in the cytoplasm and in the nucleus: while the cytoplasmic CHMP1 is represented by a single 32 kDa protein, the post-translationally modified 35 kDa form of CHMP1 is associated with the nuclear matrix. Overexpressed CHMP1 is distributed within distinct subnuclear regions colocalizing with nuclease-resistant condensed chromatin. It has been proposed that CHMP1 plays a role in mitotic chromosome condensation, acting at a transition zone between active and inactive chromatin domains. Exogenous CHMP1 decreases mitotic index and BrdU incorporation, inhibiting the transit of cells through the S-phase without increase in apoptosis (Stauffer et al., 2001). CHMP1A positively regulates the p53 signaling pathway, as its overexpression leads to the accumulation of p53 and phospho-p53 (Li et al., 2008). Moreover, CHMP1 binds to Polycomblike protein BMI1 that, together with other members of the Polycomb group (PcG), maintains the chromatin condensation and gene silencing during development. In turn, CHMP1B and CHMP5 bind to proteins involved in chromatin remodeling: SSRP1 and SMARCA4/BRG1, respectively. Several CHMP proteins participate in a network involved in nuclear sumoylation process, binding to SUMO conjugating enzyme UBE2I, E3 SUMO ligase PIAS2, and HIPK2 (Tsang et al., 2006). HIPK2 is a nuclear protein kinase that acts as a corepressor for homeodomain transcription factors, and its sumoylation is involved in the DNA damage-induced transcriptional silencing (Roscic et al., 2006).

APPL proteins (adaptor proteins containing PH domain, PTB domain and leucine-zipper motif) are nuclear-shuttling adaptors that bind Rab5, AKT2, and other signaling molecules and receptors. APPL1 and APPL2 bind to nucleosome remodeling and histone deacetylase complex NuRD/MeCP1 (Miaczynska et al., 2004). Six out of ten components of the complex were identified in APPL1 immunoprecipitates from HeLa nuclear fraction: PID/MTA2 (metastasis-associated gene 2), p66, HDAC1 and/or HDAC2, RbAp46, RbAp48, and MBD3 (methyl-CpG-binding domain protein 3) (Miaczynska et al., 2004). The NuRD complex acts as a repressor of gene expression by remodeling and deacetylating methylated nucleosomes (Feng and Zhang, 2001). Another example of transcriptional regulation by APPL1 is its involvement in the suppression of androgen receptor transactivation via enhancing AKT activity (Yang et al., 2003). Moreover, APPL1 and APPL2 have been recently identified as positive regulators of β-catenin/TCF-dependent transcription in the canonical Wnt signaling via interactions with a transcriptional repressor Reptin (Rashid et al., 2009).

Endophilin 3 has been shown to directly interact with MTA1 (metastasis-associated protein 1), which also can be a part of the NuRD complex (Aramaki et al., 2005). The functional implications of this interaction are presently not known.

5. Roles of endocytic proteins in tumorigenesis

Interestingly, most of endocytic proteins described above appear to be implicated in various aspects of tumorigenesis. A potential role of a particular protein in cancer formation and progression can be evaluated based on frequent alterations of its gene expression found in human tumors. Such changes can include either attenuation of gene expression by homozygous deletions or promoter methylation, or enhancement of its expression by gene amplifications. The rearrangement of chromosomes leading to fusion between two genes, nucleotide sequence aberrations or alternative splicing may produce alterations that can facilitate tumor formation. It is worth mentioning that such changes arising during tumorigenesis may provide a selective advantage to tumor cells or have no net effect on tumor growth. Therefore the genetic studies with transgenic or knockout animals are needed to finally confirm a potential role of a particular protein in tumorigenesis. Table 1 summarizes known cancer-related roles for several proteins with both endocytic and nuclear functions. Below we describe in detail those of endocytic proteins, which were reported to undergo genetic aberrations in human cancers and/or to exhibit tumor-related effects in animal models. It is important to mention that some of these proteins' oncogenic or tumor suppressive functions may not depend on the endocytic activities and in several cases the exact relationships between these roles are unknown.

5.1. *Proteins with tumor suppressive activities*

An alternative clathrin adaptor *Dab2* is a putative tumor suppressor protein underexpressed in human cancers of ovaries

(Yang et al., 2002), prostate (Tseng et al., 1998), breast (Wang et al., 2001), colon (Kleeff et al., 2002), in metastatic pancreatic cancer (Huang et al., 2001) and bladder cancer, including mouse models of bladder carcinomas (Karam et al., 2007). In ovarian carcinoma, colon and bladder cancers as well as in esophageal squamous cell carcinoma (Anupam et al., 2006), the loss of Dab2 seems to be an early event in tumorigenesis. At least in case of hepatocellular carcinoma (HCC) the loss of Dab2 expression correlates with the aberrant methylation in its promoter region and is associated with poor patient prognosis (Calvisi et al., 2007). However, in breast cancer the loss of Dab2 protein expression is not accompanied by promoter methylation but likely results from miRNA action (Bagadi et al., 2007). The tumor suppressor activity of Dab2 seems to be dependent on its ability either to inhibit the Ras-mediated mitogenic stimulation via interaction with Grb2 (Zhou and Hsieh, 2001), or to negatively regulate integrin-linked kinase (ILK) and c-Src (Wang et al., 2001; Zhou et al., 2003), or to inhibit canonical Wnt/β-catenin-mediated signaling due to an interaction with and stabilization of Axin (Hocevar et al., 2003; Jiang et al., 2008). In epithelial cells Dab2 also regulates adhesion to the basement membrane and cell positioning (Sheng et al., 2000). Loss of Dab2 expression appears to contribute to the uncontrolled proliferation in ovarian and breast carcinomas and its re-expression in Dab2-negative epithelial tumor cells results in cell death.

Another alternative clathrin adaptor with an anti-oncogenic activity is *Numb*, which functions as a known modulator of Notch signaling pathway (for details see the review by Fuerthauer and Gonzalez-Gaitan, 2009). The Notch receptor may act as an oncogene or a tumor suppressor, depending on the cellular context (Radtke and Raj, 2003). For example, increased Notch signaling promotes the rapid development of poorly differentiated adenocarcinomas (Gallahan et al., 1996), on the other hand it also functions as a tumor suppressor in mouse skin (Nicolas et al., 2003). Although genetic lesions of the *Notch* locus itself are not very common in human tumors, in ~50% of mammary carcinomas an increased proteosomal degradation of Numb leads to the loss of Numb-mediated negative regulation of Notch signaling (Pece et al., 2004). Lack of Numb protein results in two important cancer-related effects: (i) an activation of the receptor Notch, which influences the proliferative/differentiative balance in mammary cells (Pece et al., 2004) and (ii) a destabilization of a tumor suppressor p53 followed by increased chemoresistance, one of the features of cancer cells (Colaluca et al., 2008). Numb-negative breast tumors display poor prognosis (Colaluca et al., 2008) and an ectopic expression of Numb in these tumor cells inhibits their proliferation (Pece et al., 2004).

Among endocytic accessory proteins, frequent attenuations of wild-type *Bin1* gene expression have been detected in different types of cancer (breast, prostate, brain, colon, skin and lung; summarized in recent reviews: Prendergast et al., 2009; Ren et al., 2006) suggesting a potential role of Bin1 in cancer suppression. Moreover, tumor cells seem to accumulate specific splicing isoforms of Bin1, which are exclusively cytosolic (Ge et al., 1999). The characteristic features of these isoforms are deficiencies in tumor suppressor activities, in Myc binding (Pineda-Lucena et al., 2005) and in the activation of cell death in transformed cells. The genetic ablation studies in a mouse model established that Bin1 loss-of-function is sufficient to cause lung and liver cancer and to drive colon cancer progression (Prendergast et al., 2009). The tumor suppressor function of Bin1 is clearly related to its ability to bind and inhibit the cell transforming activity of c-Myc oncoprotein (Chang et al., 2007). *Bin1* inactivation was also shown to cooperate with Ras and drive invasive tumors in mice (Chang et al., 2007). Interestingly, *Bin1* loss also facilitates immune escape due to an increased expression of indoleamine 2,3-dioxygenase (IDO), a potent T-cell suppressor that is frequently overexpressed in human tumors where it contributes to immune tolerance (Munn and Mellor, 2007). Since Bin1 supports immune surveillance by restricting IDO, a positive selection would exist for cells that have attenuated Bin1 and elevated IDO levels. In this way the immune escape of cancer cells and tumor progression could be facilitated (Prendergast et al., 2009).

The deletion of a closely related gene *Bin3* causes an increased incidence of lymphomas in aging animals, as investigated in *Bin3* knockout mouse (Ramalingam et al., 2008). A higher incidence of lung cancer upon treatment of *Bin3*-null mice with carcinogens was reported as well. Moreover, the primary cells isolated from those mice and transformed by Ras and the SV40T antigen showed an increased proliferation and motility comparing to cells isolated from the wild-type animals (Ramalingam et al., 2008). IDO expression also appears to be elevated as a result of *Bin3* loss (Prendergast et al., 2009).

With respect to the multifunctional proteins Nm23, overexpression of *Nm23-H1* is linked to early stages of cancer and a loss of its expression to more advanced stages, respectively (for review see Hartsough and Steeg, 2000). Low levels of the Nm23-H1 expression increase the metastatic potential of a variety of tumor types and transfected cells. Re-expression of Nm23-H1 in metastatic cell lines can inhibit metastasis in the xenograft models and reduce cell motility *in vitro* without affecting proliferation (Kantor et al., 1993). The *Nm23-M1* (the mouse H1 counterpart) knockout mice when challenged to form hepatocellular carcinoma, showed higher incidence of metastasis to lung than wild-type mice with this type of cancer (Boissan et al., 2005), confirming that Nm23-H1 is mainly a metastasis suppressor protein.

Among endosomal proteins, the downregulation of *sorting nexin 1* (*SNX-1*) mRNA and protein has been observed in colon cancer (Nguyen et al., 2006). The depletion of SNX-1 in colon cancer cell lines correlated with higher activation of EGFR signaling in response to EGF, increased proliferation, decreased apoptosis and lower susceptibility to anoikis (Nguyen et al., 2006). Overexpression of SNX-1 reduced the amount of EGFR on the cell surface as a result of enhanced rates of constitutive and ligand-induced degradation (Kurten et al., 1996). Therefore most likely the putative tumor suppressor function of SNX-1 is strictly dependent on its role in targeting for degradation multiple receptor kinases, which are SNX-1 binding partners.

It became apparent that dysregulation of *ESCRT* proteins results not only in defects in vesicular transport, receptor trafficking and turnover, but is also involved in the development of many types of cancer. The regulation of tumorigenesis by ESCRT proteins is achieved in various ways, either dependent

on endocytic transport/sorting or exploiting non-endosomal functions of ESCRT subunits. First of all, ESCRT proteins acting as endosomal sorting machinery regulate targeting of tumor-related receptors for lysosomal degradation. Upon ESCRT inhibition, these receptors (e.g. EGFR, c-Met or Notch) exhibit retarded degradation, enhanced recycling and sustained signaling resulting in a transforming activity. In this context, the components of the ESCRT complexes can be considered as tumor suppressors, initially discovered in *Drosophila* and reviewed in detail by Vaccari and Bilder (2009). Consistent with this hypothesis, in mammalian cells *Vps37A* (member of ESCRT-I complex) plays a role in suppression of cell proliferation, transformation and invasion, while downregulation of its expression has been found in hepatocellular carcinoma (Xu et al., 2003). *CHMP1A* (member of ESCRT-III complex) was shown to be expressed at reduced levels and/or mis-localized in pancreatic tumors (Li et al., 2008). Stable overexpression of CHMP1A in human pancreatic tumor cells inhibits their growth and ability to form tumors in a xenograft model. Depletion of CHMP1A using RNA interference in HEK293T cells results in an increase of anchorage-independent growth in soft agar assay and of tumor formation in xenograft models (Li et al., 2008).

5.2. *Proteins with pro-oncogenic activities*

In contrast to the *ESCRT* subunits described in the previous paragraph, some other members of ESCRT complexes may also exhibit pro-oncogenic activities in mammalian cells. For example, ESCRT-0 component *Hrs* increases the malignancy of cells just by positive regulation of E-cadherin degradation. The loss of E-cadherin function by internalization and degradation is required for the epithelial-to-mesenchymal transition, an essential step in epithelial tumor progression. Consistent with the pro-oncogenic activity of Hrs, its increased expression was observed in many types of tumors while its depletion resulted in an attenuation of cell proliferation and induced transformation and metastatic potential (Toyoshima et al., 2007). The best examples of endosomal sorting-independent function of ESCRT in the regulation of tumorigenesis come from the observation that both *Alix* (ESCRT-related protein) and *TSG101* (member of ESCRT-I complex) participate in the final steps of cytokinesis, therefore their depletion results in multinuclear cells predisposed to develop aneuploidy and malignancy (Morita et al., 2007). Despite the initial indications of TSG101 playing a role in tumor suppression, the genetic experiments in knockout mice did not confirm this hypothesis (see the review by Vaccari and Bilder, 2009 for an explanation of this apparent controversy). Instead, cells deficient in *TSG101* exhibit cell-cycle arrest and cell death partially due to accumulation of p53 (Carstens et al., 2004), which is negatively regulated by TSG101 (Li et al., 2001). Furthermore, *TSG101* silencing induces the accumulation of p21 tumor suppressor protein due to a p53-independent transcriptional activation of the *p21* gene (Young et al., 2007b). ChIP assay with a TSG101-specific antibody revealed the binding of this protein to the *p21* promoter in SKOV-3 ovarian cancer cells (Young et al., 2007b). In the view of these studies, it may not be surprising that elevated levels of TSG101 are associated with poor prognosis in ovarian carcinomas, as TSG101 seems to contribute to cancer aggressiveness by a negative regulation of p21. In support of the hypothesis that TSG101 in mammalian cells possesses rather some oncogenic properties, its overexpression in the developing mammary gland causes malignant transformation in aging transgenic animals (Oh et al., 2007). Its upregulation was also found in several types of human cancer samples (including invasive breast and ovarian cancers, papillary thyroid carcinomas and gastrointestinal stromal tumors; for review see Stuffers et al., 2009).

In addition to endosomal sorting proteins, also some clathrin adaptors and accessory endocytic proteins can exhibit pro-oncogenic activities. Numerous cancer-related studies have recently focused on the stimulating role of *β-arrestins* in the regulation of cell migration and chemotaxis *in vitro* (Buchanan and DuBois, 2006). Furthermore, the impact of β-arrestin 2 on cell migration *in vivo* was clearly established by genetic ablation studies in mice. Owing to the nature of β-arrestin functions, which involve the regulation of activated GPCRs, mice lacking β-arrestins often look completely normal until exposed to a stimulus causing receptor activation. Some examples of such studies have shown that chemokine-mediated $CD4^+$ T-cell migration (Walker et al., 2003), as well as CXCL12-mediated splenocyte migration (Fong et al., 2002) was impaired in *β-arrestin 2*-deficient mice. Moreover, a constitutive overexpression of wild-type β-arrestin 1 induced metastatic phenotype in cells injected intra-splenically into nude mice (Buchanan et al., 2006). These observations highlight the possible links between β-arrestin's function and cancer development and progression. Such connections are also indicated by the fact that β-arrestins are modulators of Wnt (Chen et al., 2003) and Notch (Mukherjee et al., 2005) signaling pathways, implicated in the regulation of early development as well as tumor growth.

The relationship between *HIP1* and cancer was first reported in genetic studies of patients with chronic myelomonocytic leukemia (Ross et al., 1998). Gene translocation in those patients resulted in a fusion of the *HIP1* gene and the *platelet-derived growth factor receptor β* (*PDGFRβ*) gene. The fusion protein showed the transforming activity in mouse hematopoietic cell line and the induction of cytokine-independent growth (Ross et al., 1998). HIP1 was also found to be overexpressed in prostate and colorectum cancers (Rao et al., 2002), breast carcinoma (Rao et al., 2003), brain cancer (Bradley et al., 2007a) and lymphoid malignancies (Bradley et al., 2007b). The oncogenic activity of HIP1 was postulated to be dependent on its ability to associate with the androgen receptor and to positively regulate androgen-induced signaling in prostate tumorigenesis (Mills et al., 2005). Moreover, HIP1-transformed epithelial cells upregulate many membrane receptors, like EGFR. Therefore tumor formation promoted by elevated levels of HIP1 might be also dependent on general alterations in receptor trafficking (Rao et al., 2003). In addition, by direct interactions with EGFR, HIP1 upregulates or maintains the overexpression of this receptor in brain tumors (Bradley et al., 2007a).

5.3. *The genes undergoing chromosomal rearrangements in tumors*

Chromosomal translocations creating abnormal fusion genes are commonly observed in different types of tumors,

particularly in lymphomas. Interestingly, such fusions appear to involve also some other endocytic proteins in addition to HIP1 mentioned above.

CHC gene was found in fusion to tyrosine kinase *ALK* gene (anaplastic lymphoma kinase) due to the chromosomal rearrangements appearing in anaplastic large-cell lymphoma as well as in inflammatory myofibroblastic tumor (IMT) (Bridge et al., 2001). In pediatric renal adenocarcinoma the rearrangements of transcription factor *TFE3* gene, leading to different types of fusions, were observed. *CHC* gene appears to be involved also in such fusion to *TFE3* (Argani et al., 2003) resulting in a protein with nuclear localization, bearing the DNA-binding domains of TFE3.

The rearrangement of *CALM* gene has been observed in lymphoid and myeloid leukemias of various types (Bohlander et al., 2000; Carlson et al., 2000). The result of such rearrangement is a fusion of *CALM* and the putative transcription factor *AF10*. Importantly, this fusion seems to be critical to leukemogenesis.

In acute myeloid, lymphatic and bilineage leukemias the chromosomal rearrangements lead to a fusion between *EPS15* and histone methyltransferase *MLL* (myeloid-lymphoid leukemia) genes (Lanzetti and Di Fiore, 2008; So et al., 2003). This fusion causes activation of transcriptional properties and oncogenic conversion of MLL, leading to a cellular transformation. Moreover, expression of a closely related protein named *EPS15R* appears to be induced in human hepatocellular carcinoma as well as in the mouse model of this disease (Niehof and Borlak, 2008).

The chromosomal translocation was found in acute myeloid leukemia resulting in *MLL* gene fused with *endophilin 2* gene (Liu et al., 2004), similar to the *EPS15-MLL* gene fusion mentioned above. MLL-endophilin fusion protein exerts the transforming activity towards NIH 3T3 cells, which could result from its ability to act as an aberrant transcription factor with the DNA-binding domain of MLL and the transcription activation domain of endophilin (Liu et al., 2004).

6. Endocytic and nuclear functions: linked or disparate?

Endocytic proteins discussed in this article represent a structurally diverse group of molecules with different functions in membrane trafficking. Equally diverse are their roles in various aspects of nuclear signaling and cellular physiology, often associated with pro- or anti-oncogenic activities. Consequently, it seems that the involvement of endocytic proteins in nuclear signaling does not follow one general pattern but various mechanisms are used instead. However, it appears that these dual-function proteins do share some common features, like a multi-domain structure and an ability to associate peripherally with intracellular membranes. They often assume roles of adaptors or scaffolds in macromolecular assemblies, capable of interacting with many other partners in a transient, dynamic and repeatable manner in order to drive successive rounds of endocytic internalization and transport. Proteins endowed with such properties are well suited to act as versatile vehicles in various cellular compartments, involved in a number of activities. On the other hand, such multitude of interactions and functions makes it often difficult to assess how direct an observed effect might be. Although proteins described in this article have been demonstrated to localize to the nucleus at least under some circumstances, in several cases it is unclear whether their roles in transcriptional regulation result directly from the nuclear translocation or are due also to the interactions with other signaling molecules in the cytoplasm. Similarly, it is difficult to precisely attribute various pro- and anti-oncogenic activities of these proteins either to their endocytic or nuclear functions, also because of a significant contribution of endocytosis to tumor formation and progression (Mosesson et al., 2008).

One important, largely unresolved, question concerns the relationship between endocytic and nuclear functions of a given molecule: to what extent they are directly linked or independent from each other. The first case may represent a signaling event linking endocytosis and transcription, where the same molecule of a protein translocates from the cytoplasm to the nucleus, acting as a direct messenger. In the second alternative, which exemplifies a case of ''moonlighting'', two largely separate pools of a given protein perform distinct functions. For most proteins the exact relationships between their endocytic and nuclear functions remain unknown. Further studies aiming at the selective abrogation of a compartment-specific localization and/or activity of a dual-function protein will be required to address this issue. So far nuclear translocation upon stimulation of endocytosis has been described for β-arrestins and APPL proteins. Even though HIP1 and Nm23 proteins are imported to the nucleus upon treatment with androgen or estrogen, respectively, these events appear not to be related to the regulation of endocytosis. For a few proteins, their endocytic and nuclear roles appear to be mutually exclusive, which can result from specific splice variants localized to either compartment (e.g. Bin1), or be due to a partly overlapping binding site for cytoplasmic and nuclear partners (in the case of clathrin: clathrin light chain and p53, respectively).

The mechanisms determining the partitioning of proteins between the endocytic organelles, cytoplasm and the nucleus are likely diverse and may involve compartment-specific interactions and/or post-translational modifications, which could also differentially affect protein stability and turnover. Particularly for proteins with mutually exclusive endocytic and nuclear functions it will be important to find out whether such pools are interchangeable or confined only to certain localization and regulated independently. For proteins exhibiting different interactions in the cytoplasm and in the nucleus, an abundance of binding partners could be a determinant of the nucleocytoplasmic distribution. On the other hand, it seems that at least in some cases (e.g. ESCRT-II subunits) proteins can assemble into the same core complexes acting both in endocytosis in the cytoplasm and in transcription in the nucleus.

Finally, the presence of several endocytic proteins in the nucleus may prompt some speculations as to how the processes of endocytosis and gene expression could be linked. It is becoming apparent that a subcompartmental organization and a three-dimensional architecture of the nucleus play important roles in the regulation of transcription (Lanctot et al.,

2007). During endocytosis, endocytic adaptors and endosomal sorting complexes contribute to the formation of membrane compartments. One appealing possibility is that endocytic proteins could participate in the compartmentalization of subnuclear space or might be involved in subcompartment-specific processes within the nucleus. Such role has been proposed for CHMP1, which localizes in specific subnuclear regions believed to form boundaries between transcriptionally active and inactive chromatin domains (Stauffer et al., 2001). Moreover, it appears that the structural arrangement of a core scaffold building a nuclear pore complex resembles that of clathrin-coated or COPI/II vesicles, arguing that similar protein folds are used as membrane-curving devices in various cellular locations (Alber et al., 2007). As exemplified by the ESCRT-II complex, it is further possible that the same proteins could act locally in different compartments either as membrane-attached or DNA-bound scaffolds. Future research focusing on nuclear functions of endocytic proteins will undoubtedly shed more light on the mechanisms of molecular ''multitasking'' whereby a given protein may act in various intracellular locations. Such studies will broaden our knowledge on how molecular communication between organelles can be achieved and how its dysregulation may affect tumorigenesis.

Acknowledgements

We are grateful to A. Hupalowska and A. Torun for critical reading of the manuscript. The work in Miaczynska's laboratory was supported by an International Research Scholar grant from the Howard Hughes Medical Institute, a Senior Research Fellowship from the Wellcome Trust (076469/Z/05/Z), by the European Union LSHG-CT-2006-019050 (EndoTrack), Polish Ministry of Science and Higher Education (2P04A03828 and Mobilitas.pl network) and Max Planck Society (Partner Group programme) to MM. IP was supported by a grant from Iceland, Liechtenstein and Norway through the EEA Financial Mechanism via Homing Programme from the Foundation for Polish Science.

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