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REVIEW

Pathways of integrins in the endo-lysosomal system

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Abstract
In this review, we present recent scientific advances about integrin trafficking in the endo-lysosomal system. In the last few years, plenty of new information has emerged about the endo-lysosomal system, integrins, and the mechanism, how exactly the intracellular trafficking of integrins is regulated. We review the internalization and recycling pathways of integrins, and we provide information about the possible ways of lysosomal degradation through the endosomal and autophagic system. The regulation of integrin internalization and recycling proved to be a complex process worth studying. Trafficking of integrins, together with the regulation of their gene expression, defines cellular adhesion and cellular migration through bidirectional signalization and ligand binding. Thus, any malfunction in this system can potentially (but not necessarily) lead to tumorigenesis or metastasis. Hence, extensive examinations of integrins in the endo-lysosomal system raise the possibility to identify potential new medical targets**.** Furthermore, this knowledge can also serve as a basis for further determination of integrin signaling- and adhesion-related processes.

Keywords Integrin · Endo-lysosomal system · Internalization and recycling pathway · Lysosomal degradation

Introduction

The ability of cells to migrate and to occupy fixed positions by cell adhesion molecules is crucial from the perspective of several physiological conditions. The malfunction of cellular adhesions can lead to infiltration of cells into tissues, which may cause inflammation and metastatic formations. Integrins are transmembrane receptors and cell adhesion molecules, capable of bidirectional signaling as well. The functioning of integrins is not merely influenced by their gene expressional pattern, but also by their internalization, recycling and degradation rate, which forms a cycle. Understanding this cycle within the endo-lysosomal system may help us to provide valuable information regarding pathological conditions. Moreover, it might help in the treatment of these diseases, or in the development of tissue regenerative (or other new) biological methods. The main goal of this review is to summarize how integrins are trafficked within the endo-lysosomal system of the mammalian cells.

Integrins in a nutshell

Integrins function as cell surface receptors playing an important role in cell motility and signalization through binding various extracellular matrix (ECM) elements (Hynes 2002). (Although they bind non-ECM elements as well, we will not discuss them here (LaFoya et al. 2018)). Integrins are αβ heterodimers; currently 24 types of them were identified in mammalians, which show specificity toward different ligands (Humphries et al. 2006). The binding of these ligands determines the conformation of the integrins, affecting signal activity and receptor–ligand binding affinity. The active form of integrins has the greatest affinity toward their ligands; meanwhile, in the inactive form they show a more compact state with lower affinity (Mould 1996; Askari et al. 2009). Integrin signaling determines cell proliferation, cytoskeletal structure, motility and cell survival. The signaling can be outside-in signaling, when the extracellular domain of the integrin binds to the ligand leading to a conformational change and ultimately to the recruitment of proteins and signal elements on the intracellular

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regions. Additionally, integrins can modulate their affinity for extracellular ligands (inside-out signaling). In this case, interactions between the intracellular regions of integrins and various factors (e.g., talin) will lead to a conformational change of the extracellular domains (Hynes 2002).

The endo-lysosomal system

The endosomal system covers those membrane bound organelles, which are derived from the protrusion of the cell membrane that becomes separate during the process called endocytosis. This network shows a tight connection with the lysosomal system. The lysosomal system is a group of vesicles with degradative function, characterized by specific proteins found in their lumen and in their membranes as well (Bainton 1981). These proteins are the lysosome integral (LIMP) and lysosome-associated membrane proteins (LAMP) and enzymes with acidic pH optimum like acidic hydrolases and cathepsins (Lübke et al., 2009). While the endosomal system facilitates material intake from outside the cell, the trans-Golgi network (TGN) derived lysosomes supplement degradative enzymes with low pH optimum; thus, the digestion of the given material can happen (Hu et al. 2015). There are multiple reasons why the digestion might be beneficial. The first is to cover the metabolic necessities of the cell and to maintain homeostasis. The next is to regulate signalization, for example, through the uptake and digestion of membrane receptors (Zastrow and Sorkin 2007). The malfunction of the endo-lysosomal system is known to cause several pathologic conditions, like the lysosomal storage diseases, which covers approximately 50 genetic disorders where the degradation of certain materials is prohibited. The accumulation of these materials can lead to Parkinson or Huntington disease (Ballabio and Gieselmann 2009; Malik et al. 2019).

There are many ways of internalization; however, we will discuss just the most important ones. Based on the size of endocytosed material, the main two categories are phagocytosis, when the diameter of the engulfed material exceeds 0,5 µm and pinocytosis, when the internalized materials are smaller than that (Kumari et al. 2010). Based on the mechanism of internalization, we can differentiate clathrin-dependent and clathrin-independent endocytosis. In the case of clathrin-mediated endocytosis, an adaptor and a coat complex assemble at given membrane sites, facilitating membrane invagination and endocytosis (Kaksonen and Roux 2018). The specificity is based on sorting signals like peptide motifs, lipids or ubiquitination, which are recognized by the adaptor proteins that ensure the connection between the cargo and the coat proteins (Reider and Wendland, 2011). The other main group, clathrin-independent endocytosis, involves several types of internalization. In the case of caveolin-dependent endocytosis integral membrane proteins, the caveolins facilitate the formation of membrane invagination structures known as caveolas, which ultimately form endosomes (Bastiani and Parton 2010). Another clathrin-independent pathway is the CLIC/GEEC (clathrin-independent carriers/GPI-anchored protein enriched endosomal compartment) pathway, where GPI (glycosylphosphatidylinositol) anchored proteins are targeted to an organelle called GEEC with the help of clathrin-independent carriers. This organelle is enriched in GPI-anchored proteins (Sabharanjak et al. 2002).

So far, we have presented the endo-lysosomal system in general and the ways of internalization; in the following, we will review the most important organelles in the system. As endocytosis occurs, endocytic vesicles are formed which converge to a larger organelle called early endosome. Whatever the way of internalization might be, currently all known pathways lead to this organelle. This is where the sorting of the material occurs deciding what to degrade and what to recycle; hence, its other name is sorting endosome (Naslavsky and Caplan 2018). Early endosomes are hetero–geneous in appearance with a central vacuole of usually 100–500 nm in diameter and with tubular extensions. The vacuole is electron lucent and sometimes contains intraluminal vesicles in smaller size (40–100 nm) (Klumperman and Raposo 2014). A well-known signal during sorting is monoubiqitination, which directs the cargo toward degradation (Katzmann et al. 2001; Urbanowski and Piper 2001). It is important to note that sorting into the degradative pathway only means that the cargo is not actively transported toward the recycling pathways and stays in the early endosome. With time, early endosomes mature into late endosomes, which will be discussed later. From early endosomes, short (fast) and long (slow) recycling pathways lead back to the membrane. The short pathway is associated with Rab4 GTPase; the long is associated with Rab11. In the case of the long pathway, the cargo first arrives in a pericentriolar recycling compartment, and later from there, it continues its way toward the cell surface within tubular recycling endosomes (van der Sluijs et al. 1992; Ullrich et al. 1996).

As we mentioned earlier, early endosomes will eventually form late endosomes supposedly through maturation, which theory is fortified by observations where "Rab conversion" was detected (Rink et al. 2005; Poteryaev et al. 2010). During maturation, the composition/interactions, the pH value of the lumen and the morphology of the organelle change (Dunn and Maxfield 1992). The lumen of early endosomes is less acidic (~pH 6) than of late endosomes (Naslavsky and Caplan 2018). A frequently used marker for early endosomes is the Rab5 GTPase, and during maturation, it is replaced by Rab7, which is the marker of late endosomes (Rink et al. 2005; Poteryaev et al. 2010). Rab GTPases play an important role in membrane fusion, tethering and in vesicular

transport (on the microtubules) through recruiting other effectors depending on their GTP-/GDP-associated state (Hutagalung and Novick 2011). Constant flux of proteins and lipids between different organelles is sustained by vesicular fusion, which requires tethering factors and SNAREs (soluble N-ethylmaleimide sensitive factor attachment protein receptor), among other proteins. Tethering factors coordinate the SNARE proteins and mediate the positions of the vesicles to be fused. SNAREs, which are present on both membranes, complete the process of vesicle fusion and form an amphipathic tight four-helical complex in the final stage of the process.

There are numerous tethering factors; however, we would only like to mention two of these. The Rab5 interacting CORVET (Class-c core vacuole endosome tethering), which generally tethers early endosomes and mediates the homotypic fusion of these organelles and the Rab7 interacting HOPS (homotypic fusion and vacuole protein sorting), which mediates homotypic fusion of late endosomes and heterotypic fusion of lysosomes with late endosomes and autophagosomes (Balderhaar and Ungermann 2013). Formerly, it was a consensus that, in contrast with early endosomes, recycling of cargo does not occur in late endosomes. However, there are observations of integrin recycling from late endosomes as well, which is associated with cancer (Dozynkiewicz et al. 2012).

Late endosomes are typically 250–1000 nm in diameter and usually contain more intraluminal vesicles than early endosomes. The number of intraluminal vesicles is depen–dent on the stage of the late endosome: while early stages sometimes show only a few, later stages usually contain more, which we call multivesicular bodies. The term "multivesicular body" is frequently used as a synonym for late endosomes, while others use the term to define the intermediate stage between early and late endosomes (Klumperman and Raposo 2014). These intraluminal vesicles are formed by the ESCRT (endosomal complex required for transport) complexes, of which we currently know four (ESCRT-I, II, III and 0) (Katzmann et al. 2001; Mosesso et al. 2019). It is believed that intraluminal vesicles are formed to completely isolate proteins that are still actively continue signaling after internalization. The other aim of intraluminal vesicle formation is the entire internalization of transmembrane proteins, so they can fully interact with digestive enzymes with their (otherwise inaccessible) transmembrane and extraluminal region. Eventually, late endosomes or multivesicular bodies will fuse with lysosomes forming endo-lysosomes (Muliock et al. 1994; Futter et al. 1996). In endo-lysosomes, the acidic pH and the proper digestive enzymes ensure the degradation of the cargo. Endo-lysosomes either digest their own cargos, or reorganize and allocate their components and enzymes to other endo-lysosomes for further use (Bright et al. 1997; Luzio et al. 2000). While endo-lysosomes contain active acidic hydrolases, scientists also observed so-called terminal lysosomes containing inactive acidic hydrolases. However, they are not post-lysosomes or inert residual bodies, but they can provide digestive enzymes for reusage in the lysosome reformation process (Bright et al., 1997). The transport of lysosomal hydrolases and membrane proteins to lysosomes (and endo-lysosomes) requires receptors. Lysosomal enzymes are recognized in the TGN by a mannose-6-phosphate (M6P) signal with a M6P-receptor in mammalians (Ghosh et al. 2003). However, there are other signals, such as LIMP-2, which recognizes β-glucocerebrosidase through its luminal domain (Reczek et al. 2007). We also have to mention the retromer complex, which makes some of these receptors (for example cation-independent M6P-receptor) recycle back to the TGN for further recognition of lysosomal signals (Arighi et al. 2004; Seaman 2004). In the lack of the retromer complex, appropriate enzymes will not be properly targeted to the lysosomes, leading to insufficient degradation and accumulation of material. This might not only play a role in the earlier mentioned lysosomal storage diseases, but also in other diseases, like Alzheimer's disease (Zimprich et al. 2011).

Autophagy

Appropriate functioning of living cells requires proper cooperation of synthesis and degradation pathways. As mentioned earlier, lysosomes play pivotal role in degradation: lysosomal hydrolases degrade cargo in the acidic environment; hence, nascent monomers could be used again in synthetic pathways (Appelqvist et al. 2013). Material can reach lysosomes through heterophagy, also known as endocytosis (with extracellular cargo), or via autophagy, in which process the cargo is intracellular. Autophagy is essential for the whole organism to achieve responsiveness to stress factors, such as starvation; moreover, basal autophagy is crucial for cell survival, since it is responsible for degrading unnecessary and damaged cell components (Klionsky and Codogno, 2013). Autophagy has four main types: macroautophagy, microautophagy, chaperon-mediated autophagy and crinophagy (Li et al. 2012). Further, in our study, autophagy always refers to macroautophagy.

Although the molecular mechanisms of autophagy are not completely clarified and there are differences in engaging proteins among different organisms, the core mechanisms and Atg proteins are very similar (Klionsky and Codogno, 2013; Lamb et al. 2013). Atg proteins are expressed from the ATG (autophagy-related) genes and are crucial for the formation of autophagosomes and for the maturation of the isolation membrane (also termed as phagophore) (Mizushima et al. 2011); however, the origin of this latter is still

controversial in metazoans (Tooze and Yoshimori, 2010). In mammals, the initiation of the isolation membrane formation is controlled by the ULK1 (Atg1/Unc-51-like kinase) complex. This complex is under the regulation of mTORC1 (mechanistic Target of rapamycin complex 1) and AMPK (adenosine monophosphate activated protein kinase). mTORC1 is activated in the presence of an appropriate level of energy in the cell, and in this case it inhibits the ULK1 complex and hence negatively regulates autophagy (Kim et al. 2011; Miyazaki et al. 2010; Zoncu et al. 2011). When cellular energy level is decreased (e.g., during starvation), mTORC1 will be inhibited, while ULK1 complex will not be blocked anymore. AMPK is an evolutionarily conserved serine/threonine kinase, which can phosphorylate mTORC1 and ULK1 complexes as well (Kim et al. 2011). Under nutrient insufficient state, AMPK promotes autophagy by phosphorylating and thus inactivating mTORC1. Besides these, AMPK binds, phosphorylates and hence activates ULK1, which leads to autophagy induction. However, if sufficient amounts of nutrients are present, mTORC1 phosphorylates ULK1 on a different serine, preventing ULK1-AMPK interaction and the induction of autophagy (Inoki et al 2012). In this way, ULK1 can phosphorylate its target proteins, such as the Vps34 (Vacuolar protein sorting 34)-kinase complex (including Vps34, Beclin1, Vps15 and Atg14L) (Russell et al. 2013), which generates phosphatidyl-inositol-3-phosphate (PI3P) in membranes (Jean and Kiger, 2014). The Atg9A/ATG2-WIPI1/2 (WD repeat domain phosphoinositide interacting protein 1) trafficking system can bind PI3P via FYVE domain (Fab1-YOTB-Vac1-EEA1 domain) of WIPI1/2, and Atg9 will direct membranes to the growing phagophore (Orsi et al. 2012; Yamamoto et al. 2012). In further steps of the process, LC3 (microtubule-associated protein light chain 3) will be covalently conjugated to the membrane of the phagophore by the activity of two ubiquitin-like conjugation systems (Geng and Klionsky, 2008). Before the phagophore closes around its cargo, all Atg proteins dissociate from it, only LC3 remains on the inner side of the isolation membrane (Fujita et al. 2008), and hence, LC3 is the most commonly used autophagy marker (Klionsky et al. 2016). After phagophore closure, the autophagosome is ready to fuse with lysosome in order to degrade its cargo.

Intracellular pathway of integrins

Thirty years ago, Bretscher observed the cyclical transport of fibronectin receptors. He suggested that this process assists the cells to move along the ECM, through the reorganization of the receptors toward the leading edge of the cell (Bretscher 1989). It was also revealed that the speed of the process depends on the type of integrin receptors as well, which recycle with different speed (Bretscher 1992). As we mentioned earlier, integrins are important elements of several adhesive structures, where the assembly and disassembly of these structures are both affected by their transport. Based on the relative permanency of internalization (Sczekan and Juliano 1990) and on the fact that a large proportion of them is being recycled (Lobert et al. 2010; Layseca et al. 2019), it seems that this trafficking route is an essential part of the function of these proteins. Since their signaling function is tightly connected to conformation, which is affected by ligand binding, their deployment to the cell membrane serves as an important regulating option. The same can be stated about their rate of internalization, recycling and degradation, besides their gene expressional pattern and intensity. Integrins can both be internalized in active or in inactive conformation, but they tend to do so with a different rate. Integrins in the active conformation are degraded in a higher rate as well compared to the inactive forms (Arjonen et al. 2012). As we already mentioned, conformation is influenced by ligand occupancy. A possible way to turn back from active conformation to inactive is to lose their ligands in the early endosome (presumably caused by pH level change). Indeed, it was observed in the case of α5β1 integrins that the ones in ligand unbound state were mainly recycled while the others remaining in ligand bound state were degraded in lysosomes (Kharitidi et al. 2015). This demonstrates well that conformation also affects the transport of these receptors; however, dynamics of this trafficking is not completely understood yet. In the following, we will gather some of the current knowledge about integrin traffic in the endo-lysosomal system and we will present some of the pathways and their regulators.

Main pathways of integrins in the endo-lysosomal system are highlighted in Fig. 1.

Internalization

Clathrin-dependent endocytosis

The disassembly of focal adhesions is connected to the internalization of integrins. One possible way of internalization is dynamin and adaptor-dependent clathrin-mediated endocytosis. First, αvβ5 integrins were visualized in clathrin-coated membrane domains by ultrastructural studies in rat myotubes. Moreover, an NPXY motif of the cytoplasmic domain of β5 subunit was identified as a clathrin interaction site, which proposes the role of clathrin in the internalization of αvβ5 integrins (De Deyne et al. 1998). Next, a well-known clathrin interacting partner, the adaptor protein 2 (AP-2), showed colocalization with a fraction of αβ1 integrins in rhabdomyosarcoma (RD) cells (Boyd et al. 2002). It is of note that another research group identified AP-2 as well, as

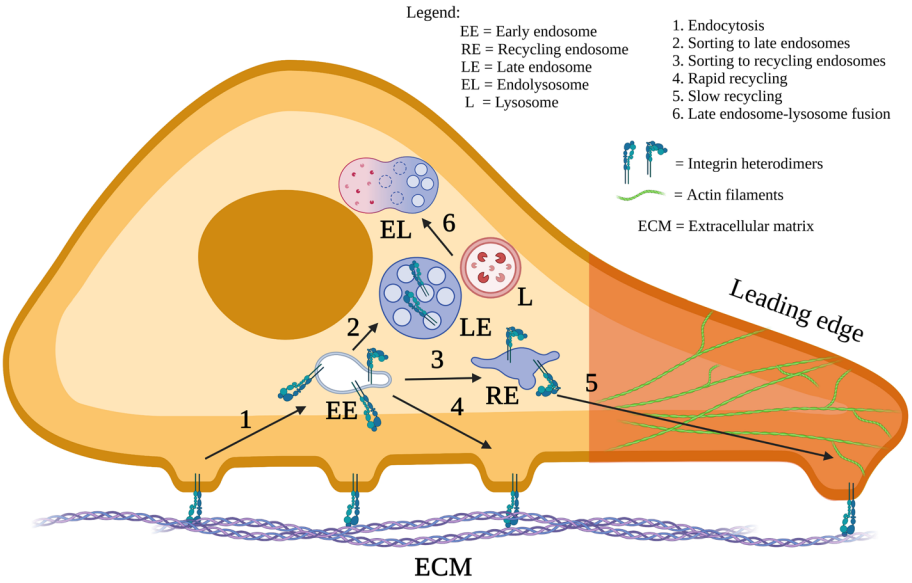

Fig. 1 Schematic overview of the pathways take part in the trafficking of integrins. After internalization (1) integrins are transferred to early (or sorting) endosomes (EE). From here, integrins can be sorted to late endosomes (LE; 2); or they can be forwarded to recycling endosomes (RE; 3) for the slow recycling route; or they can be recycled rapidly to the plasma membrane (4). The relocalization to the cell surface can occur from recycling endosomes as well (5). Late endosome (LE)-lysosome (L) fusion (6) will eventually result in the degradation of integrins. Possible recycling from late endosomes (mediated by Rab25 and CLIC3) is not indicated on the figure. The figure was created with BioRender.com

a significant factor; moreover, they observed a higher internalization rate when β1 integrins were in active conformation (Chao and Kunz 2009).

If the process is blocked with monodanzyl-cadaverin or through the silencing of dynamin 2/clathrin adaptors, the number of focal adhesions increases and cell motility decreases in fibroblast (NIH3T3) and in fibrosarcoma (HT1080) cells. Moreover, during the endocytosis-mediated dissociation, β1 integrin subunits colocalize even more with the early endosomal marker Rab5 (Chao and Kunz 2009; Ezratty et al. 2009). In these experiments, the state of focal adhesions with fluorescent microscopy in fibroblast cells was examined with the depletion of clathrins (with small interfering RNA or with other inhibitors) or treating them with nocodazole (a microtubule polymerization inhibitor). The results implied that clathrin depletion heavily reduced the adhesions that were formed by α5β1 integrin. They concluded that clathrin-mediated endocytosis and certain adaptors like Dab2 (disabled-2) and ARH (autosomal recessive hypercholestheremia) play a significant role in focal adhesion turnover (Ezratty et al. 2009). There are other results supporting the role of Dab2 in β1 subunit clathrin-mediated endocytosis in human cells. According to the work done by Teckchandani and co-workers, it seems that Dab2 adaptors, similarly to AP-2, are able to bind epsin homology (EH) domain-containing proteins. They depleted EH domain-containing proteins in HeLa cells, which resulted in the impaired internalization of the adaptor-dependent cargoes (in this case β1 integrin and transferrin receptor (TfR)). While Dab2 and AP-2 colocalized near clathrin positive structures and with one of the examined cargoes (β1 integrin, TfR), the cargoes themselves were present in different clathrin coated pits. Eliminating the ability of Dab2 to bind to EH domains impaired only β1 integrin subunit internalization, but did not affect TfR. These results suggest that this clathrin-dependent endocytotic mechanism requires β1 integrin subunits to interact (and form complex) with Dab2 and with EH domain-containing proteins (Teckchandani et al. 2012).

Caveolin- and dynamin-dependent endocytosis

The role of caveolin-1 in integrin endocytosis was revealed during the examination of ECM molecules turnover. Shi and coworkers found that β1 integrins play role in the endocytosis of matrix fibronectin (FBN): silencing of caveolin-1 reduced β1 integrin and FBN endocytosis in myofibroblasts, while re-expression of the protein could elevate the endocytic rate of β1 integrin (Shi and Sottile, 2008).

In another study, syndecan-4 was found to stimulate the internalization of the fibronectin receptor α5β1 integrin in fibroblast cells. Ligand binding of syndecan-4 leads to the decrease in cell fibronectin adhesion avidity by increasing the internalization rate of fibronectin receptors from the cell surface. In this study, cell avidity for FBN was measured by atomic force microscopy, which was decreased by

syndecan-4 interaction. This reduction could be blocked by decreasing caveolin, dynamin-2 or RhoG (Ras homology Growth-related) expression level of the cells with siRNA; meanwhile, clathrin depletion did not have the same effect. Taken together, these results imply that this is a caveolin- and dynamin-dependent pathway, which is activated by syndecan-4 and regulated by RhoG (Bass et al. 2012).

ARF6

Besides RhoG, several other GTPases are regulated by syndecan-4 and FBN, like Rac1 (Ras-related C3 botulinum toxin substrate 1), RhoA (Ras homolog family member A) and ARF6 (ADP ribosylation factor 6). ARF6 predominantly regulates recycling of β1 integrins; however, its role in the internalization was investigated as well. In HeLa cells, silencing of BRAG2 (Brefeldin-Resistant Arf GEF 2), which is a specific activator of Arf6, dramatically increased the amount of cell surface β1 integrins (Dunphy et al. 2006.) Similarly, activation of Arf6 increased integrin internalization in neurons (Eva et al. 2012), which indicates that ARF6 plays a role in the endocytosis of integrins beside recyclization. ARF6 regulates endocytosis of α6β4 integrins in hemidesmosomes in keratinocytes, and its elimination leads to decreased number of hemidesmosomes and impairs their organization as well (Osmani et al. 2018).

Galectin-3/CLIC pathway

Galectin-3 is a protein from the lectin family, which plays a role in β1 integrin internalization, recyclization and deployment of newly synthetized subunits on the apical part of epithelial cells. The depletion of galectin-3 decreased, while overexpression increased β1 subunit presence on the apical surface of the cell. Eventually, galectin-3 also regulates the distribution of these receptors through a basolateral-apical transcytosis (Hönig et al. 2018). Galectin-3 also participates in CLIC biogenesis and is able to bind to the plasma membrane but requires N-glycosylated proteins to do so. Depletion of galectin-3 decreases the rate of β1 integrin endocytosis and the number of CLIC present; thus, it is possible that galectin-3 elimination leads to a decreased internalization rate through the decrease in CLIC (Lakshminarayan et al. 2014). It is important to note though that not all CLIC structures vanished due to galectin-3 depletion suggesting that not all CLIC require galectin-3 for their biogenesis. The importance of the previously mentioned N-glycosylation is vague. In multiple cell types (MDA-MB-231, HeLa and U-251MG), mutations directed to N-glycosylation sites of certain α5 integrin subunits led to a delayed internalization of active α5β1 heterodimers. N-glycosylation is also known to influence cell motility and cell-ECM connections (Hang et al. 2017).

Interacting proteins that mediate integrin endocytosis

Not only individual proteins but well-defined protein interactions seemed to be the regulators of integrin uptake as well. Active β1 endocytosis is regulated by ERC1 (ELKS/RAB6-interacting/CAST family member 1), liprin-α1, and LL5. Silencing these proteins led to a decreased internalization of β1 integrins in active conformation. Moreover, one of the isoforms of ERC1 partly colocalized with caveolin but did not with clathrin or CLIC markers. Albeit we could assume that caveolin plays a role here, this theory lacks evidence (Astro et al. 2014). Based on further examinations Astro et al. suggested that ERC1 and liprin-α1 drive focal adhesion disassembly through active β1 integrin uptake to Rab7 positive membrane structures (Astro et al. 2016).

Other proteins were also identified to play role in the regulation of integrin uptake: the R-Ras/RIN2 (Ras and Rab interactor 2)/Rab5 complex, which localizes to nascent adhesions and regulates selectively the internalization of active β1 integrins in endothelial cells. The complex also helps supplying a downstream functioning protein, called Rac1, with GTP. Although not all the effectors of Rac1 are known, presumably WASH (Wiskott Aldrich syndrome protein and SCAR homolog) complex—playing a role in integrin recycling—is one of these (Sandri et al. 2012).

Additionally, other proteins also affect integrin internalization and are summarized in Table 1.

Recycling

A systematic, well-controlled endocytic trafficking is a part of integrin function. One way of regulation is poly- or multi-ubiquitination on the cytoplasmic tails of integrins (on their lysine residues), which will designate them to degradation. However, most of the integrins will be recycled through the early endocytic compartment; only a small portion of them will be degraded (Lobert et al. 2010).

The WASH complex and the retriever pathway

In mammalian cells, WASH (Wiskott Aldrich syndrome protein and SCAR homolog) complex was identified as a regulator of many endocytic processes, like integrin recycling, among others. The complex proved to be the activator of Arp 2/3 (Actin related protein 2/3) complex, which nucleates actin structures and hence affects transport pathways through the regulation of actin polymerization. Increased association of α5β1 integrins with multivesicular bodies was observed after the depletion of the complex, and WASH complex

Table 1 Summary of the factors regulating integrin internalisation

Regulating factors of integrin endocytosis			
Regulating factor	Supposed mechanism	Cell types	Source
Dab2, ARH, AP-2	By functioning as clathrin adaptors, they participate in the turnover of focal adhesions and in the endocytosis of α5β1 integrins	Fibroblast and fibrosarcoma cells	Ezratty et al. (2009); Chao and Kunz (2009)
syndecan-4	Stimulates the caveolin dependent endocytosis of α5β1 integrins by binding fibronectin through a PKCα and RhoG activational pathway	Fibroblasts and keratinocytes	Bass et al. (2012)
galectin-3	With the help of N-glycosylated proteins, drives CLIC biogenesis, supporting β1 integrin endocytosis and regulating the intracellular location of integrins	MDCK epithelial cells	Hönig et al. (2018); Lakshminarayan et al. (2014)
ERC1,liprin-α1, LL5	Responsible for the endocytosis of active β1 integrins as a functional complex. It is a suggested that the interaction of ERC1 and liprin-α1 sorts β1 subunits into Rab7 positive structures causing the disassembly of focal adhesions	MDA-MB-231, HeLa and COS-7 cells	Astro et al. (2014); Astro et al. (2016)
R-Ras/RIN2/Rab5	As a complex, they are responsible for the endocytosis of active β1 integrins	Endothelial cells	Sandri et al. (2012)
ARF6	Regulates the turnover and endocytosis of α6β4 integrins	Keratinocytes	Osmani et al. (2018)
PDGF and BARS	PDGF stimulation cause BARS dependent internalization of β3 integrins with macropinocytosis	Fibroblast cells	Gu et al. (2011)
fMLF	αL/β2 integrins are internalized in response to the chemotactic factor	Neutrophils and CHO cells	Fabbri et al. (2005)
ADAM9	Responsible for the endocytosis and degradation of β1 integrin subunits	cells deriving from prostate cancer and fibrosarcoma cells	Mygind et al. (2018)
Neuropilin-1	Mediates endocytosis of active α5β1 integrins in a GIPC1/Myo6 (GAIP interacting protein C terminus member 1/ myosin 6) dependent pathway	Endothelial cells	Valdembri et al. (2009)
CLIC4	Responsible for the endocytosis of β1 integrin subunits	HeLa and MDA-MB-231 cells	Argenzio et al. (2014)

Abbreviations in the table: Dab2: Disabled-2; ARH: Autosomal recessive hypercholesteremia; AP-2: adaptor protein 2; ERC1: ELKS/RAB6-interacting/CAST family member 1; LL5: potential phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P_3) binding pleckstrin homology domain; R-Ras/RIN2/Rab5: R-Ras/Ras and Rab interactor 2/Rab5; ARF6: ADP ribosylation factor 6, PDGF: Platelet derived growth factor; BARS: Brefeldin A-ADP ribosylated substrate; fMLF: N-Formylmethionine-leucyl-phenylalanine; ADAM9: Disintegrin and metalloproteinase domain-containing protein 9; CLIC4:chloride intracellular channel 4

was found to play a role in α5β1 integrin recycling from endosomes to the plasma membrane through the modulation of actin polymerization (Zech et al. 2011). The role of WASH complex seemed to be even more puzzling after it was identified as a component of a recycling pathway, where it acts together with sorting nexin 17 (SNX17) adaptor protein, the retriever and the CCC (CCDC93, CCDC22, COMMD) protein complexes. They compose a retromer-independent, but overlapping, recycling pathway. Retriever is a heterotrimer; it consists of DSCR3 (Down syndrome critical region gene 3), C16orf62 and VPS29 (DSCR3 also known as VPS26C and C16orf62 also known as VPS35L). This complex localizes on the surface of endosomes, recognizes NPXY/NXXY peptide motives containing proteins (like integrins on their cytoplasmic tail region) and recruits SNX17 in order to recycle proteins instead of degrading (Calderwood et al. 2003; Steinberg et al. 2012). CCC is essential in the localization of retriever, since in the lack of the CCC complex retriever could not localize on the endosomes. Moreover, CCC complex assembly requires FAM21 (family with sequence similarity 21), which is part of WASH complex (McNally et al. 2017).

Previously, it was thought that retromer is necessary for WASH to localize on endosomes, but newer results shed light on a retromer-independent mechanism. This notion is supported by FAM21 knockout experiments in HeLa cells: lack of FAM21 causes dispersed cytosolic localization of the retriever complex and more intensive integrin degradation. Moreover, silencing of CCC or retriever complex members causes increased integrin degradation in lysosomes just like SNX17 knockout. On the other hand, depletion of VPS35, which affects retromer functions, did not cause such elevated integrin degradation (McNally et al. 2017). It was already known that SNX17 depletion decreases the protein level of integrin α5 and β1 subunits, which could be rescued by Bafilomycin A treatment (which blocks lysosomal degradation). This implies that loss of SNX17 caused enhanced lysosomal degradation of α5 and β1 integrin subunits. In these cells, integrins accumulated in Rab4 and EEA1 (early endosomal autoantigen-1) positive recycling endosomes and in Rab7 and LAMP-1 positive late endosomes as well. Finally, SNX17 binds β1 integrin subunits through NPXY peptide motif and thus prevents their degradation (Steinberg et al. 2012).

In another study, SNX17 cellular localization was modified by GGA3 (Golgi-localized, gamma adaptin ear-containing, ARF binding) depletion: in the lack of GGA3, SNX17 colocalizes with LAMP-1. Similarly, integrins showed lysosomal localization as well, and their degradation was increased. In the light of these results, integrins could evade degradation through a recycling pathway, which is supported by GGA3 and SNX17. If GGA3 or SNX17 is missing, integrins move forward to degradation (Ratcliffe et al. 2016). Additionally, the pathway might have similar, not yet identified regulators as well.

The role of Rab GTPases in recycling

Rab GTPases are crucial regulators of membrane trafficking and integrin transport; hence, they play important role in cell motility, adhesion and cytokinesis as well. For instance, Rab21 interaction with integrins is indispensable for cytokinesis in mammalian cell lines (Pellinen et al. 2008). Integrins and their Rab regulators Rab4 and Rab11 are both key components of recycling pathways. In fibroblasts, αVβ3 integrins colocalized with Rab4 positive endosomes 15 min after internalization, while after 30 min they showed colocalization with Rab11 positive perinuclear recycling compartments; then, they appeared on the cell surface (Roberts et al. 2001). The variety in integrin regulation allows the cells a more dynamic control of receptors on their surface in order to achieve the most effective adaptation to their environment. Furthermore, recycling is more cost-effective than degrading then resynthesizing each receptor. The longer Rab11 pathway can preserve the internalized receptors until they needed again. Different integrins use different recycling pathways, as αVβ3 integrin requires Rab4, until α5β1 integrin uses Rab11-dependent recycling (Jones et al. 2009). In line with this, dominant negative form of Rab11 (and ARF6) could inhibit recycling of β1 integrin subunits in HeLa cells, while inactive form of Rab4 did not have similar effect (Powelka et al. 2004).

ARF6 in recycling

The effect of ARF6 and its regulators on integrin trafficking was examined in several studies. Internalization of integrin β1 subunit increased due to ARF6 activation through its guanosine exchange factors (GEFs), ARNO (ARF nucleotide-binding site opener) and EFA6 (Exchange factor for Arf 6), while ACAP1 (Arf-GAP with coiled coil, ANK repeat and PH domain-containing protein 1), ARF6 GTPase activating factor, did not influence the internalization of integrin β1 subunit. Additionally, ACAP1 overexpression increased, while ARNO and EFA6 overexpression had no effect on integrin recycling in PC12 (Pheochromocytoma 12) cells (Eva et al. 2012). In another study, Rab35 was identified as a negative regulator of ARF6. Rab35 depletion causes increased ARF6 activity and elevated β1 integrin recycling in a flow cytometry assay detecting internalized and resurfaced β1 integrin antibody in COS-7 (CV-1 in Origin, carrying SV40) cells. Besides these, Rab35 knock down cells showed increased cell motility in migration (scratch) assays (Allaire et al. 2013). Based on these, the regulation of integrin recycling by ARF6 seems to be controversial: modulation of two negative regulators of ARF6 (ACAP1 and Rab35) affects integrin recycling in the opposite way; both ACAP1 overexpression and Rab35 depletion increased β1 integrin recycling. However, ACAP1 is identified as a member of a clathrin-coated complex, which supports integrin recycling (Li et al., 2012). This raises the possibility that ACAP1 affects recycling through this complex instead of modulating GTPase activity of ARF6.

Besides its GEFs and other small GTPases, ARF6 activity can also be modulated by the syndecan-4 proteoglycan as well (which also plays role in the internalization of integrins, see Chapter "Caveolin- and dynamin-dependent endocytosis"). Phosphorylation state of syndecan-4 found to be an essential switch in integrin recycling through the regulation of ARF6: the phosphorylation of syndecan-4 suppresses ARF6 activity, which increases the presence of αVβ3 on the surface, but the recyclization of α5β1 decreases; hence, the focal adhesions are stabilized. Conversely, syndecan-4-mediated ARF6 activation increases the presence of α5β1 integrin on the cell surface through recyclization and blocks the presence of αVβ3 integrin. This will induce focal adhesion disassembly (Morgan et al. 2013). According to

these, the same proteoglycan–ECM interaction plays role in both endocytosis and recycling of α5β1 integrin; however, the downstream pathways are different (protein kinase Cα (PKCα) and RhoG for endocytosis (Bass et al. 2012) and ARF6 for recycling).

Relevance of conformation in transport flow

The decision, which intracellular transport pathway will be followed by a given integrin molecule, is affected by the conformation of the given molecule as well. Arjonen and coworkers investigated the trafficking of active and inactive β1 integrins in the endocytic system in various human cancer cell lines (adenocarcinoma MDA-MB-231, prostate cancer PC-3, non-small cell lung cancer cells NCI-H460). Integrins in the active conformational state may be internalized at higher rate, while inactive conformational forms showed more recycling in the Rab4 fast pathway. Both forms colocalized with Rab4, Rab5 and Rab11, which suggests no difference, but only active conformational state integrins colocalized with Rab7 positive structures. These results support the notion that active forms would be mainly degraded and only inactive forms would be mainly recycled (Arjonen et al. 2012).

Importance of amino acids and motives

Recycling can be influenced by amino acid motifs and amino acid modifications. β2 integrin subunits have a YRRF motif in their cytosolic domain, which is crucial for recycling. Localization of subunits into the membrane requires phosphorylation on the 788/789 threonine amino acids of the molecule (Rehberg et al. 2014). Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and PKC have been identified as the mediator of β1 integrin phosphorylation at this site (Suzuki and Takahashi, 2003; Stawowy et al. 2005). Furthermore, this phosphorylation is essential for sorting SNX17 recruitment, which ensures the evasion from degradation (Steinberg et al. 2012; Böttcher et al. 2012). Several integrin subunits contain NPXY/NXXY motives on their cytosolic tail region in order to bind various proteins containing phosphotyrosine binding domain, like Dab2 and EPS8 (epidermal growth factor receptor kinase substrate 8). These interactions provide further possibilities for regulation (Calderwood et al. 2003).

Role of tethering factors

Tethering factors in the endo-lysosomal system are multisubunit protein complexes (like CORVET and HOPS) or proteins with coiled coil structure (like EEA1). They mediate homo- or heterotypic fusion of vesicles in the endo-lysosomal system together with several other proteins of the fusion machinery (such as Rab small GTPases, motor or SNARE proteins). Recently, two subunits of the CORVET complex Vps3 and Vps8 were identified as a CORVET-independent two-subunit complex. Vps3 and Vps8 colocalized with early endosomal Rab5 (as CORVET subunits) and with Rab4 and Rab11 in the recycling pathways as well. Depletion of Vps3 and Vps8 decreased β1 integrin recycling in HeLa cells and reduced migration capacity of the cells on collagen-1 and fibronectin surfaces as well. Taken together, the complex is suggested to play a role in the transport of cargos from early endosomes to recycling endosomes (Jonker et al. 2018). Another, recently identified tethering factor called FERARI (Factors for endosome recycling and Rab interactions), was found to take part in the Rab11-mediated recycling pathway (Solinger et al. 2020). One subunit of the FERARI complex, Eps15-homology domain 1 (EHD1) was identified as a regulator of β1 integrin transport, as depletion of EHD1 disturbed integrin recycling in HeLa cells and in MEFs (mouse embryonic fibroblasts) derived from EHD1 KO mice as well. Moreover, cell migration and spreading on fibronectin were impaired as well in these cells (Jović et al. 2007). These results suggest that EHD1 could play a role in integrin recycling as part of the FERARI complex.

Integrins in the late endosomes and degradation pathways

Earlier results proposed that only a small portion of the Inte-grins degrade and the majority of them are recycled back to the plasma membrane (Lobert et al. 2010; Moreno-Layseca et al. 2019). Lobert and coworkers investigated the fibronectin-binding α5β1 integrins in fibroblasts, and they detected them both in early and in multivesicular endosomes as well. However, their ligand, fibronectin, could be found only in multivesicular bodies. Next, it was found that the α5 subunits are ubiquitinated in their fibronectin bound active state, and then, they are placed from early endosomes into multivesicular bodies with the support of the ESCRT complex and finally degraded together with their ligand. Moreover, the rate and speed of degradation were much lower than the recycling of the integrins in their inactive state (Lobert et al. 2010; Kharitidi et al. 2015). To make the picture complete, we note that in early endosomes FBN may dissociate

from α5β1 integrins (due to acidification), which promotes their deubiquitination and recycling back to the cell surface (Kharitidi et al. 2015).

When integrins lose their ubiquitin sign and are transformed into inactive conformational state, they get directed to recycling. SNX17 has a major role in integrin recycling thereby saving them from degradation through the retriever complex (Steinberg et al. 2012; Böttcher et al. 2012).

Earlier it was believed that no recycling occurs from late endosomes; however, integrins could be rescued from degradation in a Rab25 and CLIC3 (Chloride intracellular channel protein 3)-dependent way. Rab25 is an essential factor for sending α5β1 integrins in active conformational state to the lysosomal compartments, while CLIC3 is required for their retrograde transport and recycling to the plasma membrane. Presumably, CLIC3 has a role in proper, consecutive cell motility, since its depletion caused impaired cell movement. Additionally, elevated CLIC3 level stimulates recycling of integrins in active conformational state and hence supports tumorigenesis and metastasis formation (Dozynkiewicz et al 2012).

Autophagy and integrins

The function and transport of integrins are also connected to the autophagic machinery. Selective autophagy can sequester focal adhesion components into autophagosomes for degradation mediated by NBR1 (neighbor of BRCA1) receptor, inducing focal adhesion disassembly. An even more interesting observation is that autophagy inhibited cells show a decreased cell migratory rate and enlarged focal adhesions on the leading edge. Thus, it seems autophagy regulates migration through focal adhesion disassembly (Kenific et al. 2016). Moreover, not only the components of focal adhesions are degraded in autophagosomes but some proteins regulating assembly and maturation of adhesions as well (Belaid et al. 2013; Ulbricht et al. 2013). This review mainly focuses on integrins, and as the interconnection between adhesion and autophagy seems evident, it is also probable that integrin transport is affected as well. We have to take into account two facts: first, that integrin conformation is partly determined by ligand availability (Mould 1996; Askari et al. 2009). The second is that conformation seems to affect transport (Kharitidi et al. 2015; Arjonen et al. 2012). Consequently, the disassembly of focal adhesions, which destabilizes the connection between the receptor and the ECM, will probably affect this transport. Furthermore, autophagy seems to be able to modulate integrin recycling. In an experiment, starvation-induced autophagy increased the colocalization of β1 subunit positive vesicles with autophagosomes (LC3 positive vesicles) and this correlated with reduced migration. Inhibition of autophagy, however, resulted in a decreased lysosomal degradation of β1 subunits and increased its recycling (Tuloup-Minguez et al. 2014).

It is important to note that cell migration and adhesion will be also affected by the surrounding ECM composition. Although β1 subunits (which we also mention frequently in this review) are present in most (12 out of 24) integrin heterodimers (LaFoya et al. 2018), these heterodimers can still have different ligands. Thus, the experiments where only one subunit is examined are to be taken with caution when interpreting the results.

Previously we mentioned how autophagy might affect integrins. Importantly, however, the regulation is mutual, as the state of integrins can also affect autophagy. The lack of certain integrin-mediated cell adhesions can induce autophagy. Most probably, the aim of this is to promote cell survival for detached cells, which are highly susceptible to cell detachment-induced cell death (termed anoikis) on the long term. Indeed, RNA interference-mediated knockdown of key autophagosomal components leads to increased levels of caspase-3 activity and decreased replating efficiency in suspended cells (Fung et al. 2008). Cell detachment-induced autophagy might be beneficial in certain cases, but it delays anoikis and anoikis resistance is associated with tumor metastasis as well (Kim et al. 2012). Beyond the adhesive state of the cells, integrin signaling also plays a crucial role in autophagy. It was shown that disruption of cell adhesion by blocking β1 integrins via antibodies leads to the robust activation of AMPK (5' adenosine monophosphate-activated protein kinase), a major inhibitor of TORC1 (target of rapamycin complex 1), thereby promoting autophagy (Avivar-Valderas et al. 2012). In another case, the inhibition of α3β1 integrins via antibodies stimulated autophagy in mammary epithelial cells (Chen and Debnath 2013). Thus, we can state that the exact regulation of cell detachment-induced autophagy is of special interest, and it has to be regulated tightly to function in a beneficial manner.

Relationships between defected integrin recycling and human disorders

As mentioned earlier, surface integrin composition determines ECM and cell adhesion patterns. Endocytosis, recycling and degradation affect the availability of the receptors, and a defect in these processes can easily alter the repertoire, which can lead to various diseases, like cancer formation, tumor cell metastasis, inflammation or atherosclerosis.

Recycling routes of integrins mediated by Rab GTPases and their possible correlations with the above-mentioned diseases are intensively investigated. In one of the studies, tumor metastasis was examined in HeLa cells: overexpression of Rab5 led to increased β3-integrin—MT1-MMP (membrane type 1 matrix metalloproteinase) co-trafficking

through the Rab4 recycling pathway, which was associated with invadosome formation and matrix degradation (invadosomes are membrane protrusions specialized in ECM degradation). Additionally, poor clinical outcome was predicted for breast cancer patients overexpressing Rab5 (Frittoli et al., 2014). Breast cancer brain metastases (BCBM) are serious clinical problems, since systemic treatments are poorly effective due to the blood brain barrier. Howe and co-workers analyzed transcriptomes of early and late stage brain metastasis samples by RNA sequencing, and results were combined with a screen using *Drosophila melanogster*. Based on these results, Rab11b was identified as a functional mediator of metastasis. Breast cancer cells transfected with shRNA targeting Rab11b showed dramatically lower β1 integrin recycling rate compared to control cells, which led to impaired integrin-ECM engagement and decreased brain metastasis. These results show that Rab11b-mediated Integrins recycling plays role in BCBM (Howe et al., 2020). In another study, vascular endothelial cells (VECs) were investigated, in which ARF6 enhances hepatocyte growth factor (HGF)-induced β1 integrin recycling that promotes VECs migration and tumor angiogenesis (Hongu et al., 2016).

These results illustrate well how unbalanced expression of key regulators of integrin traffic might affect metastasis. However, there are other cases when proper integrin traffic is crucial.

ARF6-mediated integrin recycling can affect migration capacity of neutrophil granulocytes as well, which may lead to immunodeficiency disorders characterized by returning infections (Gamara et al., 2020). Additionally, α5β1 integrins play a role in lamellipodia formation of macrophages and hence regulates their migration capacities (Veale et al., 2010). During acute lung injury, microvesicles containing miRNAs are released from lung epithelium, which induce trafficking of β1 integrins to recycling endosomes in mouse bone marrow-derived macrophages (BMDMs). This process promotes macrophage recruitment and contributes to lung inflammation (Lee et al., 2017.). Several other studies showed that integrin αvβ6 mediates inflammatory response in lungs and in the gut plays a role in amelogenesis, wound healing and fibrosis (reviewed in Koivisto et al., 2018). Maintaining typical vascular structure is governed by vascular smooth muscle cells (SMCs), and the process is modulated by integrins (among other proteins). Elevated expression level of α5β1 integrin in SMCs can mediate early atherosclerosis as well (Jain and Chauhan, 2022).

Conclusion

Recent results suggest that endocytic trafficking of integrins—besides their gene expression—could affect core cell functions. The regulation of integrins has immense effect on cell motility and tumorgenesis. Previous results confirmed that clathrin-dependent endocytosis is not the only way to uptake integrins; there are several other pathways, which can ensure that. Internalization and recycling are both regulated and influenced by numerous factors that are waiting to be explored and clarified completely, like ARF6, which interactions and roles need to be examined further. On the other hand, the newly described retriever pathway clarified the role of WASH complex and SNX17 as well. Furthermore, new internalization components and their role have been discovered, such as Galectin-3, CLIC and N-glycosylation. Though more and more routes are discovered, it is not completely known yet how cells associate and send different integrins to different pathways. In summary, we should notice that investigations dealing with α5β1 integrins are overrepresented compared to others. We admit that α5β1 integrins have a crucial role in several cellular processes and β1 subunit could heterodimerize with most of the subunits, but the roles of other integrins are not negligible, and as we saw, the regulation of integrins varies greatly.

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Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

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