Seminars in Cell and Developmental Biology 132 (2022) 171–184

Contents lists available at ScienceDirect

Seminars in Cell and Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Membrane compartmentalisation of the ubiquitin system

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ARTICLE INFO

Keywords:
Ubiquitin
DUB
E3 ubiquitin ligase
Subcellular map
Proteomics
PA-TM-RING

ABSTRACT

We now have a comprehensive inventory of ubiquitin system components. Understanding of any system also needs an appreciation of how components are organised together. Quantitative proteomics has provided us with a census of their relative populations in several model cell types. Here, by examining large scale unbiased data sets, we seek to identify and map those components, which principally reside on the major organelles of the endomembrane system. We present the consensus distribution of > 50 ubiquitin modifying enzymes, E2s, E3s and DUBs, that possess transmembrane domains. This analysis reveals that the ER and endosomal compartments have a diverse cast of resident E3s, whilst the Golgi and mitochondria operate with a more restricted palette. We describe key functions of ubiquitylation that are specific to each compartment and relate this to their signature complement of ubiquitin modifying components.

1. Introduction

The subcellular compartmentalisation of biochemical reactions is a cornerstone of cell biology. Sometimes this reflects sequestration within the lumen of organelles, as is the case for degradative enzymes of the lysosome or the carbohydrate modifying enzymes of the Golgi complex [1]. With the exception of the porous nucleus, there is little evidence for intra-organelle ubiquitylation events. However, the surface of each organelle offers a unique combination of hundreds of proteins, providing a means to both generate and restrict ubiquitin signaling cascades.

We have previously described the demographics of the ubiquitin system [2]. Modern proteomic methodologies have allowed the estimation of protein copy number for each protein component. Thus, we can build a picture of the most abundant E2s, E3s and deubiquitylases (DUBs) which are likely to dominate the cellular ubiquitin exchange economy. However, a further step towards a systems level understanding is to map the location of the components. Where are they most concentrated? Which other components do they co-localise with and can this be linked with location critical functions? Here we will review the cellular geography of the ubiquitin system. The most simple separation one can make is between nucleus and cytoplasm, but our focus will be on the membranous organelles, island communities existing in the sea of cytoplasm. What are the main functions that rely on such compartmentalisation and what are the main components which govern such localised ubiquitylation events?

2. Techniques for studying protein localisation

The principal techniques for studying protein localisation are subcellular fractionation and microscopical detection using specific antibodies or epitope-tagged proteins (Fig. 1A). Classical fractionation studies are challenging and relatively few organelles can be purified to homogeneity. Those which can, include mitochondria, synaptic vesicles and clathrin-coated vesicles, for which comprehensive proteomic analyses have been published [3–6]. More recently, the Sabatini group has developed a series of 3xHA-tagged constructs that allow rapid immuno-capture of specific compartments [7–10]. Studies using this approach have generated proteome inventories for mitochondria, lysosomes and peroxisomes. A systematic analysis of localisation of GFP-tagged proteins has been reported for ~75% of the yeast proteome [11]. In mammalian cells this approach has been restricted to smaller sets, including our own analysis of DUB protein distribution [12,13]. A protein atlas of ~12,000 endogenous proteins has also been reported based on the use of specific antibodies [14]. Judging by our own experience, we would urge caution with this latter resource.

For global proteomic analyses, two complementary approaches are moving the field forwards (Fig. 1B,C). The first involves analysis of

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https://doi.org/10.1016/j.semcdb.2021.11.016
Received 5 October 2021; Received in revised form 12 November 2021; Accepted 15 November 2021
Available online 9 December 2021

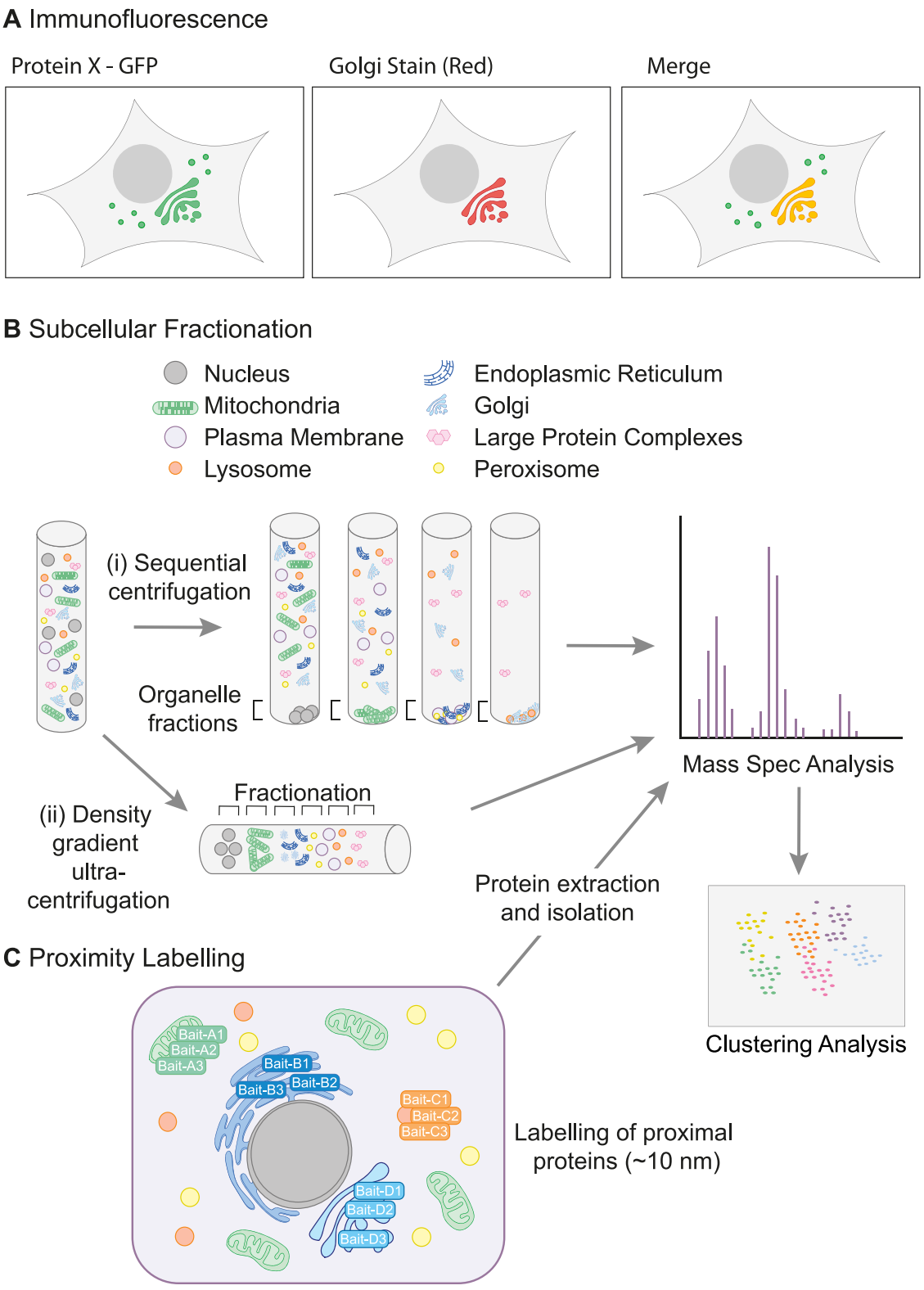


Fig. 1. Systematic Subcellular Mapping of the Proteome. A. Fluorescence microscopy using epitope tagged compartmental markers or immunostaining with specific antibodies. B. Subcellular Fractionation: This can be achieved by: (i) differential velocity sedimentation, whereby cellular fractions are sequentially pelleted at varying speeds, (ii) density gradient ultracentrifugation. Fractions from each step contain a unique profile of cellular organelles. C. Proximity labelling: APEX2 or a promiscuous biotin ligase (BioID) can be fused to a targeting motif or protein (Bait). Multiple baits are chosen for each compartment of interest. Following expression of the Bait-Enzyme fusion, proteins within ~10 nm radius are labelled with biotin, which can then be isolated. Samples from B, C are processed and analysed using Mass Spectrometry to identify proteins that are enriched in each sample. Cluster analysis is used to determine proteins with shared profiles, suggestive of co-localisation.

protein abundance distributions across a centrifugal fractionation gradient, a modern take on De Duve's classic work [15]. Proteins with predominantly overlapping locations will have similar distributions across the gradient, that are revealed by cluster analysis and linkage to organellar marker proteins [16–20]. The second involves systematic proximity labelling experiments, using BioID (BirA*, a mutant E.coli biotin ligase) or APEX (Ascorbate Peroxidase) with multiple organelle markers [21–23]. Targeting each compartment with multiple bait proteins generates comprehensive inventories that connect to provide a map of the cell [24]. Both approaches are limited when proteins are present in multiple locations and assignments can be difficult to call.

3. Integral membrane ubiquitin modifying enzymes

We will start by considering those components of the ubiquitin system that are anchored at specific locations by transmembrane (TM) domains and also consider their relative abundance in model cell lines (Table 1, Supplementary Tables 1 and 2). These will often give the most clear-cut assignments using the methods described above, and we will present the consensus picture emerging from such studies. There are just two TM-E2 paralogues, UBE2J1 and UBE2J2 which localise to the endoplasmic reticulum (ER) and two TM-DUBs which have been unambiguously assigned to ER (USP19) and mitochondria/peroxisomes (USP30) [12, 25–29]. In fact it is the RING family of E3 ligases that provide us with a larger set of examples (57 TM-RING, and 5 TM-RBR proteins).

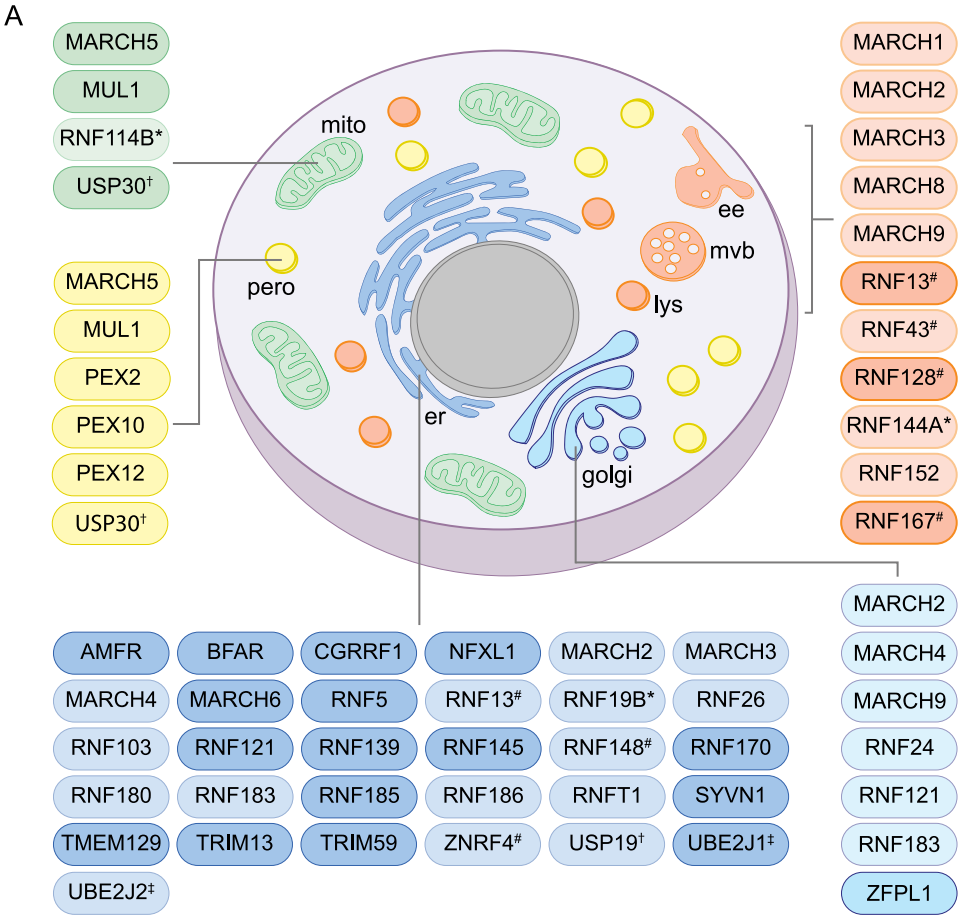
Significant families within this set include the MARCH family of multiple transmembrane proteins of which there are 11 human representatives defined by the presence of a RING-CH domain [30]. All but MARCH7 and MARCH10 have multiple predicted TM domains and distribute across multiple locations, whilst retaining a common thread of immune regulation. A further 11 are defined by the PA-TM-RING trio of domains, where PA denotes a Protease-Associated domain [31]. The PA domain was first identified in proteins that belong to different protease

Table 1
Comparison of organellar/subcellular localisation data for transmembrane ubiquitin E2, E3 and DUBs extracted from large scale quantitative proteomic studies. Localisation calls were derived from the following datasets: "The HeLa Spatial Proteome" [16] with prediction confidence shown in brackets; "Human Cell Map" [24] using NMF (non-negative matrix factorisation) analysis; "LOPIT-DC" and "HyperLOPIT" [18] with localisations not passing FDR curation shown in brackets; "Compartmental Map of the Rat Liver Proteome" [17] showing majority location, or top 2 locations for close calls, for proteins identified with > 1 peptide. Also shown are consensus localisations curated from the literature (low confidence calls in brackets). Organellar assignments are colour coded with ER and Golgi shown in shades of blue, endosomes and lysosomes in orange, mitochondria in green and peroxisomes in yellow. ER, endoplasmic reticulum; Endo, endosome; Nuc OM, nuclear outer membrane; PM, plasma membrane; Mito OM, mitochondrial outer membrane; Mito, mitochondria; Pero, peroxisomes; Lyso, lysosome; med, medium. # Indicates PA-TM-RING proteins, of which RNF43, RNF215 and ZNRF3 may be classified as atypical (Kay Hofmann, personal communication). For alternative names, TMD count, abundance and associated literature references see supplementary tables 1 and 2.

Gene Name	Uniprot ID	Class	HeLa spatial proteome	Human Cell Map - BioID (HEK293)	LOPIT-DC (U2OS)	HyperLOPIT (U2OS)	Rat proteome	Literature consensus
SYVN1	Q86TM6	E3-RING	ER (high)	ER	ER	ER	ER	ER
UBE2J1	Q9Y385	E2	ER (high)	Nuc OM, ER	ER (low)	ER (low)	ER	ER
NFXL1	Q6ZNB6	E3-RING	ER (high)	Nuc OM, ER	ER	ER	ER	
AMFR	Q9UKV5	E3-RING	ER (high)		Pero (low)	ER (low)	ER	ER
RNF139	Q8WU17	E3-RING			ER	ER (low)	ER	ER
MARCH6	O60337	E3-RING	ER (med)	ER	ER		ER, Golgi	ER
RNF145	Q96MT1	E3-RING			ER			ER
TRIM59	Q8IWR1	E3-RING			ER (low)			ER
TRIM13	O60858	E3-RING		Nuc OM,ER				ER
BFAR	Q9NZS9	E3-RING					ER, Golgi	ER
CGRRF1	Q99675	E3-RING					ER	ER
RNF170	Q96K19	E3-RING					ER	ER
TMEM129	A0AVI4	E3-RING					ER	ER
USP19	O94966	DUB	PM (v.low)			PM (low)		ER
RNFT1	Q5M7Z0	E3-RING			Golgi (low)			ER
ZFPL1	O95159	E3-RING	Golgi (high)	Golgi	Golgi (low)	Golgi (low)	Golgi	Golgi
RNF121	Q9H920	E3-RING			ER (low)		ER	Golgi
RNF24	Q9Y225	E3-RING						Golgi
RNF5	Q99942	E3-RING	ER (med)				Golgi	ER
RNF185	Q96GF1	E3-RING	ER (v.low)				Golgi	ER, (Mito)
RNF149	Q8NC42	E3-RING#	ER (low)	Golgi			PM	Lyso
RNF167	Q9H6Y7	E3-RING#	Lyso (v.high)			Lyso	Lyso	Endo, Lyso, (PM)
RNF13	O43567	E3-RING#	Lyso (v.high)				Lyso	Endo, Lyso, ER
RNF128	Q8TEB7	E3-RING#					PM, Lyso	Endo, Lyso, (ER)
ZNRF3	Q9ULT6	E3-RING#					Lyso	PM
MARCH5	Q9NX47	E3-RING	Mito (med)	Mito OM, Pero	PM (low)		Mito	Mito, Pero
MUL1	Q969V5	E3-RING	Mito (med)	Mito OM, Pero	PM (low)	Mito	Mito ,Pero	Mito, Pero
USP30	Q70CQ3	DUB		Mito OM, Pero			Mito ,Pero	Mito, Pero
PEX10	O60683	E3-RING				Mito (low)	Pero	Pero
PEX12	O00623	E3-RING	Pero (v.low)	Mito OM, Pero	Pero		Pero	Pero
PEX2	P28328	E3-RING			Pero		Pero	Pero

families, including subtilases and Zn-containing metalloproteases, and is proposed to mediate protein interactions [32].

A collection of GFP-tagged TM-RING E3s expressed in HeLa cells were mapped by Neutzner et al. [33]. More recently Christianson and colleagues have undertaken systematic co-immunoprecipitation of 21 endoplasmic reticulum resident TM-RING E3 proteins [34]. In Table 1 and Supplementary Table 2, we have collated subcellular localisation studies for 49 of the TM domain containing E3 components of the ubiquitin system, 2 TM-E2s and 2 TM-DUBs. It indicates multiple examples of consensus assignments, which include SYVN1/HRD1, NFXL1, AMFR/gp78, UBE2J1 (ER), ZFPL1 (Golgi), RNF167, RNF13 (lysosomes) and MUL1, MARCH5, USP30 (Mitochondria/peroxisomes). We have also provided data on estimated abundance of each protein in asynchronous HeLa and NIH3T3 cells, where available (Supplementary Table 1). Fig. 2 provides a summary map, incorporating this data alongside more granular literature studies (references in Supplementary Table 2) that inform upon components that have evaded the proteomics studies, most likely owing to low abundance and/or restricted expression patterns. We have previously provided a similar illustration for the DUB family of enzymes [13].



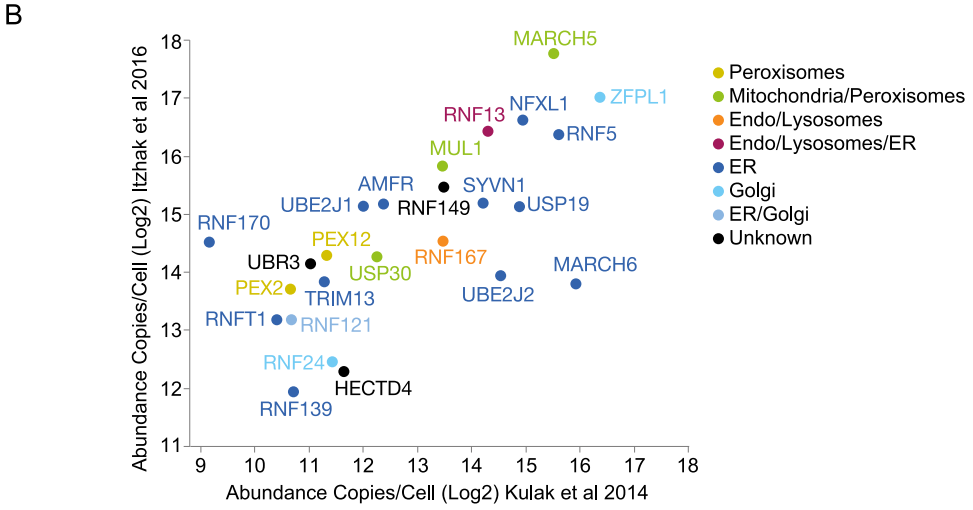


Fig. 2. Subcellular localisation of transmembrane domain containing E3 ligases (RING and RBR classes), E2 ligases and DUBs. A. Data are based on screens and individual studies (see Table 1 and Supplementary Table 2). Those shown with a pale box are based on literature curation, whilst darker boxes indicate evidence sourced from unbiased high-throughput screens, see Supplementary Table 2. * RBR E3 Ligases, # PA-TM-RING E3 Ligases, ‡ E2 Ligases, † DUBs. B. Protein copy number estimates derived from global proteomic studies of HeLa cells [16,219].

4. ER ubiquitylation

Of all subcellular membranes, the ER has the largest and most diverse community of ubiquitin modifying enzymes. This includes > 20 TM-RING E3s, 2 TM-E2s and a TM-DUB, USP19. Furthermore, the closely related DUBs USP20 and USP33 have been convincingly associated with the ER membrane [35,36]. From analyses of proteomics data we note the clear association of NFXL1 with the ER, which has so far not been tested by any alternative methods (Table 1, Fig. 2A). We also note that it is one of the most abundant TM-E3s in HeLa cells, yet remains uncharacterised (Fig. 2B, Supplementary Table 1).

4.1. Protein quality control

Proteins enter the secretory pathway following translocation across the ER membrane, typically in a co-translational manner. Nascent chains can then undergo chaperone assisted folding, disulphide bond formation, complex formation and glycosylation. The adoption of the optimal configuration is an iterative process that is inherently fallible and its comprehensive failure can lead to ER stress. Such misfolded proteins are eliminated by the ubiquitin-dependent ER associated degradation pathway (ERAD) [37]. To encounter ubiquitin modifying enzymes, misfolded ER proteins must first be retro-translocated back across the ER membrane to allow some exposure at the cytosolic face. This leads to

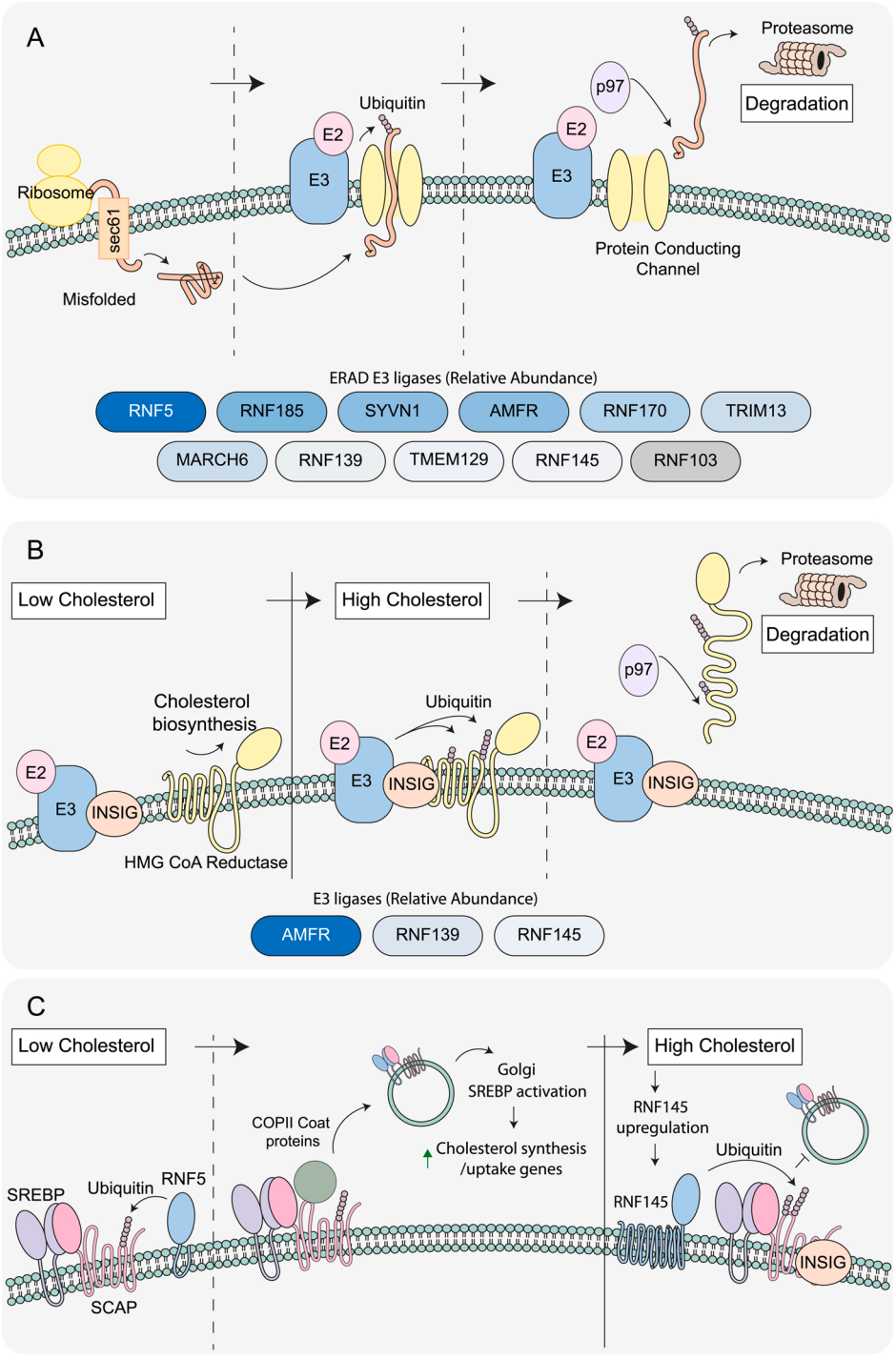


Fig. 3. E3 Ligases are critical in the control and regulation of ER-associated degradation (ERAD). A. Model of the ERAD degradation of mis-folded proteins at the ER. Associated ER-resident E3 ligases are shown below. Depth of colour indicates relative abundance reported in Itzhak et al. [16]. B. Scheme depicting sterol sensitive ERAD degradation of HMG-CoA reductase (HMGCR), with implicated E3 ligases indicated below. Depth of colour indicates relative abundance. C Scheme depicting ubiquitin control of SREBP activation. Under low cholesterol conditions, RNF5 ubiquitylates the SREBP binding protein SCAP, thereby promoting its trafficking to the Golgi which is necessary for activation. In high cholesterol conditions the SCAP/SREBP complex interaction with COPII proteins is inhibited by both the binding of SCAP/SREBP to INSIG as well as the ubiquitylation of SCAP by RNF145.

their ubiquitylation, which enables their dislocation mediated by the highly abundant VCP/p97 AAA ATPase (Cdc48 in yeast), prior to proteasomal degradation in the cytosol (Fig. 3A). In yeast, Hrd1 and Doa10 (SYVN1/HRD1 and MARCH6 respectively in human) are the central E3 players in the ERAD pathway, with somewhat different roles [38–40]. Hrd1 is responsible for ubiquitylation of lumenal and transmembrane domains, whilst Doa10 predominantly ubiquitylates transmembrane proteins which have misfolded cytosolic domains [41,42]. Studies of yeast Hrd1 have revealed that it is the core element of a protein conducting channel, via which retrotranslocation of luminal proteins occurs [43,44]. *In vitro* reconstitution studies have shown that auto-ubiquitylation of Hrd1 leads to opening of the pore, substrate binding leads to pore expansion and that deubiquitylation (by Ubp1 in yeast) leads to pore closure and may protect Hrd1 from degradation itself [45,46]. In mammalian cells, HRD1 (SYVN1) is highly up-regulated following application of an ER stress, such as the glycosylation inhibitor Tunicamycin [34,47]. HRD1 is the pre-eminent mammalian ERAD E3 ligase, but can be supported by a range of other E3s which include its closest paralogue AMFR (gp78), MARCH6 (TEB4), RNF5, TRIM13 (RFP2), RNF103 (Kf-1) and RNF139 (TRC8) [48]. One of the highest profile ERAD clients, the cystic fibrosis transmembrane conductance regulator (CFTR) ΔF508 mutant, is degraded in an HRD1 independent fashion [48]. Instead RNF5, RNF185 and AMFR/gp78 collaborate in this task [49,50]. The resident ER localised E2s, UBE2J1 and UBE2J2 have also been implicated in the ERAD pathway [25,51,52].

Ancient ubiquitous protein 1 (AUP1), in common with AMFR/gp78, contains a ubiquitin binding CUE (coupling of ubiquitin to ER-associated degradation) domain, and a G2BR (G2 binding region) at its cytosol directed C-terminus. AUP1 is a monotopic membrane protein that is found in the ER but is largely localised to lipid droplets, which in turn can themselves bind to the ER. As for AMFR/gp78, the G2BR domain can recruit the E2 UBE2G2 [53,54]. AUP1 has been linked to the ERAD processing of several substrates and a model has been proposed in which lipid droplets play a role in their partitioning prior to degradation [53,55].

DUBs could oppose the ERAD pathway allowing more leeway for correct folding to occur. A long isoform of USP19 contains a transmembrane domain which localises it to the ER and can fulfil this function [28]. Development of this concept has recently been provided by the artificial recruitment of USP21 or OTUB1 to ERAD substrates, such as CFTR, leading to a rescue in surface expression of certain disease causing mutants [56,57]. There is also likely a positive role for DUBs in ERAD via the processing of proteins extracted by p97, which is necessary for their release from this complex [58].

So-called tail-anchored proteins are synthesised in the cytosol, necessitating that their single hydrophobic C-terminal transmembrane domain is shielded prior to delivery to the correct membrane. Recent work has shown that these proteins can be ubiquitylated in the cytosol prior to insertion, whilst somehow evading proteolytic degradation. Once inserted into ER membranes tail anchored proteins are deubiquitylated by a combination of USP20 and USP33 activities [59].

4.2. Cholesterol homeostasis

The ER is the site of cholesterol biosynthesis. The rate limiting step is the reduction of 3-hydroxy-3-methyglutaryl coenzyme A (HMG coA) by HMG coA reductase (HMGCR). This enzyme has a sterol sensing domain composed of 5 transmembrane components. Under low cholesterol conditions the enzyme is relatively stable, but when cholesterol is elevated it interacts with INSIG1 and INSIG2, which in turn recruit the E3 ligase AMFR/gp78, RNF145 or RNF139 (Fig. 3B) [60–63]. Thus cholesterol synthesis is kept in check by a negative feedback loop resulting in the controlled degradation of HMG CoA reductase by the ERAD pathway. Under low cholesterol conditions, INSIG1 is itself degraded in a AMFR/gp78 dependent manner [64,65]. Squalene epoxidase (SQLE) carries out the second rate limiting reaction in the cholesterol synthesis pathway and its degradation is similarly promoted by high levels of cholesterol. In this case the sterol sensing element is its N-terminal region which enables recruitment of the E3 ligase MARCH6 which combines with the ER resident E2, UBE2J2 [66–68].

In mouse models, post-feeding, HMGCR levels and consequently cholesterol biosynthesis increase [69]. This is due to its stabilisation by the ER-associated DUB, USP20. In the post-prandial phase, high glucose and insulin levels lead to TOR activation and phosphorylation of USP20. This phosphorylation causes USP20 to associate with AMFR/gp78 and to counteract its ubiquitylating activity towards HMGCR . Liver specific genetic deletion of USP20 or its pharmacological inhibition decreases diet-induced body weight gain and changes a number of other metabolic parameters accordingly [69].

SREBP is the master transcriptional regulator of cholesterol biosynthesis. Under low cholesterol conditions it traffics from the ER to the Golgi, where it is untethered by proteases. For its stability and transport, it requires a sterol-sensing chaperone molecule, SCAP [70]. RNF5 ubiquitylates a specific lysine within a cytosolic loop of SCAP to form Lys29-linked ubiquitin chains. This provides a non-degradative signal for SREBP activation, most likely by inducing a conformational change that favours ER exit [71]. In contrast, the HMGCR regulator, RNF145, whose expression is induced by high cholesterol, exerts a second means of suppressing cholesterol biosynthesis through its alternative non-degradative ubiquitylation of SCAP that inhibits SREBP2 activation (Fig. 3C) [72].

4.3. Ca^{2+} release

The ER is the central intracellular Ca^{2+} store. Release of Ca^{2+} is elicited by binding of the second messenger molecule IP_3 to tetrameric receptors located in the ER membrane [73]. IP_3 receptors are down-regulated by ERAD when persistently activated. Following activation, the ER localised E3 ligase, RNF170 is rapidly recruited to the IP_3 receptor by cofactors Erlin 1/2 and promotes receptor ubiquitylation and degradation [74]. RNF170 mutation underlies autosomal dominant ataxia, a rare condition associated with degeneration of the posterior columns of the spinal cord and has also been associated with spastic paraplegia [75,76]. It is unclear if this reflects defects in Ca^{2+} handling, although this is a common feature of many neurological conditions [77]. Whilst, mainly residing in the nucleus, a small fraction of the tumour suppressor DUB, BAP1, associates with the ER where it acts to stabilise IP_3 receptors. The consequent mis-handling of Ca^{2+} fluxes in $BAP1^{+/-}$ cells leads to reduced apoptosis and higher rates of transformation following exposure to genotoxic stresses [78].

4.4. Immune signaling

The ER is the site of peptide loading onto MHC class I proteins. Viruses which wish to evade immune detection may dedicate resources to down-regulating this pathway. Human cytomegalovirus expresses two genes, US2 and US11 which promote degradation of MHC class I via ERAD. They do this by binding to newly translated MHC I and commandeering ER resident E3 ligases. US2 recruits RNF139 (also known as TRC8) whilst US11 indirectly recruits TMEM129, an ER resident protein with an atypical RING domain, via Derlin-1 [79–81]. US11 is highly specific for MHC I but US2 down-regulates a host of other proteins normally destined for the plasma membrane by the same mechanism [82]. In uninfected cells, mis-folded MHC 1 is degraded by the HRD1-SEL1 complex [52].

The ER resident STING (also referred to as MITA) co-ordinates innate immune responses to foreign DNA [83,84]. Its links to auto-immune and auto-inflammatory disorders necessitate a tight regulation. During HSV-1 infection, its upstream activator, the dsDNA sensor cGAS, is ubiquitylated with Lys27-linked ubiquitin chains by RNF185 leading to enzyme activation [85]. Broadly speaking, ubiquitylation of multiple

types is used either for STING turnover, as a component of the signaling cascade regulating oligomerisation or for recruiting the downstream kinase TBK1. Upwards of seven E3s have been linked to STING ubiquitylation with three different chain topologies [86]. Not all of these necessarily act at the ER, exit from which is a prerequisite for STING to activate IRF3 at the Golgi. Cytoplasmic DNA leads to recruitment of the ER resident E3 ligase AMFR/gp78 to STING in an INSIG1 dependent manner. This results in its decoration with Lys27-linked ubiquitin chains, that serve as a recruiting platform for TANK-binding kinase 1 (TBK1) [87]. The unusual linkage type, shared with its upstream activator (cGAS), conceivably spares STING from the ERAD pathway. Two ER resident TM-E3s oppose each other to control STING stability. RNF5 ubiquitylates STING at Lys150 to generate Lys48-linked chains that result in its degradation and dampening of the anti-viral response, whilst RNF26 can protect from this effect by generating Lys11-linked chains at the same position [88,89].

5. Mitochondrial ubiquitylation

Following mitochondrial depolarisation, PINK1 accumulation at mitochondria leads to the recruitment and activation of the RBR E3 ligase Parkin (PRKN). This unleashes a ubiquitylation cascade that promotes mitophagy [90]. Both of these proteins are mutated in Parkinson's disease, rendering this an intense area of research which is already well served by review articles [91]. Here we will focus on other aspects of ubiquitin function at mitochondria. The presence of at least two TM-E3s (MARCH5, MUL1) and of the TM-DUB, USP30 (Fig. 2), suggests a diverse repertoire. It is worth noting that the majority of mitophagy which occurs in vivo is Parkin independent and there is intense interest in alternate pathways [92,93]. Mitochondria must import the majority of their resident proteins and there has been much speculation as to whether a mitochondrial equivalent of the ERAD pathway may exist to alleviate any defects in import or folding. One such pathway discovered in yeast has been termed mitoTAD. In this pathway a pool of the AAA ATPase Cdc48 co-factor and ubiquitin binder, Ubx2, associates with the TOM import complex for removal of arrested precursor proteins from the TOM channel [94,95]. Other key roles for ubiquitylation at mitochondria relate to cell death and innate immune sensing pathways. Several enzymes linked to mitochondrial functions, Parkin, HUWE1 and USP30 preferentially generate or process Lys6 linked ubiquitin chains [96–98].

5.1. MAVs pathway

The RIGI-like receptor (RLR) pathway is a major arm of the innate immune response to RNA viruses that is co-ordinated at mitochondria. RIG-I interacts with mitochondrial anti-viral signaling (MAVS), which then oligomerises and transmits downstream signals that culminate in a transcriptional response [99]. Several studies now indicate that MARCH5/RNF153/MITOL may act to attenuate this pathway by degrading the active forms of both MAVS and RIG-I [100–102]. There is evidence for integration of this action with a second line of antiviral RNA signaling mediated by Toll Like Receptor 7 (TLR7), but in this case MARCH5 activity is stimulatory. It has been shown to polyubiquitylate TANK with Lys63-linked chains, which releases its inhibition of TRAF6, a downstream component of the signaling cascade. Mitochondrial localisation of MARCH5 was found to be essential for this activity [103].

5.2. Mitochondrial dynamics and architecture

MARCH5 effects on mitochondrial dynamics and architecture have been reported through control of both fission (DRP1) and fusion factors (Mitofusins) which can be extracted by p97 AAA-ATPase and degraded by the proteasome [104–108]. Buffering of ER Ca^{2+} release by mitochondria is determined by Mitochondial-ER contact sites (MERCS). MARCH5 is enriched at these sites, where it is proposed to ubiquitylate Mitofusin 2 (MFN2). This ubiquitylation enhances the GTPase activity of MFN2 which in turn promotes its ability to trans-oligomerise with ER located MFN2, facilitating MERC formation and flow of Ca^{2+} into mitochondria [109].

MUL1 contains two TM domains and localises to mitochondria [110]. Interestingly it has been implicated in sumoylation as well as ubiquitylation [111,112]. Sumoylation of DRP1 by MUL1 leads to its stabilisation and promotes mitochondrial fragmentation [111]. MUL1 has also been shown to ubiquitylate MFN2 and evidence suggests that its over-expression can compensate for loss of PINK1 or Parkin in this respect [113,114].

HUWE1 (HECT, UBA And WWE Domain Containing E3 Ubiquitin Protein Ligase 1) is a highly abundant RING-E3 with many critical functions, but without a discernible TM domain. However, proximity dependent biotinylation mapping places a fraction on mitochondria/peroxisomes, supporting previous reports based on functional studies [24]. HUWE1 preferentially generates Lys6-linked ubiquitin chains and its Lys6-rich substrates include MFN2 [98]. Like Parkin, under depolarising conditions HUWE1 association with mitochondria increases, where it facilitates a distinct AMBRA1-mediated mitophagy pathway [115].

5.3. Regulation of apoptosis

The intrinsic pathway of apoptosis involves permeabilisation of the outer mitochondrial membrane, leading to release of molecules such as cytochrome c and Smac/DIABLO. The most critical regulators are the members of the pro-survival Bcl2 family proteins and the pro-apoptotic BH3-only proteins. The balance of these proteins at mitochondria determines the likelihood of BAX/BAK activation leading to pore formation [116]. MCL1 is by far the least stable member of the anti-apoptotic Bcl2 family and enhancement of its turnover is a high value goal for drug discovery. For example, following DNA damage or cell cycle arrest, degradation of MCL1 by HUWE1 or FBXW7 enhances apoptosis [117–119]. MCL1 degradation is promoted by interaction with the BH3-only protein NOXA, but not other family members. Recently, using a CRISPR screening approach, it has been discovered that this interaction enables MARCH5-dependent MCL-1 degradation in conjunction with the E2 enzyme UBE2K and the accessory protein MTCH2 [120]. Under apoptotic conditions, the otherwise mainly cytosolic RNF144B translocates to mitochondria following mitochondrial BAX activation leading to BAX degradation, thereby applying a brake to apoptosis [121].

5.4. Mitochondrial import

The vast majority of mitochondrial proteins enter via a signal sequence-determined interaction with the TOM import complex. Recent work has suggested that MARCH5 and USP30 reciprocally modify newly synthesised mitochondrial proteins, with ubiquitylation restricting their entry [122,123]. One of the most critical of these is Polγ A, the sole catalytic sub-unit of the mtDNA polymerase. MARCH5-dependent ubiquitylation of newly synthesised Polγ A with Lys6-linked ubiquitin chains inhibits interaction with TOMM20 and thereby limits entry. Mutations in Polγ A lead to progressive external ophthalmoplegia. Some of these variants become hyper-ubiquitylated and cannot enter into mitochondria leading to reduced mitochondrial replication [124]. We and others have proposed that either these proteins or the associated TOM complex may provide the first ubiquitin substrates for PINK1 which triggers the PINK1-Parkin-dependent ubiquitylation cascade that leads to mitophagy [122,123,125,126].

6. Peroxisome ubiquitylation

There is a significant overlap in proteome composition between mitochondria and peroxisomes. For example MUL1, MARCH5 and

USP30 are associated with both organelles [125,127,128]. However, peroxisomes are perhaps unique in having reversible ubiquitylation pathways so tightly coupled to their identity. Three RING containing proteins PEX2, PEX10 and PEX12, all of which have been linked to the peroxisome biogenesis disorder Zellweger syndrome, form a complex on the peroxisomal membrane and respectively link with different E2 enzymes. Most peroxisomal matrix proteins have a peroxisomal targeting signal (PTS1) comprised of a C-terminal serine-lysine-leucine (SKL) tripeptide sequence. PEX5 acts as a receptor for such proteins in the cytosol and transports them into the peroxisomal matrix, whereupon it is recycled to the cytosol in an ATP-dependent manner by an AAA ATPase. A critical factor, in the extraction process from the peroxisomal membrane, is the specific monoubiquitylation of PEX5 at a conserved cysteine, mediated in yeast by PEX12 working with the E2 PEX4 [129–133]. Control of PEX5 protein turnover can provide a means to control peroxisome homeostasis. PEX5 can be polyubiquitylated at lysine residues by PEX2 working with UBC4 for subsequent degradation by the proteasome [129]. Alternatively, TRIM37, which localises to peroxisomes, can monoubiquitylate PEX5 at Lys464 leading to its stabilisation [134]. Loss of function mutations in TRIM37 lead to developmental defects associated with mulibrey nanism, which is now classed as a peroxisome biogenesis disorder [135].

Another means of regulating peroxisome number is through their selective autophagy, in a process termed pexophagy. In common with other autophagy events, furnishing peroxisomes with artificially ubiquitylated membrane proteins is sufficient to drive their pexophagy [136]. Under conditions that perturb PEX5 extraction, such as loss of AAA ATPase function, the surface accumulation of monoubiquitylated PEX5 itself can promote pexophagy [137]. In response to oxidative stress, ATM kinase phosphorylates PEX5 which enables its ubiquitylation by RING peroxins at Lys209 and promotes pexophagy [138]. Thus the RING peroxin complex can provide a palette of ubiquitylation on PEX5 reflecting prevailing conditions and leading to a variety of outcomes. Other work has shown that oxidatively stressed peroxisomes recruit the E3 ligase STUB1 and that this is sufficient to drive pexophagy [139]. A fraction of the otherwise mitochondrial DUB, USP30, localises to peroxisomes [125]. Our laboratory has shown that depletion of USP30 enhances basal levels of pexophagy in mammalian cells, whilst others have shown that USP30 overexpression can counteract E3 activity of PEX2 during starvation induced pexophagy [125,140]. In a similar vein, the mitochondrial E3, MARCH5, has recently been shown to be recruited to peroxisomes via interaction with PEX19 where it can promote pexophagy through ubiquitylation of PMP70 [128]. USP30 has previously been shown to deubiquitylate MARCH5 substrates at mitochondria and to limit mitophagy [123]. This new work suggests the possibility of a parallel reciprocal relationship between USP30 and MARCH5 on peroxisomes.

7. Golgi ubiquitylation

Subcellular proteomics clearly identifies ZFPL1 as a very high confidence Golgi-associated TM-E3 protein and in fact this is one of the highest abundance TM-E3s in the cell (Table 1, Supplementary Table 1 and Fig. 2). Detailed study has shown that it associates with the cis-Golgi and is important for structural integrity as well optimal trafficking into the Golgi from the ER. The RING finger is required for these functions but candidate ubiquitylation substrates have not so far been identified [141]. The Cullin E3 ligase, $Cul7^{Fbxw8}$, localises to the Golgi via binding to OBSL1 (Obscurin Like Cytoskeletal Adaptor 1) and appears to colocalise best with a trans-Golgi network (TGN) marker [142]. $Cul7^{Fbxw8}$ regulates dendrite formation and Golgi morphology in neurons and one relevant substrate has been identified as the cis-Golgi protein GRASP65, a known regulator of Golgi morphology. Interestingly GRASP65 interacts with GM130 which has been shown to bind to ZFPL1, suggesting that this complex may be a major target for ubiquitylation at the Golgi, which merits further examination [143].

RNF24 has been convincingly localised to the Golgi complex and is known to bind to and retain transient receptor potential channels (TRPCs) intracellularly, but a role for ubiquitylation has not so far been established [144]. MARCH9 is up-regulated by stimulation of dendritic cells with LPS. There is conflicting evidence on its localisation. However, one recent study has suggested that at endogenous levels it functions at the TGN where its ubiquitylating activity is used to promote the sorting of MHC class I to the endocytic pathway [145].

8. Plasma membrane to lysosome ubiquitylation

We will consider the endosomal pathway as a whole, demarcated by the plasma membrane at one end and the degradative lysosomal compartment at the other. Between them lie various vesicles mediating receptor internalisation (principally AP2/clathrin-coated vesicles), which deliver to the early or sorting endosome, that gradually matures into MVBs that fuse with lysosomes. The major discovery of ubiquitin as a sorting signal for lysosomal degradation was based on studies of vacuolar protein sorting in yeast cells [146]. In yeast and mammals ubiquitylated proteins are captured by multiple components of the ESCRT machinery at the limiting membrane of endosomes, for inclusion into lumenal vesicles, the defining feature of multivesicular bodies (MVBs) [147]. Mature MVBs go on to fuse directly with lysosomes [148]. Critical early work in mammalian cells showed that appendage of ubiquitin to Transferrin Receptor (TfR) could redirect it from an endosomal recycling pathway towards lysosomal degradation [149]. Although the plasma membrane is difficult to purify by conventional fractionation techniques, it allows for selective labelling of surface proteins for example via biotinylation. This kind of approach simply indicates presence of a fraction at the plasma membrane rather than enrichment relative to any other compartments. Even with this proviso, few TM-RINGs can be assigned to the plasma membrane. For example only two TM-RINGs were identified from $>$ 2000 surface proteins in HeLa cells, ZFPL1 (see section on Golgi above) and the PA-TM-RING protein RNF150 [150]. The constituent proteome of the lysosome has similarly been addressed using a so-called lyso-IP (IP from cells expressing TMEM192–3xHA) which identified four further members of the PA-TM-RING family, RNF167, RNF13, RNF149, RNF128 [8]. The composite picture suggests that the sorting endosome is likely to contain the largest set of TM-E3s along this pathway. In common with the equally diversified ER, this may reflect the responsibility for governing the fate of ubiquitylated proteins. The entire pathway is also known to provide platforms for signaling cascades which frequently involve reversible ubiquitylation. In this respect the TM-RING E3, RNF152 has been shown to localise to lysosomes and act as a negative regulator of the mTORC1 pathway. It does this by targeting the GTPase RagA for Lys63-linked ubiquitylation, which in turn leads to recruitment of the inhibitory GAP complex GATOR [151].

8.1. EGFR, CBL and ESCRT dependent sorting

Most activated receptor tyrosine kinases (RTKs) become ubiquitylated and follow this same route, providing a means for signal termination. For RTKs such as EGFR and MET, the critical RING E3 ligase is CBL, which is recruited via phosphotyrosine binding [152–155]. Loss of function mutations in CBL can lead to cell transformation due to the consequent dysregulation of RTK signaling [156,157]. In general, whilst ubiquitylation of activated receptors may occur at the plasma membrane, this is not usually the primary internalisation signal. However, it is the key mediator of active sorting towards lysosomes [154]. As RTKs continue to actively signal after internalisation, we propose that CBL is recruited to endosomes and is critical for maintaining their ubiquitylation in the face of opposing DUB activities, for lysosomal sorting to occur [158]. The TM containing RBR E3-ligase, RNF144A partitions between plasma membrane and intracellular vesicles. After acute EGF stimulation it largely relocates to endocytic compartments and

re-equilibrates at the plasma membrane within an hour [159]. Evidence has been presented for a direct interaction between activated EGFR and RNF144A resulting in EGFR ubiquitylation. Puzzlingly, this has a stabilising effect on EGFR, in distinction to the well characterised destabilisation by CBL-dependent degradation [159]. We note that at least in HeLa cells, a comprehensive proteomic interactome for EGFR, readily identified CBL family proteins at multiple time points following acute stimulation but no other E3 representatives [160]. RNF144A is also not picked up in the global proteomic studies we have utilised herein and may be restricted in its expression profile. In our view CBL is the dominant E3 in dictating the itinerary of activated EGFR.

The surface of the sorting (or early endosome) is distinguished by high levels of the phosphatidylinositol PtdIns3*P*, which recruits proteins containing a FYVE domain motif from the cytosol [161,162]. Amongst these is HRS (also called HGS), which together with STAM forms the ESCRT-0 complex [163]. ESCRT-0 facilitates initial capture of ubiquitylated receptors within specialised domains at the endosome [164]. STAM provides a common interaction site for two DUBs, USP8 and AMSH (also known as STAMBP), which are recruited to the endosome surface, via a complex set of interactions [165–168]. USP8 has variable effects upon receptor fate depending on its expression levels, but one key property dominates, which is its ability to stabilise components of the ESCRT complex, particularly ESCRT-0 [169]. Concordantly, CRISPR /Cas9 gene knock-out screens for cell viability across large numbers of cell lines reveal co-essentially between USP8 and ESCRT machinery components [170]. The physiological role of AMSH is less well defined. It displays a high stringency for Lys63 ubiquitin chain linkages and consequently does not influence ESCRT-0 stability [167]. Most data are consistent with a role in deubiquitylating cargo at the endosome, such as EGFR, to favour recycling [165,171,172]. Recruitment of both AMSH and USP8 to endosomes relies on binding to a distinct, but overlapping set of ESCRT III proteins via their respective MIT domains [168,173,174]. One of these, CHMP1B is known to undergo ubiquitylation in an EGF-dependent manner which can be opposed by USP8. An interesting model has been proposed in which this deubiquitylation step favours the subsequent assembly of CHMP1B into an ESCRT III polymer, which drives MVB formation [175].

8.2. GPCRs

The seven TM G-protein-coupled receptors (GPCRs; ~700 members) represent the largest family of membrane proteins. Endocytosis occurs upon stimulation, but in many of the best studied examples the GPCR will at first recycle back to the plasma membrane. In fact cycling through endosomes can be a necessary step for resensitisation of the receptor (e.g. β2-adrenergic receptor) [176]. The down-regulation rates vary widely across the family and some enter the lysosomal pathway only following chronic stimulation. Several family members use the HECT E3-ligase atrophin-interacting protein 4 (AIP4) and then engage the ESCRT machinery as first discovered for CXCR4 [177,178]. A related E3, NEDD4 is recruited by the β2-adrenergic receptor via an adaptor protein β-arrestin [179]. Platelet acting factor (PAF) and proteolytically activated receptor 2 (PAR2) utilise CBL in common with most RTKs (discussed above) [180,181]. The ubiquitylation status of the GPCR adaptor proteins, β-arrestins, may determine their association with consequences for receptor fate [182]. MDM2 has been proposed as an E3 ligase for β-Arrestin-2 that can be countervailed by the ER associated DUB USP33 [183]. It has been established that the ER plays a critical role in regulating endosome position, motility and maturation. It does this by providing ubiquitylated p62 anchor points, at the perinuclear region of the ER, which are generated by the ER TM-RING and TM-E2 combination of RNF26 and UBE2J1 [184]. This association may then enable ER resident enzymes, such as USP33, to act (*in trans*) upon endosomal cargoes.

8.3. Endosomal PA-TM-RING proteins

At least six of the twelve PA-TM-RING proteins have thus far been linked to endocytic compartments (Fig. 2, Table 1 and Supplementary Table 1 and 2). Four (RNF13, RNF128/GRAIL, RNF149 and RNF167) were found in a proteomic analysis of highly enriched lysosome fractions [8]. RNF13, RNF167 and a structurally related protein in *Drosophila* called Godzilla also localise to endosomes [185,186]. The latter two, can both ubiquitylate the SNARE protein VAMP3 to negatively regulate endosomal recycling [186]. Deletion analysis of RNF13, RNF167 and Godzilla suggests that the lumenal PA domain can act as an endosomal targeting signal, but this is not universally dominant, since the PA-TM-RING protein ZNRF4-GFP is localised to the ER [187]. RNF128/GRAIL principally localises to recycling endosomes as judged by co-localisation with internalised Transferrin [188]. GRAIL becomes highly expressed following the induction of anergy in T cells. It has been shown to bind to the co-stimulatory molecule CD40 ligand (CD40L), as well as the tetraspanin proteins CD81 and CD151, via its lumenal PA domain, and to mediate their ubiquitylation on cytosolically exposed lysine residues [189,190]. RNF43 is involved in the suppression of Wnt-β-catenin signaling. Mis-sense mutations of RNF43 found in tumours relocalise the protein from endosomes to the ER [191]. Both RNF43 and another PA-TM-RING protein, ZNRF3, have been shown to be involved in negative feedback regulation of Wnt signaling by promoting lysosomal degradation of the Fzd receptor [192,193]. Interestingly ZNRF3 requires tyrosine dephosphorylation by PTPRK to undergo endocytosis, which is necessary for its role in WNT receptor turnover [194]. The Wnt signaling pathway is emblematic for the multiple ways that it can be regulated by ubiquitylation either at the plasma membrane or endosomes. This property is shared by other signaling cascades such as the Hedgehog, Notch and inflammatory pathways. The fine details of these systems provide a vast subject matter, we are unable to cover here, and aspects of which have been reviewed elsewhere [195–199].

8.4. Endosomal MARCH proteins

Several TM MARCH proteins have been linked to endosomal trafficking and particularly to the stability of immuno-receptors [200]. The cytoplasmic tail of MHC class II chain is constitutively ubiquitylated by MARCH1 in antigen presenting cells. This selects it for lysosomal degradation via the ESCRT pathway at the expense of recycling to the plasma membrane [201–203]. Acute activation of dendritic or B cells terminates MARCH1 expression with consequent stabilisation of MHC II for presentation to T cells [203]. Interestingly, the co-stimulatory protein, CD86 is similarly regulated by MARCH1 in dendritic cells [204]. MARCH8 has been linked to sequestration of the tetraspanin and co-stimulator of T cell signaling, CD81 into lumenal vesicles of MVBs [205]. MARCH3 and MARCH8 attenuate IL-1β mediated inflammation by ubiquitylating the receptor I and IL1 receptor accessory protein (IL1RAP) respectively. In both cases it appears that Lys48 chains predominate, but the degradation pathway is lysosomal nevertheless [206,207]. When artificially expressed in HeLa cells, MARCH9 principally localises to Cathepsin D positive lysosomes at steady state and apparently spills over to the TGN at higher levels of expression [208]. Transfection of MARCH9 can lead to downregulation of CD4, MHC I and ICAM-1 and a variety of other proteins [208–210]. A later study has suggested that this may be an artefact of over-expression and that endogenous MARCH9 may in fact regulate exit of MHC I from the TGN (see above) [145].

8.4.1. RFFL

The endosomal recycling compartment is a pericentriolar compartment with a tubular aspect, through which recycling receptors such as TfR transit en route to the plasma membrane. It is the site of RAB11 accumulation, a small GTPase that has been identified as a critical regulator of endosomal recycling [211]. One RING finger protein RFFL

(also called RIFIFYLIN) contains a FYVE-like domain which is necessary for its localisation to recycling endosomes, albeit independent of PtdIns3*P* generation. Furthermore, RFFL over-expression inhibits endosomal recycling [212]. BioID labelling studies revealed proximity with multiple RAB11 effectors [213]. Of these, only RAB11-FIP1 showed reduced ubiquitylation in RFFL knock-out cells, where TfR recycling kinetics appeared to be normal [213].

Mutant CFTR proteins which escape the quality control mechanisms at the ER and reach the plasma membrane are partially functional, but nevertheless significantly less stable than wild-type counterparts. This is because they are subject to peripheral quality control pathways, that utilise ubiquitylation to direct proteins towards lysosomes [214,215]. The relevant ligases directing this process have been identified as the HSC70 chaperone associated CHIP together with RFFL. In this study, RFFL was colocalised with early and late endosomal markers as well as the plasma membrane [216]. Wild-type CFTR also undergoes lysosomal degradation, albeit at a slower rate [214]. The endosomal ubiquitylation of CFTR that dictates lysosomal sorting can in principle be countered by DUB activity. A screen for this effect identified USP10 and further showed endosomal localisation of this DUB [217].

9. Concluding remarks

The general map of the cell is beginning to emerge. For many proteins we can make compartmental assignments based on orthologous data sets or approaches. The TM-domain proteins of the ubiquitin system provide a good test of where the field stands. However, at this point it still resembles a half assembled jigsaw puzzle, with many pieces still not assigned, which may be due to their low abundance or restricted expression patterns. Future iterations will look at membrane translocation of cytosolic proteins as a function of prevailing conditions. Our analysis here has highlighted several areas and questions that we think will be important to study in more detail. For example, what is the function of the abundant TM-RING NFXL1 at the ER? What are the substrates of the predominant Golgi TM-RING, ZFPL1? We have a particular interest in the endocytic pathway and are intrigued by the large collection of PA-TM-RING E3 ligases associated with endosomal compartments, that are relatively poorly understood. We hope this manuscript also serves as an example to cell biologists to engage with the large data sets that have become available, to which one can then add value by the application of specialist knowledge [218].

Acknowledgements

FF is supported by a Marie Sklodowska-Curie Action Innovative Training Network fellowship (UbiCODE, GA No. 765445), AB was supported by Parkinson's UK (G-1902) and is currently a Marie Sklodowska-Curie Fellow (Horizon 2020), MC is the recipient of a Royal Society Industry Fellowship. We thank Kay Hofmann (University of Cologne) for helpful discussion of domain assignments.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semcdb.2021.11.016.

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