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REVIEW ARTICLE

Cell organelles as targets of mammalian cadmium toxicity

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Abstract

Ever increasing environmental presence of cadmium as a consequence of industrial activities is considered a health hazard and is closely linked to deteriorating global health status. General animal and human cadmium exposure ranges from ingestion of foodstuffs sourced from heavily polluted hotspots and cigarette smoke to widespread contamination of air and water, including cadmium-containing microplastics found in household water. Cadmium is promiscuous in its effects and exerts numerous cellular perturbations based on direct interactions with macromolecules and its capacity to mimic or displace essential physiological ions, such as iron and zinc. Cell organelles use lipid membranes to form complex tightly-regulated, compartmentalized networks with specialized functions, which are fundamental to life. Interorganellar communication is crucial for orchestrating correct cell behavior, such as adaptive stress responses, and can be mediated by the release of signaling molecules, exchange of organelle contents, mechanical force generated through organelle shape changes or direct membrane contact sites. In this review, cadmium effects on organellar structure and function will be critically discussed with particular consideration to disruption of organelle physiology in vertebrates.

Keywords Mitochondria · Heavy metal · Lysosomes · Vesicles · Membrane fusion

Abbreviations

3-MA	3-Methyladenine
AIF	Apoptosis-inducing factor
ANT	ADP/ATP translocase
AQP	Aquaporin
ATG	Autophagy
BBM	Brush border membrane
BER	Base excision repair
BKA	Bongkrekic acid
CLCE	Chronic low cadmium exposure
COX	Cytochrome c oxidase
CsA	Cyclosporin A
cytC	Cytochrome C
DMT1	Divalent metal transporter 1
DSB	Double strand break
EE	Early endosome
ER	Endoplasmic reticulum
ERAD	ER-associated degradation
ETC	Electron transport chain
HR	Homologous recombination
HSF-1	Heat shock factor 1
IMM	Inner mitochondrial membrane
IMS	Intermembrane space
LE	Late endosome
LMP	Lysosomal membrane permeabilization
MAMs	Mitochondria associated membranes
Man-6-P	Mannose-6-phosphate
MCS	Membrane contact sites
MCU	Mitochondrial uniporter
MMR	Mismatch repair
mPT	Mitochondrial permeability transition
MT	Metallothionein
mTORC	Mammalian target of rapamycin complex
MV	Microvesicles
MVB	Multivesicular body
NER	Nucleotide excision repair
NHEJ	Non-homologous end-joining
NSB	Nuclear stress body
OMM	Outer mitochondrial membrane
OXPHOS	Oxidative phosphorylation
PG	Perichromatin granules

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PGC-1	PPAR coactivator 1
PKC	Protein kinase C
PM	Plasma membrane
PPAR	Peroxisome proliferator-activated receptor
PTC	Proximal tubule cell
PTP	Permeability transition pore
RE	Recycling endosome
RME	Receptor-mediated endocytosis
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
TEM	Transmission electron microscopy
TFEB	Transcription factor EB
TFE3	Transcription factor E3
UPR	Unfolded protein response
V-ATPase	Vacuolar H^+-ATPase
VDAC	Voltage-dependent anion channel

Introduction

Intensified industrial and agricultural activities have expanded cadmium wastes, which when once released into the environment cannot be further degraded, and have become a major concern for public health. Cadmium has been listed as one of the top 20 hazardous substances (Faroon et al. 2012). The incidence of acute cadmium toxicity in industrial working places has been greatly reduced in the past five decades as regulations have been tightened. Yet cadmium still poses a real and serious health problem for humanity in the twenty-first century. Rather than acute exposure to high cadmium concentrations, chronic, low cadmium exposure (CLCE) is a significant health hazard for ~ 10% of the world population with increased morbidity and mortality (Moulis and Thévenod 2010; Jarup and Akesson 2009).

Dietary sources and cigarette smoking are the predominant ways of CLCE for the general population (Pan et al. 2010; Satarug and Moore 2004). For non-smokers, food grown in cadmium-containing rock phosphate fertilizers, which are used in intensive arable agriculture to increase harvest yields, is the only major route of CLCE (Pan et al. 2010). Bioaccumulation of cadmium in plants, including tobacco, is the first step in entering the human food chain either through direct consumption or indirectly through metal transfer to animals consumed for meat. Diverse organs are targets of CLCE, causing kidney damage, osteoporosis, neurotoxicity, genotoxicity, teratogenicity, or endocrine and reproductive defects (Jarup and Akesson 2009). Moreover, there is no doubt that smoking is pivotal to the risk of chronic diseases, such as cardiovascular disorders or cancer, and evidence is accruing that cadmium in tobacco smoke is a major contributor in the development of smoking-associated chronic diseases (Abu-Hayyeh et al. 2001; Grasseschi et al. 2003).

Together, the kidneys and liver (Jarup and Akesson 2009) contain ~ 85% of the cadmium body burden, and more than 60% is found in the kidneys in the age range of 30–60 years (Jarup and Akesson 2009; Salmela et al. 1983). The accumulation of cadmium in kidneys and liver occurs because intracellular cadmium upregulates detoxifying molecules, such as metallothionein (MT) (Freisinger and Vasak 2013), which sequester the metal ion and thereby counteract its toxic effects. Though this may seem beneficial at first sight, these "detoxified" cadmium complexes actually pose a double edged-sword, because they are an endogenous source of large amounts of potentially toxic cadmium.

No mammalian physiological process has a requirement for cadmium. Hence, as a non-essential metal ion, cadmium mimics essential metal ions, crossing membrane barriers by competing for their modes of transport (Thévenod et al. 2019), or displacing them from intracellular macromolecules (Moulis 2010). Combined with binding at the essential sites of biomolecules (e.g. thiol (SH) groups), cadmium disrupts cellular functions and may lead to death or disease (Moulis 2010; Thévenod and Lee 2013b). The molecular interactions of cadmium with proteins involve metal substitution reactions with many zinc-proteins, such as enzymes or transcription factors (Maret and Moulis 2013; Petering 2017), substitution for calcium in cellular signaling, interaction with SH-dependent redox systems, and impacting levels of second messengers, growth and transcription factors (Templeton and Liu 2010; Thévenod 2009; Thévenod and Lee 2013b). Cadmium does not undergo Fenton chemistry in biological systems, yet it does initiate reactive oxygen species (ROS) formation, indirectly through depletion of endogenous redox scavengers, inhibiting anti-oxidative enzymes or the mitochondrial electron transport chain (ETC), and/or displacing redox active metals, such as iron or copper (Cuypers et al. 2010). Designated a class I carcinogen, cadmium interacts indirectly with DNA consequent to elevated ROS, interferes with major DNA repair systems, and inactivates tumor suppressor functions by targeting proteins with zinc-binding structures. This may cause genomic instability and promote tumor initiation and progression (Hartwig 2013a).

Approximately half the volume of a cell is attributed to organelles, membrane-bound intracellular organs with dedicated functions. Similarly to an integrated system in organisms, communication between organelles is needed to maintain homeostasis and to relay and execute adequate cell responses. Mechanical force through change in organelle shape or direct membrane contact is prerequisite for interorganellar communication. Cadmium disrupts organelle structure and function, including mitochondrial dysfunction, stress response in the endoplasmic reticulum (ER), altered nuclear architecture and chromatin organization, lysosomal

damage, autophagic flux, and interference with vesicle trafficking, which are the topics of this review.

Cadmium and lipid membranes

A lipid membrane boundary is characteristic of cell organelles, creating distinct structures with a microenvironment that is optimal and congruent for specialized organellar functions. This is, for example, the case for protein degradation and storage of lipids in lysosomes, protein synthesis and calcium storage in the ER, ATP synthesis in mitochondria, internalization of extracellular signals and signal transduction through the endo-/lysosomal pathway, as well as cargo trafficking and degradation in autophago(lyso)somes (Voeltz and Barr 2013). Interorganellar communication is essential for cell function, behavior, and adaptation to intracellular and extracellular cues therefore organelles do not exist, and should not be considered, as single entities but rather as an extended interactive network (Elbaz-Alon 2017). In emphasis: ER membranes exist in continuation with the nuclear membrane (Anderson and Hetzer 2008), the ER has intimate contact with mitochondria and the plasma membrane (PM), trafficking vesicles fuse with multiple organelles as well as maturing into different vesicles, and existing organelle membranes are used to generate new membrane-bound structures, e.g. phagophores during autophagy.

Lipid bilayers of cell membranes provide structural separation, appropriate membrane curvature, optimal lipid microenvironment to functionalize membrane proteins, such as receptors or transporters, maintain intraorganellar homeostasis, and dictate fusogenicity. Lipid composition varies between organelles albeit differing ratios of phospholipids, cholesterol and sphingolipids are found across all organelles (van Meer and de Kroon 2011). Consequent of an unsaturated carbon bond in the fatty acid chains of lipid bilayer phospholipids, a kink forms in the hydrophobic tails allowing more spatial movement between the lipid molecules and resulting in membrane fluidity in the liquid-crystalline phase. Membrane fluidity can be altered by tighter packing of lipids or a change in lipid composition wherein more saturated or smaller lipids are present; both result in membrane stiffening or a liquid-gel phase. Similarly, increased membrane fluidization can be consequent of loss of saturated or smaller lipids or through further spatial separation of the lipid molecules (Eeman and Deleu 2010). Sphingomyelin and cholesterol are also key components of lipid or membrane rafts, specialized liquid-ordered membrane nanodomains wherein recognition and transporting proteins are activated, and are present in the PM as well as in selected organelles (Garofalo et al. 2015; Lu and Fairn 2018). Notably, both these lipid species are well documented to be elevated in transformed cells (Lee and Kolesnick 2017).

Whereas cadmium uptake and cadmium transport mechanisms into the intracellular space have been well characterized, less is known about the impact of cadmium on lipid bilayers. Using liposomes to mimic the outer leaflet of the erythrocyte PM, cadmium interacts preferentially with phosphatidylethanolamine, but not with cholesterol (Le et al. 2009), causing tighter lipid packing through dissipation of opposing negative charges and thus increasing membrane rigidity though without changes in lateral organization (reviewed in Payliss et al. (2015)). Increased PM rigidity by cadmium could be confirmed in PMs isolated from human kidney proximal tubule cells (PTCs) exposed to 5 µM cadmium for 6 h (Sule, K., Prenner, E.J., Lee, W.K., unpublished data). Sphingomyelin is the most abundant sphingolipid in the outer leaflet (Devaux and Morris 2004) and is an important determinant of membrane fluidity and, together with cholesterol and glycosphingolipids, the formation of specialized membrane domains termed lipid rafts. Thus, in conjunction with cadmium-induced altered metabolism of sphingolipids (Lee et al. 2011, 2017), cholesterol (Toury et al. 1985), and phospholipids (Modi and Katyare 2009a; Sivaprakasam et al. 2016), it may be envisaged that cellular responses, such as membrane transport or second messenger signal transduction at the PM, as well as organellar functions are affected by cadmium. Indeed, interrogation of membrane fluidity using the lipid-incorporating dye laurdan, which changes its fluorescence emission depending on the packing of the surrounding lipids, demonstrated fluidization of lysosomal membranes in rat NRK-52E cells or human PTCs by cadmium, culminating in leakage of lysosomal contents (Lee et al. 2017). This effect seems to be mediated directly by cadmium since in vitro experiments wherein cadmium was added to isolated lysosomes also resulted in membrane fluidization as when intact cells were treated with cadmium and lysosomes were isolated (Sule, K., Prenner, E.J., Lee, W.K., unpublished data). It remains to be seen how other organelle membranes are affected by cadmium.

Cadmium and mitochondria

Mitochondria represent the central hub of bioenergetic metabolism as the largest cellular generator of ATP to fuel the cell's energy-dependent reactions and processes. Comprising of a relatively permeable outer mitochondrial membrane (OMM), a highly selective inner mitochondrial membrane (IMM), the intermembrane space (IMS) and the matrix core, where substrates for ATP production, i.e. electron donors, are formed through the citric acid/Krebs cycle in the matrix and passed onto the ETC located in the IMM to drive ATP synthesis. Additional functions of mitochondria include fatty acid degradation via β-oxidation, biosynthesis of various protein cofactors (e.g. heme, molybdenum

cofactor, biotin, lipoic acid, iron–sulfur (Fe/S) clusters), lipids and amino acids) and calcium storage/signaling.

In the ETC, four large protein complexes shuttle electrons via redox reactions, releasing energy to generate a matrix-directed electrochemical H^+ gradient necessary to fuel F1-F0 ATP synthase-mediated conversion of kinetic rotary energy to force energy and finally to chemical energy (Klusch et al. 2017), which is stored in phosphoanhydride bonds in the ATP molecule through oxidative phosphorylation (OXPHOS). Supplementing Mitchell's chemiosmotic hypothesis is a lateral chemical H^+ gradient from complex IV of the ETC (lower local pH) to F1-F0 ATP synthase (higher local pH) that results from the proton sink generated by proton transport through the F1-F0 ATP synthase and is particularly apparent in active mitochondria (Rieger et al. 2014). Energy is then liberated in exergonic hydrolysis reactions by ATPases. Damaging ROS, usually superoxide anion ($O_2^{\cdot -}$) or hydrogen peroxide (H_2O_2), are generated as byproducts of single electron escape from ETC complexes, OXPHOS and matrix biochemical reactions but are detoxified by antioxidants, such as glutathione, or ROS-metabolizing enzymes, such as superoxide dismutases and catalase. The effects of cadmium on the mitochondria are summarized in Fig. 1.

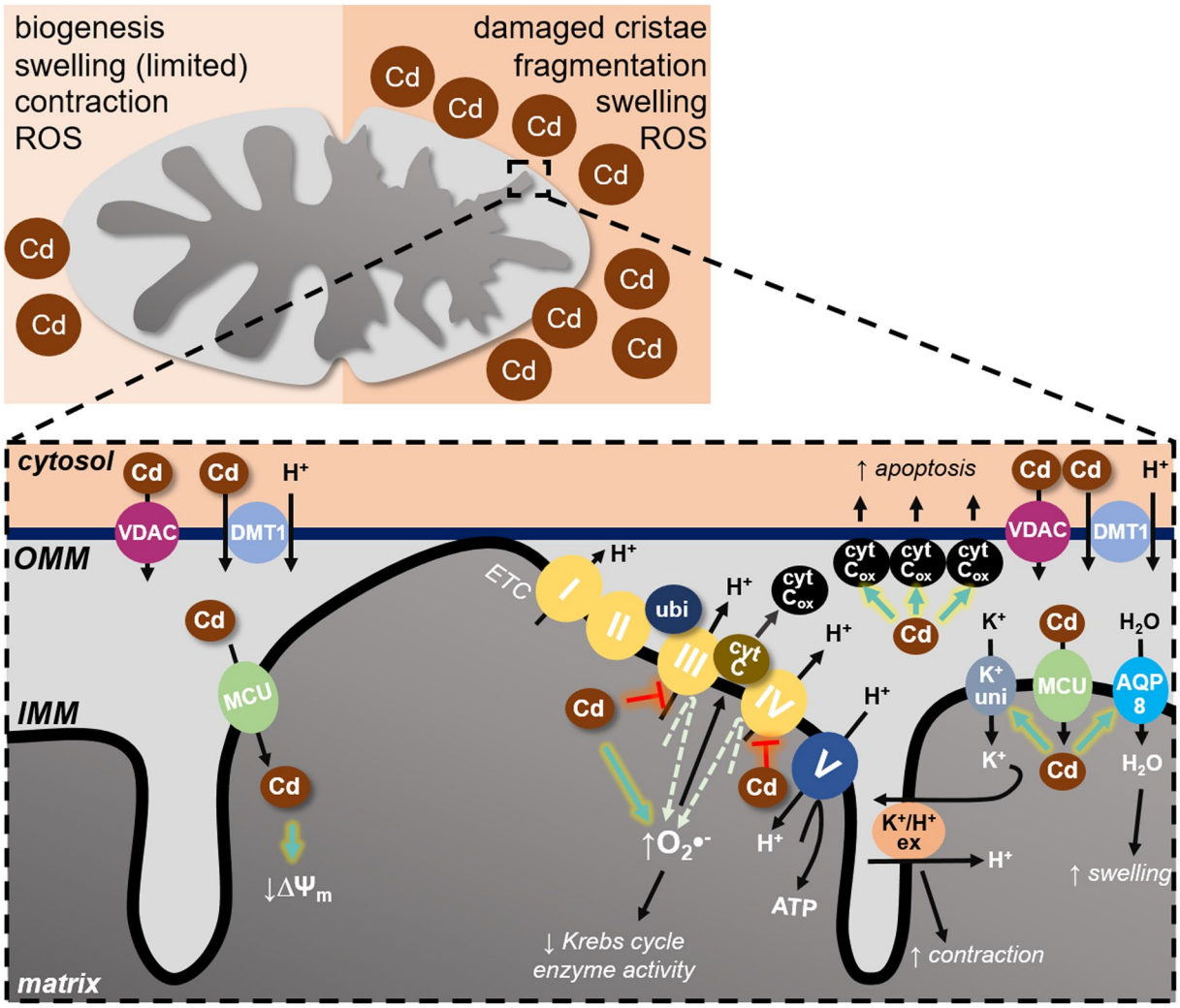

Fig. 1 Cadmium effects on mitochondria. Low cadmium induces mitochondrial fusion, contraction, and biogenesis which are elicited by mild oxidative stress and engages in adaptive responses. High cadmium leads to mitochondrial damage, such as cristae loss, fragmentation, swelling and high ROS. Cadmium putatively permeates the outer mitochondrial membrane (OMM) via VDAC or DMT1 and the inner mitochondrial membrane (IMM) through the mitochondrial calcium uniporter (MCU). From within the matrix, cadmium blocks complexes III and IV, increasing superoxide anion which oxidizes cytochrome c (cytC to $cytC_{ox}$) facilitating its release into the cytosol and induction of apoptosis. Cadmium also activates aquaporin-8 (AQP8), which results in influx of water and swelling of the matrix, K^+-cycling for contraction and dissipates mitochondrial membrane potential ($\Delta\psi m$). See text for further details

Mitochondrial membranes: ultrastructure and lipid composition

The IMM and OMM function together to maintain intramitochondrial spaces with defined ionic and proteinaceous composition that are highly regulated by a multitude of channels and transporters mainly expressed in the selective IMM. The differing functions of the mitochondrial membranes is exemplified by their lipid-to-protein content, which is approximately two-fold greater in the OMM compared to the IMM (Comte et al. 1976; Hallermayer and Neupert 1974).

The IMM can be separated into tubular invaginations called cristae, compromising of the cristae membrane, intracristal space, and the inner boundary membrane, which juxtaposes the OMM and forms the peripheral space. Upon discovery of a dual membrane system in mitochondria, the Baffle model wherein cristae formed large openings between the IMM and IMS entered textbooks and has prevailed. However, recent EM tomography studies confirm the crista junction model, which describes presence of small diameter openings that physically restrict exchange between the IMS and intracristal space (reviewed in Mannella et al. 2001; Zick et al. 2009).

Mitochondrial cristae were once thought to exclusively increase surface area for ETC proteins and transport proteins and thereby increasing IMM permeability. However, accumulating evidence indicates that they are integral to communication between intramitochondrial compartments: they foster interactions between the single complexes of the ETC to increase efficiency of OXPHOS and ultimately, greater capacity for ATP synthesis (Chaban et al. 2014; Letts and Sazanov 2017), and they also preserve local H^+ concentrations (Klotzsch et al. 2015; Song et al. 2013), possibly governing composition of the intracristal and peripheral spaces (Klotzsch et al. 2015; Mannella et al. 2001). Compelling data from the last ten years have pieced together a picture of how certain types of cristae are formed (Harner et al. 2016; Schorr and van der Laan 2018), how cristae adapt to metabolic status (Mannella et al. 2001) and how cristae indicate mitochondrial functionality (Rampelt et al. 2017; Stoldt et al. 2018). Correct curvature of the IMM to form the cristae ultrastructure requires an interacting combination of proteins (F1-F0 ATP synthase dimers) (Blum et al. 2019; Davies et al. 2012; Paumard et al. 2002), mitochondrial contact site complex (MICOS) (Harner et al. 2011; Schorr and van der Laan 2018), lipids (cardiolipin) (Ikon and Ryan 2017) and local microenvironment (acidic pH) (Khalifat et al. 2008).

Changes in the cristae ultrastructure during stress conditions leads to breakdown of interactive and communicative means between ETC proteins as well as diminished mitochondrial function and plasticity. Numerous reports using transmission electron microscopy (TEM) evidence deleterious effects of cadmium on mitochondrial cristae, such as reduction in number and shortening, in various animal systems (Asar et al. 2004; Braeckman et al. 1999; Early et al. 1992; Ord et al. 1988; Yang et al. 2016) and has been correlated with reduced expression of cytochrome c oxidases (COX), essential components of ETC complexes, indicating compromised mitochondrial function (Takaki et al. 2004; Toury et al. 1985). In view of recent discoveries, future studies are required to elucidate the molecular targeting of cadmium on protein complexes that govern cristae organization.

Compared to the PM, mitochondrial membranes contain relatively low amounts of cholesterol allowing for selective permeabilization by digitonin (Diaz and Stahl 1989; Niklas et al. 2011). CdAc (2 mg/kg/day, i.p. 7–30 days) increases cholesterol at the expense of selected phospholipids (phosphatidylethanolamine, phosphatidic acid) in mitochondrial membranes derived from rat liver (Modi and Katyare 2009b) and brain (Modi and Katyare 2009a) albeit with no change in membrane fluidity. Intriguingly, sphingomyelin is also increased (Modi and Katyare 2009a), which together with cholesterol, could impact lipid raft formation and membrane protein functionalization. Moreover, increased cholesterol has been suggested to underlie the metabolic switch from OXPHOS to anaerobic glycolysis in cancerous cells (Ribas et al. 2016) and could be part of cell alterations initiated during the process of cadmium carcinogenesis (Hartwig 2013a; Thévenod and Lee 2013b).

Cardiolipin, a mitochondrial phospholipid, is localized exclusively in the IMM whereupon the ETC shuttling and pro-apoptotic protein cytochrome c (cytC) is tightly bound by electrostatic interactions (Iverson and Orrenius 2004; Ott et al. 2002). Oxidized cardiolipin serves two purposes: release of cytC from the tightly bound pool into the IMS and its translocation from the IMM to OMM , both facilitating cytC leakage into the cytosol, a point of no return in the intrinsic apoptotic pathway. To this end, oxidation of cytC by COX promotes its inclusion into the cytosolic apoptosome complex, which in turn activates pro-apoptotic caspase proteases (Brown and Borutaite 2008). Cadmium weakly interacts with cardiolipin, increasing membrane rigidity and liposome aggregation (Kerek and Prenner 2016), and could possibly promote cytC release in apoptotic signaling (Lee et al. 2005a; Robertson and Orrenius 2000; Thévenod and Lee 2013a) through interference with electrostatic interactions and membrane biophysical properties.

Mitochondrial dynamics

As cellular energy demands fluctuate, mitochondria adapt through redistribution within the cell, trafficking to sites of high metabolic demand, and undergo fusion and fission/fragmentation. Fusion events strive to mitigate cell stress

responses and limit the impact of damaged mitochondria by mixing them with healthy mitochondria. Thus, fusion occurs during stress conditions as well as during high-energy demands. Conversely, fission quality controls mitochondrial health, helping to triage dysfunctional/damaged mitochondria, leading to their repair or removal, and usually precedes cell death execution (Youle and van der Bliek 2012). In addition to fusion and fission of existing mitochondria, chronic stress and high metabolic demand can induce mitochondrial biogenesis, which is partially regulated by the transcription factors peroxisome proliferator-activated receptor (PPAR) and PPAR coactivator 1 (PGC-1), members of the nuclear co-regulator family (Dorn 2019; Scarpulla 2012), as well as by mitochondrial porin, which regulates protein import across both the OMM and IMM (Doan et al. 2019).

Mitochondrial fragmentation is induced by cadmium in the brain (10 µM cadmium) (Xu et al. 2016), in cultured liver cells (6–12 µM cadmium) (Pi et al. 2013; Xu et al. 2013) and pancreatic β-cells (2 µM cadmium) (Jacquet et al. 2018). However, when mitochondrial dynamics regulators are defective, yeast cells become more resistant to cadmium (20 µM; 48 h) (Luz et al. 2017), where mitochondrial fusion gene *fzo-1* mutants exhibited the least growth inhibition by cadmium. In contrast to the aforementioned mitochondrial fragmentation studies (Jacquet et al. 2018; Pi et al. 2013; Xu et al. 2013, 2016), the findings from Luz et al. suggest mitochondrial fusion could be a prerequisite for execution of cadmium stress, possibly by inducing stress-induced mitochondrial hyperfusion (Tondera et al. 2009) that may result in apoptotic cell death (Zhang et al. 2017).

In a more extensive study examining mitochondrial biogenesis, Nair et al. monitored the mitochondrial response in the kidney, both in vitro and in vivo, using a range of cadmium concentrations at subchronic exposures (Nair et al. 2015). At 1–10 µM $CdCl_2$ for 24 h, Pparγ and mitochondrial DNA (mtDNA) were augmented in cultured renal PTCs whereas Pparα and Pgc-1β were not affected, and correlated with minor or low glutathione loss and low rates of apoptosis (Nair et al. 2015). In contrast, 30 µM $CdCl_2$ attenuated Pparα, Pgc-1β and mtDNA, despite sustained Pparγ increase, and was associated with increased oxidized glutathione and proapoptotic markers. Similarly in subtoxic subchronic $CdCl_2$-treated Fischer rats (1 mg/kg/day, s.c., 2 weeks), Pparα and mtDNA significantly increased whereas glutathione was unchanged compared to saline-treated controls (Nair et al. 2015), further confirming mitochondrial biogenesis as part of an adaptive mechanism to chronic oxidative stress by cadmium. Conversely, PGC-1α activity was turned off (assessed by its acetylation status), and mtDNA content and mitochondrial mass were reduced in hepatocellular carcinoma HepG2 cells exposed to < 10 µM $CdCl_2$ for 12 h (Guo et al. 2014). Despite increased ROS in both liver and kidney models, and even at low non-toxic $CdCl_2$ concentrations, no adaptive responses involving mitochondria were documented in HepG2 cells. This discrepancy can only be explained by the different cell models used, that is, non-cancerous versus cancerous cells (i.e. renal PTCs versus HepG2), which likely harbor divergent antioxidant status and could result in cadmium-induced generation of ROS subspecies to varying degrees and thus culminating in different alterations in mitochondrial biogenesis.

Permeation of cadmium into mitochondria

The OMM has long been thought to be a leaky membrane with little to no selectivity allowing unregulated passage of molecules intended for the mitochondrial matrix. It is widely assumed that OMM permeability is solely governed by the predominant mitochondrial porin, also known as voltage-dependent anion-selective channel (VDAC), which constitutes approximately 50% of OMM proteins, VDAC permits all sorts of molecules up to 5 kDa to pass (Colombini 2016), despite the range of negatively and positively charged ions as well as small molecules and metabolites that must first cross the OMM and traverse the IMS to reach the matrix. However, in addition to modulating protein import during mitochondrial biogenesis (Doan et al. 2019), it appears that VDAC can switch between different open or half-open/closed conformations and alternate between anion and cation conductive states. For calcium, no conductance is measured in the open state (Pavlov et al. 2005; Schein et al. 1976) whereas calcium conductance increased in the closed state (with concomitant lower permeability to metabolites) or in the half-open conformation (Pavlov et al. 2005; Tan and Colombini 2007). It is not quite clear how VDAC switches between these states but appears to be regulated by structural changes (Mertins et al. 2012; Zachariae et al. 2012) or extramitochondrial cues, such as cytosolic proteins (Queralt-Martin et al. 2020; Rostovtseva and Bezrukov 2008), mitochondrial lipids (Rostovtseva and Bezrukov 2008), and cytosolic pH (Teijido et al. 2014). Interestingly, VDAC3 interaction with α-synuclein is regulated by cysteine residues (Queralt-Martin et al. 2020), a target of cadmium.

This simplified view of OMM permeation has been challenged in recent reports identifying further OMM permeation pathways for electrolytes, small organic molecules and precursor proteins [reviewed in (Becker and Wagner 2018)], such as the cation-selective mitochondrial import MIM complex (Kruger et al. 2017; Vitali et al. 2018), cation-selective NADPH-regulated Ayr1 channel (Kruger et al. 2017), anion selective channels OMC7/OMC8 (Kruger et al. 2017) and proton-coupled symporter divalent metal transporter 1 (DMT1) (Wolff et al. 2014a, b,2018). The presence of DMT1 in the OMM paves the way for mitochondrial uptake of divalent cations via an alternative route to VDAC. Immunofluorescence studies evidenced DMT1 co-localization

with VDAC thus supporting its OMM localization (Wolff et al. 2014a, b) and functional studies in isolated mitochondria demonstrated DMT1-mediated uptake of iron and manganese, well-known permeating ions of DMT1 (Wolff et al. 2018).

At first, one would hypothesize that cadmium permeates the OMM in a similar manner to calcium, that is, via VDAC in its half-open/closed state (Colombini 2016). However, taking recent findings into consideration, we posit that cadmium passes the OMM through DMT1, of which it is a known substrate (Thévenod et al. 2019).

Undoubtedly, the IMM is highly selective and equipped with an array of transport proteins that tightly regulate access into the mitochondrial matrix and in the reverse direction into the IMS (Palmieri and Monne 2016). Ion movement requires uniporters, symport and antiport transporters, such as the mitochondrial calcium uniporter (MCU) (Kamer and Mootha 2015; Mammucari et al. 2017), K^+ channels (e.g. calcium-dependent mitoK_{Ca}, ATP-dependent mitoK_{ATP}, large conductance calcium-dependent BK_{Ca} (Augustynek et al. 2017; Szabo et al. 2012), the iron transporters mitoferrin 1/2 (Paradkar et al. 2009) and the K^+/H^+ exchanger (Zotova et al. 2010). Small nucleotides are transmitted by the adenine nucleotide translocator (ADP/ATP translocase, ANT) and nascent proteins are moved by TOMs and TIMs, across the OMM and IMM, respectively (Pfanner et al. 2019). Due to their similar hydrated ionic radii, calcium and cadmium can imitate each other at recognition sites (Marcus 1988). Cadmium permeates certain types of calcium channels, but also blocks other Ca^{2+} channels (see Choong et al. 2014; Thévenod et al. 2019). Thus, a plausible hypothesis for cadmium permeation of the IMM is via the MCU, the major IMM Ca^{2+} channel. Using isolated mitochondria from kidney or liver, pharmacological MCU inhibitors ruthenium red, Ru360 or La^{3+} abolished cadmium effects on mitochondrial function, including swelling, loss of membrane potential and proapoptotic cytC release (Dorta et al. 2003; Lee et al. 2005a, b; Li et al. 2003) demonstrating cadmium transport by the MCU into the matrix. These observations were confirmed in cell line studies using ruthenium red to prevent mitochondrial cadmium entry and subsequent apoptosis (Lemarié et al. 2004; Shih et al. 2005).

Electron transport chain and citric acid cycle

The ETC comprises five multimeric complexes (CI-CV) localized in the IMM wherein electrons are shuttled from the multivalent metal core of one complex to the next, aided by ubiquinone and cytC on either side of CIII, and generating energy for shunting of protons from the matrix to the IMS via CI, CIII and CIV (Letts and Sazanov 2017). Consequently, a proton-motive force and a mitochondrial membrane potential ($\Delta\Psi_m$) are created across the IMM. Complex V, the F1-F0 ATP synthase, uses the energy stored in the H^+ gradient to drive its rotor to form ATP.

As consequence of electron shuttling, mitochondria are the major site of ROS production, in particular CI and CIII produce highly reactive superoxide anions ($O_2^{\bullet-}$). Other ROS species generated include hydroxyl radicals ($OH^{\bullet}$) and hydrogen peroxide (H_2O_2) (Munro and Treberg 2017). Cadmium is well-evidenced to increase ROS levels either by affecting mitochondrial function, ROS-producing/metabolizing enzymes, or negatively targeting antioxidants, such as glutathione. Early studies in chronically treated rats exposed to cadmium (50 ppm, up to 9 months) via drinking water reported a fall in succinate dehydrogenase (CII) and cytochrome c oxidase (CIV) activities after 3 months (Toury et al. 1985). Whereas CIV activity was partially restored after 6 months cadmium exposure, CII activity progressively decreased. This differentiated response could be explained by additional in vitro experiments using isolated liver mitochondria and IMM vesicles wherein cadmium directly blocked CII activity, but not CIV, possibly as a result of cadmium interaction with SH groups on CII (Toury et al. 1985). By inhibiting CII and CIV activity, electrons cannot be transferred from CI and CIII, resulting in increased superoxide anion generation, and therefore contributing to oxidative stress induced by cadmium. In contrast, in an elegant study in isolated liver mitochondria from guinea pig, 20 µM cadmium inhibited ETC complex activities (CIII > CII >> CI > CIV) where CIII was maximally inhibited by ~ 75% at 20 µM $CdCl_2$ that could be reversed by EDTA (Wang et al. 2004). The small inhibitory effect on CIV in the study by Wang et al. versus Toury et al. could be explained by an indirect mechanism of cadmium on CIV activity, which cannot be seen in in vitro experiments with isolated mitochondria. The inhibition of CIII corroborates a previous study wherein electron transfer from ubisemiquinone to cytochrome b_T, a component of CIII, is blocked by 30 µM $CdCl_2$ (Miccadei and Floridi 1993). CIII catalyzes the transfer of electrons from ubiquinol to cytC and was deemed the target of cadmium, which acts through competitive binding at the zinc binding site, preventing electron transfer and resulting in increased superoxide (Wang et al. 2004). It remains to be seen whether cadmium inhibition of CIII also affects the formation of respiratory supercomplexes, which have been implicated in regulating ROS levels in mitochondria (Lopez-Fabuel et al. 2016). Since the oxidative status of cytC appears to be prerequisite for its transfer from a tightly-bound to a loosely-bound pool (Petrosillo et al. 2003), which is then ready for liberation in apoptosis signaling, ROS production by cadmium in the immediate vicinity of cytC makes for a favorable mechanism by enhancing cytC apoptogenicity (see Fig. 1).

Substrates for the ETC and thus ATP generation, so-called reducing equivalents, are supplied in part by the citric

acid/Krebs cycle. A recent report analyzed lung tissue from cadmium-exposed rats (up to 2 mg/L cadmium in drinking water, 16 weeks) using high resolution metabolomics and redox proteomics as well as performing metabolic pathway analyses. Cadmium was found to induce oxidation of multiple citric acid cycle proteins, leading to impaired enzyme activities and accumulation of citric acid cycles intermediates (Hu et al. 2019). The loss of ATP generation through the citric acid cycle and ETC could be an important step in the transformation progression of normal cells, ultimately making the switch to glycolysis, also known as the Warburg effect, which is a hallmark of cancer cells (Potter et al. 2016).

Mitochondrial membrane potential ($\Delta\Psi_m$)

Consequent to the proton shifting by the ETC, a $\Delta\Psi_m$ is generated across the IMM where the matrix is more negatively charged compared to the IMS (Reid et al. 1966). Mitochondrial damage and dysfunction can be indicated through dissipation of $\Delta\Psi_m$, which has been well-documented for cadmium in isolated kidney mitochondria (Belyaeva et al. 2004; Lee et al. 2005b) as well as in a variety of cell types (reviewed in Thévenod and Lee 2013a; Thévenod and Lee 2013b), and could be linked to ETC block [see above and (Miccadei and Floridi 1993; Wang et al. 2004)].

Mitochondrial permeability transition (mPT) and permeability transition pore (PTP)

As aforementioned, under physiological conditions, the IMM is selectively permeable. Apoptotic stimuli, such as calcium or ROS, can induce the IMM to undergo permeability transition (mPT) such that it is no longer selective, and solutes and water can freely pass the IMM into the matrix, leading to an increase in matrix volume consequent of osmotic pressure increase, and subsequent swelling of mitochondria. With sufficient expansion of the matrix, the IMM, with its larger surface area, disrupts the OMM culminating in the release of proapoptotic factors, such as cytC or apoptosis inducing factor (AIF), from the IMS and general mitochondrial dysfunction. This mPT is thought to be due to the formation of the so-called permeability transition pore (PTP) at contact sites between the IMM and OMM and inducing a sudden increase in the permeability of the IMM to solutes up to 1500 Da. However, the molecular identity of the PTP still remains a mystery. Once thought to be comprised of OMM VDAC, IMM ANT and matrix cyclophilin D, apoptosis execution was observed despite genetic deletion of VDAC (Baines et al. 2007) or ANT (Karch et al. 2019; Kokoszka et al. 2004). This brought into question the molecular composition of PTP and also the interpretation of studies using the commonly used pharmacological PTP inhibitor cyclosporin A (CsA) to target cyclophilin D (Crompton et al. 1998) and bongkrekic acid (BKA) or atractyloside to target the ANT, leading to inhibition or activation of the PTP, respectively (Novgorodov et al. 1991).

Based on its molecular interactions with cyclophilin D, ANT and mitochondrial phosphate carrier SLC25A3, the F1-F0 ATP synthase has been proposed to form IMM pores with similar conductance properties as the PTP (Bonora et al. 2013; Giorgio et al. 2013). Whilst the group of Bernardi used a targeted screening approach to identify cyclophilin D-interacting subunits of the F1-F0 ATP synthase followed by pharmacological inhibition of reconstituted F1-F0 ATP synthase dimers in electrophysiological studies (Giorgio et al. 2013), the group of Pinton focused on the c-ring of the F1-F0 ATP synthase based on its conductive properties (McGeoch and Guidotti 1997) and its putative role as a PTP regulator (Azarashvili et al. 2002) using genetic manipulation and mitochondrial function studies (Bonora et al. 2013). Subsequent reports by both groups (Bonora et al. 2017; Urbani et al. 2019) and others (Mnatsakanyan et al. 2019) have sought to confirm and validate their observations, yet their findings have already been disputed by others (He et al. 2017a, b; Zhou et al. 2017) (reviewed in Baines and Gutierrez-Aguilar 2018; Biasutto et al. 2016; Bonora and Pinton 2019), leaving the molecular identity of the PTP yet unresolved in an enduring saga.

Does cadmium induce PTP opening as part of its cell death signaling? Numerous light scattering studies have reported PTP participation in cadmium cell death signaling using isolated mitochondria from rodent liver or kidney and monitoring mitochondrial volume/swelling by light scattering measurements, in combination with pharmacological modulators (CsA, BKA, atractyloside) of the originally postulated PTP components (Belyaeva et al. 2002; Dorta et al. 2003; Lee et al. 2005a; Li et al. 2003). In contrast, lack of specific inhibitors of VDAC makes it difficult to target; the use of DIDS is not suitable as it affects multiple ion channels and transporters resulting in off-target effects. Multiple groups have reported the participation of the PTP in cadmium cell death signaling. In particular, the group of Belyaeva have extensively examined the role of the PTP in mitochondrial swelling and dysfunction. In one study, different buffer compositions were used to investigate the effect of PTP modulators CsA, ADP, atractyloside and Mg^{2+} on cadmium-induced swelling of energized and non-energized rat liver mitochondria (Belyaeva et al. 2002). A combination of CsA, ADP and Mg^{2+} could abolish cadmium-induced swelling, however CsA alone was ineffective in energized mitochondria, in line with our own observations (Lee et al. 2005a, b). The ANT had been proposed to be the target of cadmium for PTP opening by modification of thiols that would be accessible to cadmium from within the matrix (Zazueta et al. 2000). However, decisive experiments of that

study were performed on liposomes reconstituted with ANT and examined sucrose release as a function of cadmium concentration rather than PTP opening. In addition to the high EC_{50} ~ 50 μM cadmium needed to increase sucrose release, indicative of ANT transport function, it cannot be presumed that increased translocase activity equals induction of PTP opening since it is not known how functions of individual PTP components are affected when they form the PTP.

Considering the current literature, wherein VDAC and ANT as PTP components has been challenged in knockout mouse studies (Baines et al. 2007; Karch et al. 2019; Kokoszka et al. 2004), it seems even more important to draw conclusions only from studies employing modulation of cyclophilin D, which has escaped molecular scrutiny (Gutierrez-Aguilar and Baines 2015). Ablation of calcium-induced mitochondrial swelling and cytC release in cyclophilin D-null mice leaves no doubt to its contribution to the molecular composition of the PTP (Baines et al. 2005). In light of the recent putative role of F1-F0 ATP synthase as a molecular component of the PTP, it is intriguing that the F0 portion is subject to cysteine modifications and cadmium directly inhibits passive H^+ transport by F0 reconstituted in liposomes (Steed et al. 2014). Taken together, the ineffectiveness of CsA on cadmium-induced mitochondrial swelling (Belyaeva et al. 2002; Lee et al. 2005a; Li et al. 2003) indicates that the PTP is not a ubiquitous mitochondrial swelling mechanism elicited by cadmium. Indeed, opening of the water channel aquaporin-8 (AQP8) by cadmium has been evidenced to be the entryway of water influx into the matrix to cause swelling (Calamita et al. 2005; Lee et al. 2005a; Lee and Thévenod 2006).

Shortly after these observations were made, the group of Alan Verkman performed a set of studies investigating osmotic permeability from mitochondria isolated from $AQP^{-/-}$ mice to ascertain the contribution of AQPs in mitochondrial shrinkage under physiological conditions (Yang et al. 2006). Using mitochondria isolated from $AQP1^{-/-}$ mice for kidney, $AQP4^{-/-}$ mice for brain and $AQP8^{-/-}$ mice for liver and heart and suspended in hypertonic mannitol solution to create an osmotic gradient, no significant differences in osmotic permeability were detected between wildtype and knockout mitochondria after 1 s at 10 °C. The authors concluded that rapid osmotic equilibration in mitochondria was a result of their small size and thus high surface-to-volume ratio rather than activation of AQPs in the IMM. Omitted from these studies was the impact of AQP8 in kidney mitochondria [which is involved in cadmium-induced mitochondrial swelling (Lee et al. 2005a)] as well as the role of AQPs in rapid expansion of the mitochondrial matrix, such as during active OXPHOS, or under pathophysiological conditions, such as metal toxicity. Despite the findings by Verkman's group, subsequent studies indicate that mitochondrial AQPs are relevant for healthy functional mitochondria (Ikaga et al. 2015; Marchissio et al. 2012) and can transport H_2O_2 (Almasalmeh et al. 2014; Marchissio et al. 2012), ammonia (Soria et al. 2010) or glycerol (Amiry-Moghaddam et al. 2005) in an isoform-dependent manner. Moreover, additional metals have been shown to affect AQP function: Pb^{2+} increased water permeability of AQP4 in astrocytes (Gunnarson et al. 2005), albeit in a calcium calmodulin dependent manner, and Hg^{2+} increased plant AQP functionality (Frick et al. 2013) thus strengthening a role for toxic metal-induced AQP functionalization in mitochondria. To this end, mitochondrial AQP8 expression is negatively impacted by mitochondrial oxidative stress (Liu et al. 2018a) and cholesterol depletion (Danielli et al. 2017). In addition, overexpression of mitochondrial AQP8 increases de novo cholesterol synthesis by increasing expression of the sterol regulatory element-binding protein 2 (SREBP-2) transcription factor and the rate-limiting enzyme HMGCR (Danielli et al. 2019), suggesting cholesterol is required for AQP8 function.

How might these more recent data influence interpretation of earlier findings with cadmium? In isolated mitoplasts, cadmium-induced swelling was relatively slow reaching a maximum after approximately 1 min suggesting that other indirect mechanisms in addition to direct activation of AQP8 could be involved (Lee et al. 2005a; Lee and Thévenod 2006). A direct mechanism could involve binding of cadmium at calcium binding sites found on AQP (Fotiadis et al. 2002). Indeed, cadmium binds to putative calcium binding sites in both the N- and C-terminus to stabilize the structure, which is central for AQP gating by phosphorylation (Frick et al. 2013). Alternatively, cadmium could indirectly activate AQP8 by modulating the biophysical properties of the IMM lipid bilayer. AQP functionality is increased in membranes with high fluidity (Tong et al. 2012). Since cadmium fluidizes organellar lysosomal membranes (Lee et al. 2017), it would be attractive to hypothesize an increase in mitochondrial membrane fluidity by cadmium would enhance AQP8 activation.

Mitochondrial volume dynamics

In response to energetic demands of the cell, mitochondria do not only undergo fusion and fission but can also swell and contract through monovalent cation cycling to regulate chemical reactions (Lizana et al. 2008; Nowikovsky et al. 2009). Swollen mitochondria exhibit decreased β-oxidation, Krebs cycle activity and respiration and can be made to contract by ATP, ADP, Mg^{2+} or potassium cyanide, depending on the swelling stimulus (Garlid and Paucek 2003). Furthermore, it has been proposed that mitochondrial shape and volume changes through swelling serve as mechanical signals to communicate with other cell organelles (Kaasik et al. 2010).

In light scattering experiments, isolated rat kidney cortex mitochondria, suspended in KCl buffer and energized with rotenone/succinate, undergo swelling followed by contraction completed within 2 min after 5–20 μM $CdCl_2$ addition (Lee et al. 2005b)(see Fig. 1). Non-energized mitochondria swell upon cadmium addition but do not contract. Using pharmacological inhibitors, cadmium entry occurred via the MCU and elicited K^+ influx (via a K^+ uniporter) to induce matrix swelling, dissipation of $\Delta\Psi_m$, and triggering activity of a quinine-sensitive K^+/H^+-exchanger that culminates in mitochondrial contraction (Lee et al. 2005b). Intriguingly, the contraction phase appears to be activated very soon after cadmium addition because swelling does not reach the same magnitude as that observed in non-energized mitochondria, which indicates rapid induction of K^+-cycling that is dependent on the chemical diffusion gradient (Lee et al. 2005b). Transient limited mitochondrial swelling by low cadmium may represent a mechanical signal to neighboring organelles as part of an adaptive stress response and could precede mitochondrial fusion/fission, damaged mitochondria removal by mitophagy, temporary switches in energy metabolism, and altered expression of mitochondrial proteins.

Cadmium and ER

The ER is an expansive and very dynamic network, maintaining contacts with all other organelles and may be regarded as the governor, sensing signals and giving instruction in cellular responses (Saito and Imaizumi 2018). Through mitochondria-associated membranes (MAMs), the ER directs calcium flux to and from mitochondria in addition to dictating and aiding mitochondrial fission (Carreras-Sureda et al. 2018; Friedman et al. 2011). Furthermore, ER membranes supply autophagophore formation (Sanchez-Wandelmer et al. 2015). ER-PM contacts mediate store-operated calcium entry through STIM1/Orai (Putney 2018) and maintain lipid homeostasis at the PM, for instance, during second messenger signaling (reviewed in Balla 2018).

Primary ER functions are mRNA translation into (poly) peptides, protein folding, some protein modifications, such as N-linked precursor glycosylation, and lipid synthesis that demand an oxidizing and calcium-rich environment in the ER lumen (Bulleid and van Lith 2014; Lam and Galione 2013; Schwarz and Blower 2016). Protein folding is prone to errors therefore several quality control and damage-limiting mechanisms protect from potential stress elicited by large amounts of misfolded proteins (Hetz 2012). ER-resident chaperones (GRP78/BiP, GRP94) occupy ER stress sensor proteins, maintaining them in an inactive state, and bind polypeptides to aid protein folding as well as offering opportunities for refolding, if mistakes are made. Should these refolding endeavors prove unsuccessful, unfolded proteins are directed to the ER-associated degradation (ERAD) machinery that results in proteasome-driven destruction in the cytosol. Increased unfolded protein load shifts ER chaperone distribution, such that ER stress sensor proteins become unoccupied, and initiate the unfolded protein response (UPR), which initially delays cell damage by reducing mRNA translation but subsequently engages cell death promoting pathways, culminating in upregulation of proapoptotic GADD153/CHOP and caspase-12 activation (Hetz and Papa 2018; Woehlbier and Hetz 2011).

Intralumenal homeostasis

Folding a polypeptide into its tertiary conformation requires formation of disulfide bridges. The intralumenal oxidizing environment of the ER is optimal for this process; but too oxidizing or too reducing results in aberrant disulfide bridge formation and thus, malformed protein structure (Malhotra and Kaufman 2007). It is not yet clear as to exactly how the ER maintains correct redox balance though cytosolic glutathione could be involved (Margittai et al. 2015). Cadmium complexation with cytosolic glutathione (Jacquart et al. 2017) or glutathione oxidation via cadmium-induced ROS generation (Nair et al. 2015) will most likely have an impact on ER lumen redox status, increasing misfolded proteins and initiating the UPR though this has yet to be investigated.

High ER lumenal calcium is maintained by a pump-leak system whereby the thapsigargin-sensitive sarco-/endoplasmic reticulum calcium ATPase (SERCA) actively transports calcium back into the ER lumen following passive leakage into the cytosol (Camello et al. 2002). Using aqueorin-based probes, cadmium (15 μM, 12 h) diminishes SERCA activity without effect on leakage that resulted in ER calcium depletion and evoked the ER stress response in parallel with the mitochondrial apoptosis pathway suggesting communication between these pathways through calcium (Biagioli et al. 2008).

ER stress

ER stress is initiated by decreased intralumenal calcium and oxidative stress that contribute to accumulation of unfolded proteins, activating UPR and ERAD (Malhotra and Kaufman 2007). When unfolded proteins sequester lumenal chaperones, ER stress sensor proteins PERK, IRE1 and ATF6 become activated. The PERK-eIF2α-ATF4 pathway blocks further mRNA translation to prevent ER overloading so the cell has time and capacity to attempt correction of misfolded proteins. Failure to do so results in shunting to ERAD machinery where proteins are irreversibly degraded. In acute and prolonged ER stress, ATF6 is truncated in the Golgi, and IRE1 activation leads to splicing of XBP1 mRNA, both

culminating in upregulation of proapoptotic genes (Woehlbier and Hetz 2011).

Amongst transition metals, cadmium is particularly effective in inducing ER stress (Lee et al. 2012, 2017; Liu et al. 2006), which has been well documented in various models [reviewed in (Thévenod and Lee 2013a, b)], wherein ER chaperones (GRP78/BiP, GRP94), all UPR arms, and GADD153/CHOP are upregulated. In mammalian cells, it appears that ROS/reactive nitrogen species (RNS), specifically superoxide anion ($O_2^{\bullet-}$) or peroxynitrite ($ONOO^-$) (Yokouchi et al. 2008), or an increase in cytosolic calcium (Biagioli et al. 2008), precede ER stress and UPR. However, caution should be taken when potential cadmium chelators, such as BAPTA, N-acetylcysteine and Fura-2, are used to investigate calcium and ROS signaling and could potentially lead to false positive signals (Thévenod 2009). In contrast, ER accumulation of cadmium in yeast elicits UPR but not through inhibition of protein disulfide bond formation (Gardarin et al. 2010). Analogous to the biphasic response in autophagy (see paragraph below), mild ER stress by cadmium triggers the PERK-eIF2α-ATF4 pathway, which precedes signs of damage (Liu et al. 2006), acting in a protective manner that can act in concert with autophagy (Lee et al. 2017), whereas major ER stress recruits the pro-death UPR arms culminating in the upregulation of proapoptotic GADD153/CHOP (Lee et al. 2012, 2017).

ER restructuring

Swollen rough ER has been reported for chromium (Cr^{6+}; $K_2Cr_2O_7$) (Venter et al. 2017) suggesting that toxic metals can affect ER structure but no evidence for ultrastructural ER changes for cadmium have been observed in electron microscopy studies of liver and kidney rat tissue (Asar et al. 2004; Venter et al. 2017). In contrast, swollen, disorganized and damaged rough ER by cadmium was observed in insect cells (66 µM $CdCl_2$, 24 h) (Braeckman et al. 1999), neuroblastoma cells (20–40 µM $CdCl_2$, 24 h) (Ge et al. 2019) and rat liver (0.84 mg/kg, i.p. CdAc, 48–96 h) (Early et al. 1992). The effect of cadmium on physical ER contacts has hitherto not been investigated.

Cadmium and the nucleus

Genetic material in the nucleus is partitioned from the cytosol by the nuclear membrane, consisting of outer and inner membranes. An underlying nuclear lamina surrounds the nuclear matrix, which comprises cytoskeletal proteins and nuclear sap, acting as a support framework for intranuclear macromolecules. Nuclear pores span both nuclear membranes and permit communication and translocation of gene regulatory molecules between the cytosol and nucleus in a regulated manner (Hampoelz et al. 2019; Ungricht and Kutay 2017).

The central subcellular localization of the nucleus poses a spatial hurdle for cadmium as it must cross the PM followed by the cytosolic minefield to encounter the nucleus. Atomic absorption spectroscopy evidenced cadmium uptake into isolated nuclei, plateauing at ~ 1 nM extranuclear free cadmium (Hechtenberg and Beyersmann 1994). Further, radioactive cadmium (^{109}Cd or ^{115}Cd) data evidence nuclear cadmium, driven by a concentration gradient, within and peaking at 1 h of exposure (Bryan and Hidalgo 1976; Fighetti et al. 1988), was weakly bound, and subsided over time. Upregulation of cytosolic cadmium-binding sites shifts equilibrium towards the cytosolic compartment wherein cadmium is complexed (Bryan and Hidalgo 1976). Intriguingly, similar findings were made using ^{109}Cd-metallothionein (MT) in a rat model (Squibb et al. 1979) despite a different route of entry into the cell: membrane transporters for inorganic cadmium versus receptor-mediated endocytosis for CdMT. Primary cadmium exposures probably trigger genetic and epigenetic changes from within the nucleus as its journey encounters less cytosolic hurdles whereas secondary and repeated cadmium exposures will have less impact because augmented intracellular cadmium-binding sites, such as those on MT, sequester cadmium before it can reach the nucleus (Goering and Klaassen 1983) this strongly implies that cadmium-induced effects from within the nucleus are short-lived and dependent on the level of cadmium-sequestering proteins in the extranuclear compartment. The multifaceted effects of cadmium on gene transcription, DNA repair and epigenetics can be attributed to the presence of zinc finger domains in DNA binding proteins and enzymes. Zinc finger domains are structural motifs and classically involve co-ordination of two cysteine and two histidine residues through zinc ions (so-called C2H2 type) to maintain protein tertiary structure, though zinc finger motifs also exist in different coordinations (Cassandri et al. 2017; Witkiewicz-Kucharczyk and Bal 2006). In a fundamental mechanism, a conformational change ensues through displacement of zinc by cadmium at the zinc finger motifs, and ends in altered protein function or activity (Witkiewicz-Kucharczyk and Bal 2006).

Nuclear architecture

Ultrastructural TEM studies of cadmium-exposed animal tissues and cell lines generally indicate dilated nuclei, dilated or ringed nucleoli, nuclear indentation and aberrant chromatin condensation (Matsuura et al. 1991; Ord et al. 1988; Peereboom-Stegeman and Morselt 1981), accumulation of RNA-storage perichromatin granules (PG) at the nucleolar edge (Banfalvi et al. 2005; Ord et al. 1988), and micronuclei formation (Cervera et al. 1983; Ord et al. 1988; Puvion and Lange 1980), wherein damaged chromosomes

reside and are indicative of chromosome instability. Isolated nuclei exposed to high levels of cadmium (2 mM) exhibited redistribution of lamin A, but not lamin B, from the nuclear periphery to across the nuclear matrix (Neri et al. 1999b) and could represent adaptive stiffening of the nuclear lamina in response to extranuclear mechanical signals (Ungricht and Kutay 2017), such as mitochondrial swelling. Incidentally, large holes in the nuclear membrane after cadmium (Banfalvi et al. 2005) could be a result of either nuclear lamin cleavage (Hashimoto et al. 2017) or tighter lipid packing and increased membrane rigidity (Payliss et al. 2015), causing the nuclear membrane to become fragile and brittle and therefore prone to breakages.

Chromatin organization and epigenetics

Chromatin comprises repeating units called nucleosomes and describes DNA wound around and condensed by histone proteins, influencing the accessibility of a gene (Adriaens et al. 2018; Cremer et al. 2004; Wolffe and Guschin 2000). Histone proteins are susceptible to posttranslational modifications, for example, acetylation or methylation, and can affect gene transcription through changes in DNA winding/unwinding and masking or exposing sites for transcription (Kouzarides 2007). PGs were first identified as storage sites for newly synthesized heterogenous nuclear RNA, including pre-mRNA (Chiodi et al. 2000) as well as sites of ribonucleoprotein complex (consisting of RNA and RNA-binding protein) recruitment, but are now considered nuclear stress bodies (NSBs), which appear following stress stimuli in human cells, and are associated with activation of heat shock factor 1 (HSF1) and indicative of increased transcriptional activity (Biamonti and Vourc'h 2010). Low cadmium (1 µM $CdCl_2$) treatment caused changes in chromatin structure (Banfalvi et al. 2005) and appearance of PGs/NSBs (Banfalvi et al. 2005; Cervera et al. 1983; Puvion and Lange 1980), which were mostly associated with chromatin by fibers (Banfalvi et al. 2005; Cervera et al. 1983; Puvion and Lange 1980). The appearance of PGs/NSBs after cadmium exposure could be interpreted in two ways: (1) increased transcriptional activity mediated by HSF1 activation or (2) RNA processing is hindered, such that nuclear RNA accumulates in PGs/NSBs. It has been evidenced that cadmium sulfate (5 µM, 6 h) increases expression of satellite III (SatIII), which is associated with sites of transcription in NSBs in a general stress response (Valgardsdottir et al. 2008). How could cadmium affect gene transcription when mRNA processing is hindered? A possible explanation is biphasic responses concerning RNA: low/acute cadmium augment whereas high/chronic cadmium attenuates RNA synthesis and mRNA activity, probably due to interactions with zinc-dependent enzymes, such as RNA polymerase. Further, topoisomerase IIα, which alters the topological state of nucleic acids, is redistributed in the nuclei of cadmium-exposed K562 cells (Neri et al. 1999a) as well as directly inhibited, putatively through interaction with thiol groups (Wu et al. 2011) and could affect gene transcription.

Epigenetics describe inheritable changes in gene expression without modifications to the DNA sequence and is strongly influenced by environmental factors (Mathers et al. 2010). Histone modification and DNA methylation have been implicated in protection against cadmium toxicity as well as in malignant transformation [summarized in (Thévenod and Lee 2013b)] whereas cadmium effects on noncoding RNAs, namely microRNAs, are currently emerging [reviewed in (Humphries et al. 2016) and (Fay et al. 2018; Yuan et al. 2020)]. Recently, histone methylation by cadmium has been linked to cell proliferation and transformation (Gadhia et al. 2015; Xiao et al. 2015). In mouse embryonic stem cells, monomethylation of histone H3 at K27 (H3K27me1) was decreased by IC_{25} $CdCl_2$ and was associated with prolonged mitosis, decreased population doublings, and compensatory increased total histone protein production. Importantly, daughter cells inherited these alterations and even when the impact of cadmium on cell cycle progression was reversed, reduced H3K27me1 and population doublings were still detected (Gadhia et al. 2015). In cultured lung cells, carcinogenesis-associated histone methylation marks H3K4me3 and H3K9me2 were elevated by $CdCl_2$ (≤ 2.5 µM, 6-48 h), which inhibited histone demethylases (Xiao et al. 2015). In transformation studies with 2 µM $CdCl_2$, H3K4me3 and H3K9me2 were elevated at 4 weeks but no longer at 20 weeks suggesting transient changes in histone methylation is sufficient to bring about persistent genetic changes associated with transformation (Xiao et al. 2015). Thus, cadmium-epigenetic changes are associated with a cell protective response that may translate into cell transformation and contribute to cadmium-induced carcinogenesis.

DNA damage, repair and genomic instability

Lesions to the DNA can stem from both endogenous and exogenous sources, such as metabolism, ROS, replication errors, ionizing radiation, environmental carcinogens or UV, leading to alterations in DNA bases or the DNA strand (Bantele and Pfander 2019; Chatterjee and Walker 2017; Weeden and Asselin-Labat 2018). A high frequency of DNA lesions through imbalance in lesion occurrence and DNA repair systems can result in genomic instability, which is central to cell transformation and thus carcinogenesis (Boulianne and Feldhahn 2018; Tubbs and Nussenzweig 2017). Depending on the type of DNA damage elicited, a defined repair program is initiated (Friedberg 2003; Iyama and Wilson 2013; Polo and Jackson 2011; Sirbu and Cortez 2013). Excision pathways repair damage or breaks to a single strand of

DNA. The remaining intact strand of DNA serves a template for nucleotide replacement. Nucleotide excision repair (NER) is activated by pyrimidine dimers and DNA adducts or crosslinks that are commonly elicited by UV and carcinogens and involves removal of short sequence of single stranded DNA, which contains the lesion, and restoration of the missing sequence by action of the DNA polymerase and DNA ligases (Liakos et al. 2017). When DNA bases are damaged, for example through oxidation or hydrolysis, base excision repair (BER) is engaged to remove the damaged bases utilizing a process of recognition by DNA glycosylases, cleavage by apurinic/apyrimidinic (AP) endonucleases and finally repatched by nucleotide synthesis and ligation (Limpose et al. 2017). BER also repairs single-strand DNA breaks. During DNA replication and recombination, bases can be erroneously inserted, deleted or incorporated and are corrected by DNA mismatch repair (MMR) (Liu et al. 2017a). "Mut" proteins recognize the mismatches and make an incision at the mismatch site in the DNA, which is excised by exonucleases, filled by DNA polymerases and the ends are ligated.

In contrast, homologous recombination (HR)—a form of homology directed repair (HDR)—or non-homologous end joining (NHEJ), that is, when homologous DNA is absent, is used to repair double strand breaks (DSBs) in the DNA incurred by ionizing radiation, ROS or stalled replication forks (San Filippo et al. 2008; Scully et al. 2019; Weeden and Asselin-Labat 2018). From all of the DNA repair mechanisms described, NHEJ is the most prone to error and has been implicated to play a major role in the development of genomic instability and tumor progression (Jeggo and Lobrich 2015; Mladenov et al. 2016). Upon a DSB, local histone H2AX is phosphorylated by PI3-like kinases (ATM, ATR or DNA-PK) (Blackford and Jackson 2017) to form γH2AX, which serves as a mediatory signal for accumulation of DNA damage response proteins, such as BRCA1/2 during HR, at the lesion, and is indicative of changes in chromatin (Georgoulis et al. 2017). In HR, Rad51 nucleoprotein filaments are generated on the ends of single-stranded DNA, formed at the DSB, and "search" for homology. Once found, the DNA polymerase uses the homology to generate the correct missing DNA sequence and repair is completed by annealing and ligation. HR can only take place during the S and G2 cell cycle phases when homologous DNA is present (Ceccaldi et al. 2016; Daley and Sung 2014). Conversely, during NHEJ, which takes place in the G1 cell cycle phase, the ends are simply processed, DNA is synthesized and ligated with variable base pair sizes that are deleted or inserted into the sequence (Ceccaldi et al. 2016).

Cadmium is per se weakly genotoxic yet augments DNA damage, mutations and genomic instability through numerous indirect pathways, including ROS generation and perturbation of DNA repair enzymes (Bertin and Averbeck 2006; Candeias et al. 2010). For more comprehensive reviews, the reader is referred to the following articles (Filipic 2012; Hartwig 2013a, 2013b; Templeton and Liu 2010). Through increased activity of ROS-generating enzymes and inhibition of ROS-metabolizing enzymes, cadmium induces oxidative stress (Thévenod and Lee 2013a), which, in turn, causes lesions to the DNA, including potentially lethal DSBs. Moreover, DSBs can be elicited through high transcriptional activity (Schwer et al. 2016), which is also a characteristic response as gene expression changes following cadmium exposure. Repair enzymes pose a major inhibitory target of cadmium, culminating in accumulation of mutations in the DNA to promote cadmium-induced carcinogenesis (Candeias et al. 2010; Dally and Hartwig 1997). Displacement of zinc at zinc finger motifs by cadmium is a pivotal mechanism for inhibition of DNA repair enzymes and propagation of carcinogenesis (Hartwig 1994; Witkiewicz-Kucharczyk and Bal 2006).

Cadmium has been shown to inhibit MMR at 5 µM in an in vitro cell extract experiment (Jin et al. 2003) and was later discovered to act through inhibition of ATPase activity of the mismatch binding MSH2-MSH6 complex by targeting its cysteine and histidine residues (Banerjee and Flores-Rozas 2005; Wieland et al. 2009). The BER pathway has also been reported to be affected by cadmium: AP-endonuclease inhibition by cadmium occurred at concentrations greater than 10 µM in vitro (Candeias et al. 2010) or in whole cell extracts from human HEK 293T cells (McNeill et al. 2004) and 8-oxoguanine-DNA glycosylase was inhibited by high cadmium (1 mM) under in vitro conditions (Zharkov and Rosenquist 2002) or at non-toxic 60 µM cadmium for 18 h in MCF7 breast cancer or HeLa cervical cancer cells (Bravard et al. 2010). Targeting of cysteine or histidine residues, which are favored by transition metals for binding, at the active site would be a plausible hypothesis for inhibition of these enzymes by cadmium. Intriguingly, cadmium has been suggested to act by supplantation of catalytic water that is required for activity of the uracil-DNA glycosylase (Gokey et al. 2016). Maximal activity inhibition was observed with 100 µM cadmium and cadmium ions were bound at residues D145 and H148 in the active site (Gokey et al. 2016), thus offering an alternative mechanism to zinc displacement and structural disorganization in inhibition of DNA repair enzymes. Finally, appearance of micronuclei and γH2AX, indicative of DSBs, occurs at 30 µM cadmium within 1 h and the repair capacity of DNA-PK, which is essential for NHEJ repair, was reduced after irradiation in the presence of cadmium (Viau et al. 2008).

How might cadmium affect the regulation of DNA repair enzyme expression? This aspect of the impact of cadmium on DNA damage and genomic instability is less well-evidenced. Emerging reports suggest transcriptional inhibition of key enzymes involved in repair of DNA, including the

DNA polymerase (Antoniali et al. 2015), DNA glycosylase OGG1 (Al Bakheet et al. 2013; Pizzino et al. 2014; Youn et al. 2005; Zhou et al. 2012) as well as epigenetic modifications that impact DNA repair, such as mitotically-inherited histone methylation (H3K27me 1) (Gadhia et al. 2015), long non-coding RNAs (Zhou et al. 2015b) or DNA hypermethylation (Zhou et al. 2012) could be key. Moreover, it has been suggested that translocation of OGG1 into stress granules is induced by cadmium, thereby preventing OGG1 from reaching its site of action, has been suggested (Bravard et al. 2010).

Nuclear matrix proteins

The nuclear matrix and perichromatin space contain a plethora of regulatory proteins that maintain composition of the nuclear sap, execute signaling cues, govern turnover of proteins, and modulate gene transcription (Hancock 2000; Verheijen et al. 1988).

DNA fragmentation is the penultimate step in the apoptotic signaling cascade, prior to apoptotic body formation and engulfment by macrophages, and is executed by Ca^{2+}/Mg^{2+}-dependent apoptotic endonucleases that cleaves the DNA at intranucleosomal linker regions (Gaido and Cidlowski 1991). In isolated bovine liver nuclei, cadmium was demonstrated to be internalized already at 1 pM extranuclear free cadmium (Hechtenberg and Beyersmann 1994) as well as to activate apoptotic endonuclease and induce DNA laddering only at low concentrations (< 10 µM free Cd^{2+}), therefore corroborating apoptosis is induced by low cadmium, but also potently inhibiting DNA laddering by calcium (Lohmann and Beyersmann 1993, 1994). The same group also reported cadmium blockade of nuclear calcium ATPase, resulting in lowered nuclear calcium accumulation (Hechtenberg and Beyersmann 1994) thus it is unclear whether the cadmium effects are consequent of nuclear calcium uptake inhibition or direct blockade of the endonuclease. Distinct from apoptotic endonucleases are DNA repair endonucleases, such as Ape1 and MutLa, which are inhibited by cadmium (McNeill et al. 2004; Sherrer et al. 2018), and hence lead to augmented DNA damage and culminating in either apoptosis induction through cell cycle checkpoints or in increased mutations and contribution to cell transformation.

Activation of nuclear protein kinase C (PKC) by phorbol esters is potentiated in the presence of cadmium by ~ twofold (Beyersmann et al. 1994; Block et al. 1992). Astonishingly, PKC binding to nuclear proteins is enhanced by 0.1 nM free Cd^{2+} compared to 1 nM free Zn^{2+} in rat liver nuclei (Beyersmann et al. 1994; Block et al. 1992). These findings could affect the phosphorylation status of histones and therefore chromatin organization. Lastly, it was proposed that inhibition of 8-oxo-dGTPase by CdAc (20 µmol/kg/bw, s.c., 2-48 h) in rat testis may lead to incorporation of promutagenic 8-oxo-2′-deoxyguanosine, promoting carcinogenesis, but time course inconsistencies of cadmium inhibition of the enzyme and 8-oxo-2′-deoxyguanosine incorporation question a causal relationship (Bialkowski et al. 1999).

Transcriptional regulation

Typically, activated cytosolic transcription factor proteins are stabilized and shuttle to the nucleus wherein transcription is initiated after promoter binding. A multitude of factors determines whether a gene is "switched on" or "turned off" such as nuclear abundance and activating modifications of transcription factor proteins, levels of accessory regulatory proteins, accessibility of response elements, and the presence of metal ions, in particular zinc (Klug 2010; Spitz and Furlong 2012).

Cadmium's pleiotropic effects on cells lies in part in its ability to modulate the cell's stress response and defense systems by positively and negatively regulating gene transcription. Extensive reports in the literature evidence altered gene expression upon cadmium exposure that involve classical transcription factors, such as nuclear factor kappa B, AP-1, c-Myc, and Nrf2 [reviewed in (Thévenod and Lee 2013a)]. It is important to note that most of these studies allude to altered regulation by upstream signaling pathways initiated by cadmium, and not a direct effect [reviewed in (Thévenod 2009)]. To date, only a single study has identified direct participation of cadmium on transcription factor activity. The tumor suppressor gene p53 is a zinc finger protein and is often quoted as the guardian of the cell, overseeing genotoxic and non-genotoxic-induced stress responses, primarily by DNA quality control, and is mutated in over 50% of cancers. In a set of elegant experiments, Meplan et al. utilized recombinant wildtype p53 and conformation-specific antibodies to show that 10–30 µM cadmium in MCF7 cells induces a conformational change in p53, through displacement of zinc, resulting in dissipation of its DNA binding capacity, preventing activation of p53 target genes (Meplan et al. 1999) to remove mutated cells by apoptosis, and thus contributing to cadmium-induced carcinogenesis.

Additional zinc-finger harboring transcription factors, such as metal transcription factor 1 (MTF-1) [reviewed in (Moulis 2010; Petering 2017)], could also be affected by cadmium. Furthermore, nuclear export of transcription factors (Suzuki et al. 2003) or mRNA (Topisirovic et al. 2002), changes in nuclear architecture that prevent access to response elements, and modification of accessory transcription complex proteins or transcriptional machinery may all be susceptible to alteration by cadmium.

Cadmium and lysosomes

Lysosome biogenesis, maturation and functions

Lysosomes are commonly known as intracellular acidic organelles involved in degradation and recycling (Luzio et al. 2007) by receiving and digesting cargo delivered by endocytosis, autophagy, and phagocytosis. Typically, cargo is taken up from the extracellular environment, e.g. via receptor-mediated endocytosis, and the resulting components are recycled in cellular metabolism. In the process of self-digestion, so-called autophagy, lysosomes maintain cellular quality control and stress adaptation by digesting damaged organelles and misfolded proteins that are harmful to cells and delivered to lysosomes by autophagosomes (Huotari and Helenius 2011).

In the canonical endocytic/endo-lysosomal pathway, early endosomes (EEs) bud off the PM and can either return to the PM as a recycling endosome (RE) or enter the late endosomal (LE) pathway (Huotari and Helenius 2011; Scott et al. 2014). LEs are acidified to pH ~ 5.5 by the vacuolar H^+-ATPase (V-ATPase) (Casey et al. 2010) and acquire lysosomal proteins, which are specifically recognized as lysosomal components and are correctly sorted to this organelle through endosomes. Lysosomal transmembrane proteins contain consensus motifs in their cytosolic regions (tyrosine or dileucine-based) that serve as sorting signals to (late) endosomes, whereas most lysosomal acid hydrolases acquire mannose 6-phosphate (Man-6-P) moieties that mediate binding to two membrane receptors with endosomal sorting motifs in their cytosolic tails. These tyrosine and dileucine-based motifs are targeting sequences for clathrin-coated carriers that transport their cargo from the trans-Golgi network and plasma membrane to the endosomes (Luzio et al. 2007; Staudt et al. 2016). To degrade cargo, lysosomal hydrolytic enzymes, which target proteins, nucleic acids, carbohydrates and lipids, require an intralysosomal pH of ~ 4.5 for optimal activity that is generated by the concerted action of a V-ATPase and a counterion transporter (Mindell 2012).

Lysosomes interact with other intracellular organelles, such as ER, mitochondria and peroxisomes (Oyarzun et al. 2019), to regulate their function and thereby serving as major signaling platforms that regulate cell growth, division and differentiation to maintain cellular homeostasis (Lamming and Bar-Peled 2019). The most well-known signaling hub is the master growth regulator mTORC1 (mammalian target of rapamycin complex 1), a multi-protein complex, which is activated on the lysosomal surface in response to nutrient and growth signals and phosphorylates various cell growth-related substrates, including the transcription factors EB (TFEB) and E3 (TFE3) (Lawrence and Zoncu 2019). When mTORC1 is inactivated, specific phosphatases, such as calcineurin, are activated, which leads to TFEB/TFE3 dephosphorylation and their nuclear translocation, where they operate as master regulators of lysosome biogenesis (Raben and Puertollano 2016), by regulating (1) levels of lysosomal enzymes, lysosomal acidification and the number of lysosomes, (2) autophagy by regulating the number of autophagosomes and the fusion between autophagosomes and lysosomes, and (3) docking and fusion of lysosomes to the plasma membrane in the process of lysosomal exocytosis (Raben and Puertollano 2016). The concerted action of these three processes leads to clearance of cellular molecules and organelles by lysosomal degradation (Settembre et al. 2013). Lysosomes also act as intracellular Ca^{2+} stores, which can release Ca^{2+} into the cytosol, but can also crosstalk with ER Ca^{2+} stores to shape intracellular Ca^{2+} signaling (Hesketh et al. 2018).

Intriguingly, micromolar cadmium inhibits phosphomannose isomerase from *Saccharomyces cerevisiae* by competition with the substrate Man-6-P (Ki = 19.5 µM) (Wells et al. 1993) thereby increasing its levels, which could promote lysosome biogenesis. Accordingly, increases in heteromorphous lysosome size and number by cadmium have been observed using TEM in an embryonic insect cell line (66 µM $CdCl_2$, 24 h) and rat renal cortex (Asar et al. 2004; Braeckman et al. 1999; Matsuura et al. 1991), identified by neutral red uptake and acid phosphatase staining (Braeckman et al. 1999), and fluorescent dye labeling of acidic compartments (Messner et al. 2012). Lysosomal system expansion could represent early adaptive processes (Goyer et al. 1984) resulting from: (1) lysosomal homotypic fusion and fission; (2) inhibition of lysosomal trafficking; (3) inhibition of RE formation forcing endosomes into lysosomal maturation; and (4) increased delivery of lysosomal proteins from Golgi to LEs to drive lysosomal maturation. Enlargement of the Golgi apparatus by cadmium in fibroblasts and hepatocytes (Ferri 1980; Ord et al. 1988) could contribute to increased lysosome biogenesis, however, how cadmium affects these processes is unknown. Although recent studies from one laboratory has claimed that cadmium (12.5–50 µM, 24 h) increases nuclear translocation of TFE3 and/or TFEB to promote lysosomal biogenesis in cultured neuronal and bone mesenchymal cell lines, the experimental evidence provided is not entirely convincing (Pi et al. 2017, 2018, 2019). The impact of cadmium on lysosomal function and biology is summarized in Fig. 2.

Lysosomal function and autophagy

Autophagy is an evolutionarily conserved intracellular process in which cellular proteins and organelles are engulfed by specific organelles, called autophagosomes, for degradation

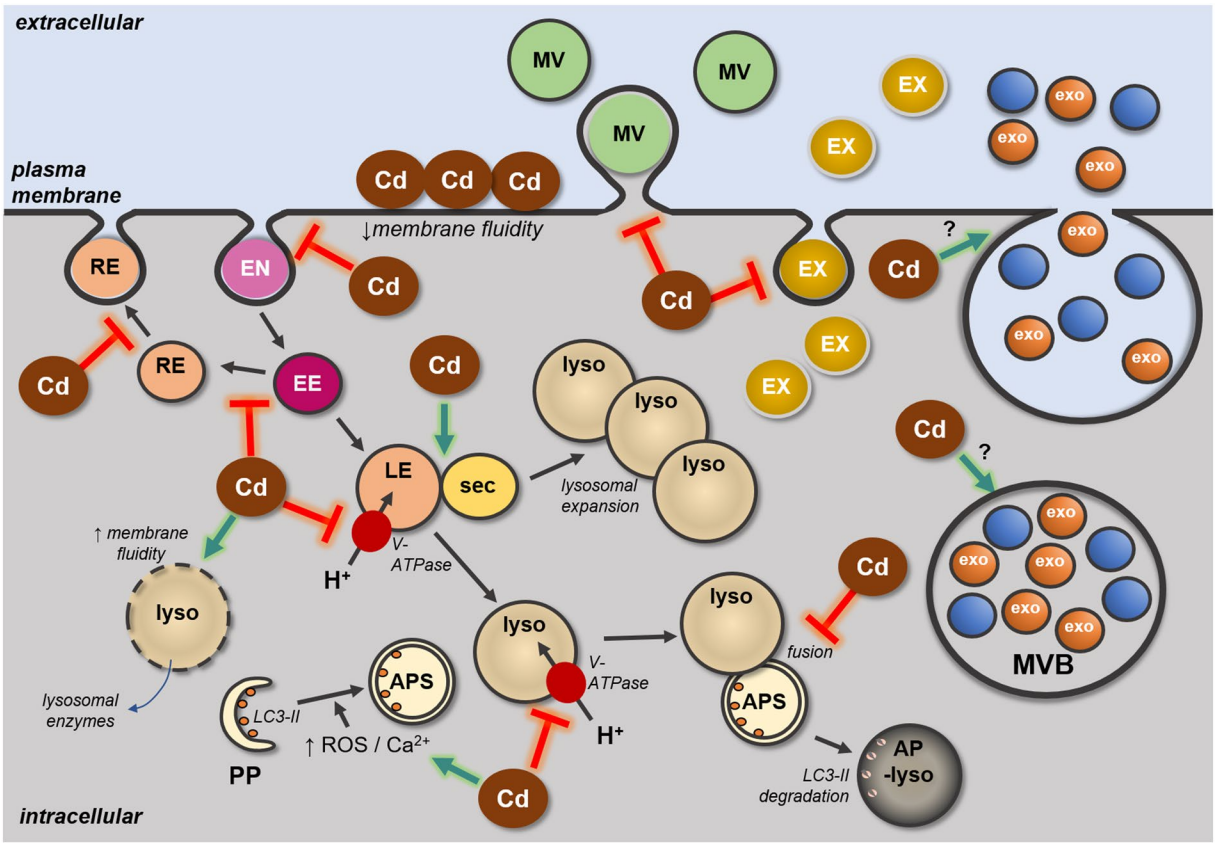

Fig. 2 Cadmium effects on endocytosis, exocytosis, autophagy and lysosomes. Through molecular mimicry, cadmium inhibits calcium-dependent processes, such as regulated synaptotagmin-dependent exocytosis (EX) and microvesicle (MV) formation. Blockade of the vacuolar H^+-ATPase (V-ATPase) prevents late endosome (LE) and lysosome (lyso) acidification and thus endocytosis (EN) endpoints. Further, cadmium prevents recycling endosome (RE) formation from early endosomes (EE) or RE exocytosis. Cadmium expands lysosome number, possibly due to increased secretory vesicles (sec) containing lysosomal proteins. Fluidization of the lysosomal membrane by cadmium may result in lysosomal membrane permeabilization and could lead to cell death. Autophagopore (PP) formation precedes autophagosomes (APS), which are prevented from fusing with lysosomes to form autophagolysosomes (AP-lyso) by cadmium and thus hindering autophagy. Cadmium could be involved in mobilizing multivesicular bodies (MVB) during augmented exosome (exo) secretion. See text for further details

and eventually delivered to lysosomes (Shen and Mizushima 2014). This process is quite distinct from endocytosis-mediated lysosomal degradation of extracellular and plasma membrane proteins (Mizushima 2007). Autophagy occurs at basal levels in all eukaryotic cells but may also be induced by multiple cell stress signals, including hypoxia, ROS or DNA damage (Kroemer et al. 2010). By degrading damaged proteins and organelles, the cell can increase its chances of survival during stress or nutrient starvation conditions; this works in a complementary fashion to ERAD (Mizushima and Komatsu 2011) (see "Cadmium and ER").

Cells display three types of autophagy (Thévenod and Lee 2015): Microautophagy refers to the direct lysosome engulfment of cytoplasm. Chaperone-mediated autophagy denotes the process of direct transportation of unfolded proteins via the lysosomal chaperone protein hsc-70. These complexes then bind to LAMP-2A, a lysosomal membrane receptor, and translocate across the lysosomal membrane. The third type of autophagy, macroautophagy, is the most important type and refers to the de novo synthesis of a double membrane structure, the so-called phagophore or isolation membrane, at the phagophore assembly site. The latter consists of the phagophore and the core molecular machinery (Autophagy-related genes, *Atg*), which control autophagosome formation. The phagophore expands and engulfs entire cytoplasmic components, including organelles, long-lived proteins, protein aggregates, and other cytosolic material either in a targeted (ERphagy, mitophagy) or non-targeted (macroautophagy) manner. By fusing its two ends, the phagophore forms a double membrane compartment or vesicle called the autophagosome (Eskelinen and Saftig 2009). The membranes of the autophagosomes are pinched off from intracellular organelles, such as the ER or mitochondria (Hailey et al. 2010; Mari et al. 2010), and used to form

the double-membraned vesicles (Boya et al. 2013), which link cytosolic LC3 to phosphotidylethanolamine. Lipidated LC3, also known as LC3-II, serves as an anchorage point for autophagosomal chaperones that direct cargo destined for degradation but are also subject to degradation themselves. Indeed, LC3 degradation is used as a measure of autophagic flux (Klionsky et al. 2016). Once autophagosomes are formed, most of the Atg proteins dissociate, which allows maturation by fusion with lysosomes to form autolysosomes. This results in the degradation of the engulfed content and autolysosome inner membrane proteins by lysosomal acidic hydrolases. The resulting degradation products (e.g. amino acids) are released into the cytosol and recycled.

Upstream, autophagy can be regulated by ROS and Ca^{2+} release. The regulation of autophagy by ROS occurs by redox reactive transcription factors (e.g. HIF1, p53, Nrf2, and Foxo3), which increase the expression or activity of autophagy-related proteins (Scherz-Shouval and Elazar 2011). Moreover, oxidative stress can also act directly on AMPK, leading to disinhibition of mTORC1 and increased autophagy whereas $[Ca^{2+}]_{cyt}$ has a dual role in autophagy regulation (Bootman et al. 2018).

Autophagy activation can also occur as a direct consequence of ER stress and activation of the UPR, possibly as a mechanism to eliminate aggregated proteins and damaged cellular components (Senft and Ronai 2015; Woehlbier and Hetz 2011). Hence, autophagy may decrease cellular stress levels by removal of ER membranes, which contain UPR sensors, or decrease the amplitude of stress by clearing aberrant proteins from the ER. In most cases, this autophagic induction is protective and may prevent ER-stress-associated cell death as part of an early adaptive and survival response (Ogata et al. 2006). However, in some instances, autophagy is a means of killing cells when ER stress is prolonged and substantial (Ding et al. 2007; Ullman et al. 2008).

Pharmacological agents modulate autophagy at multiple stages: Rapamycin inhibits mTORC and thereby promotes autophagy induction. The PI3K inhibitors wortmannin and 3-methyladenine (3-MA) prevent the formation of autophagosomes, blockers of lysosomal hydrolase activity operate either by neutralizing the intralysosomal acidic pH (the weak bases NH_4Cl and chloroquine), inhibiting the lysosomal V-ATPase (bafilomycin A1), or preventing activity of lysosomal proteases (pepstatin/E64) (Fleming et al. 2011; Pasquier 2016). More recently, a novel inhibitor, which targets autophagosome-lysosome fusion, called liensinine has given insights into the mechanism of autophagy disruption (Zhou et al. 2015a).

Without doubt, cadmium induces autophagy (Fig. 2). However, the consequences for cell fate are disputable. The survival role of autophagy has led to the hypothesis that autophagy induction by cadmium is protective and prevents tissue damage or overcomes cell death, respectively [(reviewed in (Thévenod and Lee 2013a; Thévenod and Lee 2015)]. The role of autophagy in the fate of cadmium-exposed cells is hampered by the exclusive use of rapamycin, which inhibits mTORC1, an autophagy suppressor, without consideration that mTORC2, an activator of anti-apoptotic Akt signaling, is also blocked by rapamycin during chronic exposure in some cells, leading to cell death (Thévenod et al. 2015). Nevertheless, autophagy as an early stress response has been observed in kidney cortex of rats exposed to subtoxic cadmium (0.3 mg/kg/bw $CdCl_2$, i.p. 1–5 days), suggesting that autophagy is protective (Chargui et al. 2011). In contrast, in the same study, cadmium (5 µM, 5 h) promoted toxicity of cultured cells along with increased LC3-II, which was reduced by 3-MA, but increased with bafilomycin A1 (Chargui et al. 2011), which suggests that autophagy contributes to toxicity. The lack of protection by bafilomycin A1 may possibly be the consequence of cadmium inhibition of the V-ATPase [see (Herak-Kramberger et al. 1998)] and/or lysosomal membrane permeabilization (LMP).

Recent evidence clearly demonstrates several molecular mechanisms by which cadmium disrupts autophagy execution, that require kinetic considerations: In addition to interrupting autophagic flux, cadmium seems to prevent autophagosome-lysosome fusion and diminishes lysosomal function, but these processes are time-dependent (Lee et al. 2017; Li et al. 2016; Zou et al. 2020). In NRK-52E rat kidney PTCs, 5 µM $CdCl_2$ induced transient protective autophagy within 3 h (↑LC3-II/↓p62), which occurred concomitantly with activation of UPR signaling (Lee et al. 2017) and appeared to be triggered by upstream increase of ROS and or cytosolic Ca^{2+} (Lee et al. 2012). Yet cadmium disrupted autophagy execution at 6–8 h (↑LC3-II/↑p62), and autophagy disruption was not overcome by the autophagy inducer rapamycin, which—conversely to previous reports—was also ineffective against cadmium-induced cell death (Lee et al. 2017; Thévenod et al. 2015). This suggests that during longer exposures, cadmium disrupts autophagic flux to an extent that is not reversed by autophagy inducers and that cadmium may also interfere with a late stage of autophagy. In neuronal cells, blockade of autophagic flux by cadmium (10 µM, 8 h) also concurs with decreased prosurvival signaling and accumulation of autophagosomes resulting in cell death (Zhang et al. 2019). Further experiments using the autophagosome-lysosome fusion inhibitor liensinine and isolated lysosomes evidenced that autophagy delayed the onset of apoptosis induced by low cadmium stress whereas accrual of cadmium stress over time decreased effectiveness of lysosomal inhibitors on LC3-II/p62, increased lysosomal membrane fluidity and caused lysosomes to become instable with reduction of lysosomal LAMP1 and cathepsin B (Lee et al. 2017). These changes elicited by cadmium may alter the fusion capacity of lysosomes (Pi et al. 2017; Wang et al. 2017; Zou et al. 2020)

and, potentially in concert with elevation of cytosolic calcium (Liu et al. 2017b), prevent autophagy execution. In mouse neuroblastoma cells or primary rat PTCs exposed to cadmium (2.5–50 μM) for 12–24 h, co-localization of LAMP1 with LC3 or Rab7, a component of the autophagosome-lysosome fusion machinery, or colocalization of an additional lysosomal marker LAMP2 with LC3 puncta (Li et al. 2016; Liu et al. 2017b) was significantly reduced by cadmium. Moreover, cadmium in the absence or presence of 3-MA or ATG5 siRNA, respectively, increased LC3-II and p62 as well as loss of neuroblastoma cell viability, suggesting that cadmium targets the latter stages of autophagy execution (Li et al. 2016). Finally, cadmium increased lysosomal pH and lysosome biogenesis-related genes but decreased overall lysosomal protease and cathepsin D activities (Li et al. 2016). Though lysosome biogenesis-related genes were augmented by cadmium via nuclear translocation of TFEB, the contribution of TFEB on cadmium autophagy and consequent cell viability was not investigated. The authors further demonstrated that melatonin reverses the detrimental lysosomal effects by cadmium, but these data need to be taken with caution (Li et al. 2016) because melatonin, though a powerful antioxidant, binds cadmium (Limson et al. 1998).

Lysosomal membrane permeabilization

Loss of lysosomal membrane integrity results in the leakage of lysosomal contents, including acid hydrolases, into the cytosol, which leads to lysosomal cell death (Aits and Jaattela 2013). LMP is most likely caused by alterations in lysosomal membrane lipid composition and/or membrane fluidity because inhibitors of lysosomal acid sphingomyelinase (ASMase) (and hence increased sphingomyelin in the lysosomal membrane) induce lysosomal instability and LMP (Kallunki et al. 2013; Petersen et al. 2013). Cadmium has been shown to bring about LMP in various cellular models. In PTCs, compromised lysosomes were observed with 5 μM $CdCl_2$ after 6 h as assessed by decreased lysosomal LAMP1 and cathepsin B (Lee et al. 2017), suggesting cadmium induces LMP (Fig. 2). Furthermore, increased total cellular sphingomyelin levels were associated with increased lysosomal membrane fluidity, which could cause detachment of lysosomal proteins, e.g. ASMase or LAMPs, from the lysosomal membrane, leading to their degradation and/or leakage. Cadmium-induced LMP has also been indicated by loss of acidic compartment labeling in endothelial and hepatoma cell lines (Fotakis et al. 2005; Messner et al. 2012), leakage of lysosomal DNase II in necrotic endothelial cells (Messner et al. 2012), and selective leakage of β-glucuronidase but not acid phosphatase, from isolated lung lysosomes (Giri and Hollinger 1995). The ability of lysosomes to accumulate dyes, such as LysoTracker, acridine orange or neutral red, upon their protonation has also been used to assess diminished lysosomal integrity after cadmium exposure (Braeckman et al. 1999; Fotakis et al. 2005; Messner et al. 2012). However, lack of lysosomal dye accumulation could also be consequent of cadmium inhibition of the V-ATPase and thus increasing lysosomal pH (Herak-Kramberger et al. 1998).

Cadmium and vesicular trafficking

Intracellular trafficking vesicles exist as numerous distinct and interconnected subpopulations involved in endocytosis, transcytosis and exocytosis. Their multiple functions encompass communication between the intra- and extracellular space, ferrying soluble cargo proteins to their final destination, selecting and sorting cargo transmembrane proteins, such as receptors and transporters (Bonifacino and Glick 2004), or operating as a pipeline to regulate lipid dynamics (Balla et al. 2019; Funato et al. 2020). Though it is not a focus of this review, it is essential to note the effects of cadmium on cytoskeletal proteins, on which trafficking vesicles and organelles travel around the cell interior. Since the cell's cytoskeleton, such as actin filaments, is regulated by calcium (Izadi et al. 2018), it is clear to see how cadmium affects the formation of filamentous actin (Liu et al. 2018b; Templeton and Liu 2013) and decreases expression of tau, DBN-1 and α-synuclein cytoskeletol proteins (Ge et al. 2019). Disruption of these protein tracks will undoubtedly affect organelle communications, vesicular mobility, and downstream signaling (Moujaber and Stochaj 2020). The effects of cadmium on vesicular trafficking are summarized in Fig. 2.

Endocytosis

Invagination and budding from the PM membrane occurs with the aid of clathrin (Kaksonen and Roux 2018), caveolin (Cheng and Nichols 2016) or through clathrin- and caveolin-independent endocytosis (Sandvig et al. 2018), resulting in formation of EEs that develop into REs or into acidic LEs and subsequently lysosomes in a GTPase-dependent manner (Huotari and Helenius 2011).

Cadmium impairs endocytosis. The PTC in the kidney is the primary site of accumulation of cadmium complexed to proteins, peptides and/or amino acids (Fels et al. 2019) and has high endocytic turnover at its apical brush border membrane (BBM) because of its role in mass protein reabsorption via receptor-mediated endocytosis. In PTC, cadmium exposure diminished receptor-mediated endocytosis of fluorescently-labeled ligands in both an in vivo rat model (Herak-Kramberger et al. 1998) and an in vitro cell line model (Choi et al. 1999): In opossum kidney (OK) PTCs, FITC-albumin receptor binding, B_{max} and uptake were maximally attenuated by 100 μM $CdCl_2$ after

1 h whereas no effect was seen on fluid-phase endocytosis measured by FITC-inulin uptake. Although the latter observation was interpreted as evidence for intact endocytic vesicle formation, FITC-inulin endocytosis amounts to about 10% of total endocytosis, which places that conclusion into question. In addition to impaired FITC-albumin uptake, decreased apical FITC-albumin binding was observed and attributed to a lower number of binding sites since B_{max} was diminished in cadmium-exposed cells (Choi et al. 1999). In more intricate studies in a rat model (2 mg/kg/day s.c. $CdCl_2$, 14 days), BBM were damaged and isolated BBM vesicles harbored ~ 40% less V-ATPase protein expression and bafilomycin-sensitive ATPase activity (Herak-Kramberger et al. 1998). Moreover, uptake of FITC-dextran, another marker of fluid phase endocytosis, was reduced (Herak-Kramberger et al. 1998), which contrasts with the results obtained in OK cells using FITC-inulin (Choi et al. 1999), Since acidification is essential for endocytic trafficking, cadmium inhibition of vesicular acidification would impair endocytosis and endosome maturation. Indeed, in studies in vitro, cadmium inhibited V-ATPase activity in a concentration- and time-dependent manner in both isolated BBM and endocytic vesicles from non-treated rat kidneys; moreover in endocytic vesicles, cadmium inhibited ATP-driven intravesicular acidification (quenching of acridine orange, which accumulates in acidic compartments) and accelerated the dissipation of transmembrane pH gradients (Herak-Kramberger et al. 1998). Furthermore, CdMT exposed rats exhibited redistribution of apical membrane proteins, such as megalin and Na^+-H^+-exchanger, into vesicles suggesting that trafficking of REs is also perturbed by cadmium inhibition of vesicular acidification (Sabolic et al. 2002). Downregulation of the protein receptors megalin:cubilin as well as of endosomal ClC5 Cl^- channels involved in vesicular acidification by cadmium has also been discussed, which complements the abovementioned observations (Gena et al. 2010; Santoyo-Sanchez et al. 2013). Overall, these data suggest that dissipation of endosome acidification by cadmium prevents receptor-mediated protein endocytosis culminating in loss of protein capture and proteinuria.

As a caveat, the in vitro studies showing effects of cadmium on isolated endosomes imply that PTC mainly take up "free" cadmium, which does not occur in vivo. As mentioned above, cadmium filtered by the glomerulus is largely found complexed to proteins and peptides (Fels et al. 2019). Cadmium bound to proteins and peptides is taken up into PTC by RME, e.g. via the receptor complex megalin:cubilin (Thévenod and Wolff 2016), suggesting that cadmium may also damage the endosomal-lysosomal pathway from within the vesicular lumen where cadmium is released from proteins degraded by lysosomes (Abouhamed et al. 2006; Lawrence and Zoncu 2019).

In addition to fluid-phase and receptor-mediated endocytosis, cells with high rates of exocytosis retrieve exocytosed membrane by compensatory endocytosis to prevent significant changes in membrane surface area (Wu et al. 2014). This is of particular importance during embryonic development as well as in the physiology of specialized cell types, such as endocrine cells, absorptive and secretory epithelial cells, and nerve cells. Compensatory endocytosis in response to calcium-triggered regulated exocytosis is also calcium-dependent (Leitz and Kavalali 2016; Nanclares et al. 2018), however, the role of calcium is extremely complex, and calcium sensors, such as the EF-hand proteins calcineurin and calmodulin, or synaptotagmin, contribute to this complicated picture (Leitz and Kavalali 2016). Therefore, it is not surprising that cadmium, which interacts with these proteins (Kakalis et al. 1995; Katti et al. 2017; Yuan et al. 2004), and also blocks calcium influx through P-type calcium channels (Thévenod et al. 2019) and triggers compensatory endocytosis (Smith et al. 2000), prevented only compensatory endocytosis in sea urchin embryos (Covian-Nares et al. 2008). In contrast, following calcium-independent constitutive exocytosis (Jaiswal et al. 2009), constitutive endocytosis was not affected by cadmium (Covian-Nares et al. 2008).

Secretory vesicles and exocytosis

Secretory vesicles derived from the trans-Golgi network migrate along microtubules to the PM for exocytosis whereby their membrane proteins are incorporated into the PM or their cargo is released into the extracellular space (Burgoyne and Morgan 2003).

An increase in cytosolic calcium often triggers regulated exocytosis (Pang and Sudhof 2010). In addition to neutralizing opposing surface negative charges between the cell and vesicle membranes, calcium is required for activation of membrane fusion proteins, such as synaptotagmin and the SNARE complex, which mechanically pull the two membranes tightly together to exert the force required for fusion (Sudhof 2013; Sudhof and Rothman 2009). Based on the similar ionic radii and interplay of calcium and cadmium (Choong et al. 2014; Marcus 1988), an effect of cadmium on exocytosis is likely. A recent report examined the effect of using cadmium as a neutralizing ion as opposed to calcium for the insertion of synaptotagmin into a lipid bilayer (Katti et al. 2017). Isolated single synaptotagmin C2 domains, which harbor calcium-binding sites, do not associate with lipid membranes when complexed with cadmium, in contrast to full-length synaptotagmin containing multiple C2 domains, highlighting that cadmium binds single C2 domains with high affinity, but is unable to directly coordinate the lipids (Katti et al. 2017). Moreover, the association of cadmium-complexed full-length synaptotagmin with lipid membranes was shallower than when calcium was used

(Katti et al. 2017) and could have an impact on fusogenicity of membranes during exocytosis events.

Cadmium and other cell organelles

Extracellular vesicles

Intercellular communication can occur through gap junctions, secretion of extracellular signaling molecules or through secreted extracellular vesicles that transfer information via bioactive molecules, including proteins, lipids, signaling molecules, mRNA and microRNAs (miRNAs), into recipient cells (Valadi et al. 2007; van Niel et al. 2018). Based on the current knowledge of their biogenesis, extracellular vesicles can be broadly divided into two main categories: microvesicles (MVs) and exosomes: MVs are derived from budding of the PM whereas exosomes are produced in multivesicular bodies (MVBs). Exosomes tend to be smaller in size (50–150 nm compared to 50–500 nm (but up to 1 µm) MVs) and are enriched in tetraspanins, flotillin and a number of lipids, including sphingomyelin and cholesterol (Maas et al. 2017) (see also Fig. 2).

Presently, cadmium has not been documented to affect exosome formation or secretion though it would be plausible since cadmium increases ceramide (Lee et al. 2007, 2011) which promotes exosome formation and release (Trajkovic et al. 2008) (Fig. 2). In line with this assumption, cigarette smoke, which contains cadmium, induces release of ceramide-rich exosome-containing microparticles from lung endothelial cells (Serban et al. 2016). Similarly to synaptic vesicle exocytosis, budding of the PM in MV formation is a calcium-dependent process thus, not unexpectedly, cadmium, a potent blocker of voltage-gated L- and N-type calcium channels (Hirning et al. 1988; Thévenod and Jones 1992) prevents MV-mediated release of glutamate from rat pineal gland cells (Yamada et al. 1996).

Peroxisomes

Although metabolic functions of peroxisomes vary in different organisms, including plants, protozoa, fungi, and animals, oxidation of fatty acids and H_2O_2 degradation by catalase are common functions, irrespective of the organism type (Walker et al. 2018). Surrounded by a single membrane, peroxisomes are characterized by the expression of H_2O_2-producing and -degrading enzymes, and are largely associated with oxidative status (Lodhi and Semenkovich 2014). Hence, they execute similar biochemical reactions as mitochondria: β-oxidation of lipids, lipid synthesis and regulation of ROS/RNS homeostasis, though the enzymatic machinery employed by each organelle is entirely different. For instance, acyl CoA dehydrogenase in mitochondria versus acyl CoA oxidase in peroxisomes catalyze the first step of β-oxidation (Poirier et al. 2006; Reddy and Hashimoto 2001). Because β-oxidation is not completed, it is thought that peroxisomes perform initial β-oxidation of very long-chain fatty acids ($> C_{26}$), which are not accepted by the mitochondrial system, and release shorter-chain fatty acids to the mitochondria wherein they undergo further β-oxidation and generate ATP via redox reactions involving $FADH_2$ and the ETC (Demarquoy and Le Borgne 2015). In contrast to mitochondria, peroxisomes do not possess an ETC, therefore electrons from $FADH_2$ are passed onto O_2 to form H_2O_2. H_2O_2 is metabolized to water and oxygen by peroxisomal H_2O_2-metabolizing enzymes, mainly involving catalase, however this does not prevent H_2O_2 release into the cytosol—that is thought to be mediated by the non-selective porin PXMP2 (Rokka et al. 2009)— where in it may either serve as an intracellular messenger or cause an imbalance of the cellular redox status. Hence, peroxisomes and mitochondria co-operate in various metabolic and signaling pathways (Fransen et al. 2017).

Peroxisomes have been largely overlooked in cadmium toxicity, despite their well-described ROS/RNS generating capacity, probably due to their functional similarity to mitochondria, which are a known principal target of cadmium toxicity. With the ubiquitous presence of H_2O_2-producing and H_2O_2-metabolizing enzymes, peroxisomes represent the ultimate ROS/RNS production and detoxification stations and with great likelihood could be a target of cadmium-induced damage and oxidative stress (Demarquoy and Le Borgne 2015). In yeast, 1 mM $CdCl_2$ for 24 h inhibited cell growth but increased peroxisome number and catalase activity (Chen et al. 1995). This was recently confirmed in developing chicken embryos where 2–8 µg cadmium/egg at E1, E14 or E18 showed peroxisomal extension and/or increased peroxisome number in glomerular cells, suggesting adaptive protection against cadmium-induced oxidative stress (Dzugan et al. 2018). Yet, this interpretation may be too simple: Despite catalase's detoxifying function, oxidative stress has also been associated with peroxisome proliferation because H_2O_2-producing enzymes are augmented by > 10 times over the increase in H_2O_2-metabolizing enzymes (Rao and Reddy 1991) suggesting that cadmium-induced peroxisome proliferation may rather contribute to oxidative stress. In renal PTCs, 10–50 µM $CdCl_2$ increased catalase activity (Lee, W.K. and Thévenod, F., unpublished data), but peroxisome number was not determined. In contrast, a study in mussels found cadmium had no effect on catalase activity and decreased peroxisome volume density (Orbea et al. 2002). Moreover, cadmium (10–40 µM $Cd(NO_3)_2$, 24 h) weakly interacted with and inhibited catalase activity in the liver of zebrafish (Wang et al. 2015). Along these lines, cadmium (2.5–10 µM for 24 h) increased oxidative stress and inhibited catalase activity in cultured inner medullary collecting duct

cells ($mIMCD_3$), yet divalent iron was protective, suggesting that cadmium displaces redox active iron from the catalase enzyme (Thévenod, F., unpublished data). These conflicting data of cadmium on catalase activity and peroxisomes could lie in the diverse model systems used, dosage and/or exposure time.

Specialized organelles

The effect of cadmium on other more specialized organelles, such as melanosomes, phagosomes or secretory lysosomes, has not yet been notably documented.

Cadmium and organelle interactions

As stated in the introduction, organelles do not function independently from one another. Rather they form a continuous functional network in the cytosolic compartment with constant transient connections to one another to build an intricate communication system. These interorganellar communication signals may be transmitted through membrane-membrane interactions, membrane-protein interactions, protein–protein interactions, intraorganellar content transfer or organelle-to-organelle signaling. At membrane contact sites (MCS), tethering proteins drive membranes together to allow them to come into close proximity but without membrane fusion (Prinz et al. 2020; Scorrano et al. 2019). Vesicle docking, also known as "kiss and run", involves transient membrane fusion (Das et al. 2016; Saffi and Botelho 2019). Fusion and fission are complex orchestrated events that have distinct molecular definitions (de Araujo et al. 2020; Farmer et al. 2018). For further reading, please consult the following excellent recent reviews on ER-mitochondria contact sites through the ERMES complex (ER-mitochondria encounter structure) (Ellenrieder et al. 2017; Kruger et al. 2017; Murley and Nunnari 2016) or mitochondria-associated membranes (Morciano et al. 2018; Simmen and Herrera-Cruz 2018), ER-lysosome interactions (Cabukusta and Neefjes 2018), mitonuclear communication (Melber and Haynes 2018; Vendramin et al. 2017), mitochondria-endolysosome interactions (Lackner 2019; Soto-Heredero et al. 2017; Wong et al. 2019), and mitochondria-peroxisome contacts (Fransen et al. 2017; Lackner 2019; Murley and Nunnari 2016).

Unexpectedly, and surprisingly, at the time of writing, no reports investigating the impact of cadmium on interorganellar communication could be found, despite cadmium's well-documented effects on the cytoskeleton (see "Cadmium and vesicular trafficking"). Based on the extensive effects of cadmium on organelle morphology, function and behavior, as detailed in this review, MCSs and interorganellar signaling are most certainly to be adversely affected.

Summary and conclusions

Separation of the intracellular space through lipid membranes creates organelles with specialized ionic, enzymatic and cellular functions, which is crucial for optimal cell behavior. Moreover, complex cellular functions that require several interacting components, reactions and/or energetic considerations necessitate membranes as a guardrail for efficient reactions. Cadmium is a non-essential metal with numerous effects and disrupts organelle function through the following fundamental mechanisms: (1) altered biophysical properties of lipid membranes (Payliss et al. 2015); (2) ionic mimicry (Choong et al. 2014; Petering 2017); and (3) direct macromolecular interactions, such as with thiol groups (Jacobson and Turner 1980). With relevant chronic low cadmium exposure, organelle function could initially be compromised but stress adaptive responses, which include organelle biogenesis and strengthened interorganellar communication, would strive to restore this loss of function. However, acute and/or high cadmium exposures could negatively affect organelle function such that it cannot be compensated, becomes irreversible, and is detrimental to the cell. Our current knowledge clearly evidences cadmium effects on organelles as single entities in cellular processes, but further understanding of how organelles interact and communicate with each other to coordinate the adaptive response under cadmium stress would be crucial to delineate and predict chronic cadmium toxicity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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