Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Page 2-3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 11-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 8-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 1. Statistical analyses of outcome in interorganellar communication.

OR & RR for outcome of renal disease				
Mt-ER (Group I)	1	7	RR=0.25	0.37
Mt-nucleus (Group II)	1	1	OR=0.14	
Mt-ER (Group I)	1	7	RR=2.67	0.49
Mt-Po (Group II)	1	2	OR=3.5	
Mt-Po (Group I)	1	2	RR=1	1
Mt-nucleus (Group II)	1	2	OR=1	
OR & RR for outcome of age-related disorders				
Mt-Po (Group I)	1	1	RR=1.5 & OR=2	1
Mt-lysosome (Group II)	2	4		
OR & RR for CVD outcome				
Mt-ER	4	8		
RR & OR for metabolic syndrome				
Mt-ER (Group I)	1	8	RR=0.56	1
Mt-lysosome (Group II)	1	4	OR=0.5	
RR & OR for cancer outcome				
Mt-Po (Group I)	1	2	RR=1	1
Mt-lys (Group II)	2	4	OR=1	
RR & OR for metabolic disorders outcome				
Mt-ER	1	7		
RR & OR for CNS disease outcome				
Mt-ER (Group I)	2	8	RR=0.4	0.32
Mt-Lys (Group II)	4	4	OR=0.25	
RR & OR for inflammation outcome				
Mt-lys	1	4		

CVD, cardiovascular disease; ER, endoplasmic reticulum; Lys, lysosome; OR, odds ratio; Po, peroxisome; RR, relative risk.

Appendix 2. Cochrane Collaboration's tool for assessing risk of bias in included studies.

Domains / Authors	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Other bias	Publication Bias	Funding source
Yuan et al, 2012	1	1	1	1	1	1	0	0	present
Raharijaona et al, 2015	1	1	1	1	1	1	0	0	present
Safiedeen, 2017	1	1	1	1	1	1	0	0	Absent
Kawakami et al, 2015	1	1	1	1	1	1	0	0	present
Pacher et al, 2008	1	1	1	1	1	0	0	0	present
Hacki et al, 2000	1	1	1	1	1	0	0	0	present
Gomez et al, 2016	1	1	1	1	1	1	0	0	present
Diwan et al, 2009	1	1	1	1	1	1	0	0	present
Garofalo et al, 2016	1	1	1	1	1	1	1	0	present

Basso et al, 2018		0	0	1	UC	1	1	1	UC	Present
Abuaita et al, 2018		0	0	1	0	0	1	UC	UC	Present
Fernandez-Sanz et al, 2014		0	0	1	UC	UC	UC	UC	UC	Present
Sala-Vila et al, 2016		0	0	1	UC	UC	UC	UC	UC	Present
Naon et al, 2016		0	0	0	0	0	1	0	0	Absent
Hwang et al, 2012		1	1	1	1	1	1	0	0	present
Ivashchencko et al, 2011		1	1	1	1	1	1	0	0	present
Fernandez-Mosquera et al, 2015		1	1	1	1	1	1	0	0	present
Ghavami et al, 2010		1	1	1	1	1	1	0	0	present
Baixuali et al, 2015		1	1	1	1	1	1	0	0	present
Brahimi-Homet et al, 2015		1	1	1	1	1	1	0	0	present
Frequency	Low risk	15/20	15/20	19/20	15/20	16/20	16/20	2/20		P: 18/20 A: 2/20
	High risk	5/20	5/20	1/20	2/20	2/20	2/20	15/20	16/20	
	Unclear				3/20	2/20	2/20	3/20	4/20	

Percent	Low risk	75%	75%	95%	75%	80%	80%	10%		P: 90% A: 10%
	High risk	25%	25%	5%	10%	10%	10%	75%	80%	
	Unclear				15%	10%	10%	15%	20%	

The Cochrane risk of bias categories were dichotomized by recording low risk as 1 and high or unclear risk as 0.This score has been assessed based on Author's opinion on evaluating published articles.

Appendix 3a. Animal studies of interorganellar communication (mitochondria with other organelles) in health and kidney diseases.

Ref/Author/Year	Study design	Study method	Results	Conclusion
6-Yuan, et al, 2012	Animal experimental study	Aldosterone-infused mice received vehicle or RSV. Apoptosis analysis was performed in podocytes. Then cytochrome c release from mitochondria, caspase-3,8 ,9 activities measurement were performed. IF of PGC-1α was performed and then total DNA and RNA of cultured podocytes, isolated glomeruli were extracted. Western blotting in podocyte was performed. ATP measurement, mitochondrial complex enzyme activity assay, assessment of ROS production, PGC-1α acetylation, kidney histopathological analysis, TEM, MDA concentration measurement, urine analysis of albumin and F2-isoprostanes excretion were performed.	1. Aldosterone-induced injury decreased PGC-1α expression and induced mitochondrial and podocyte damage in dose and time dependent manners. 2. The suppression of endogenous PGC-1α by RNAi caused podocyte mitochondrial damage and apoptosis while its increase by infection with an adenoviral vector prevented aldosterone-induced mitochondrial malfunction and inhibited injury. 3. Overexpression of the SIRT-1prevented aldosterone-induced mitochondrial damage and podocyte injury by upregulating PGC-1α at both the transcriptional and post-transcriptional levels. 4. Resveratrol, a SIRT1 activator attenuated aldosterone-induced mitochondrial malfunction and podocyte injury in vitro and in aldosterone-infused mice in vivo.	1. Endogenous PGC-1α may be important for maintenance of mitochondrial function in podocytes under normal conditions. 2. Activators of SIRT1, such as resveratrol, may be therapeutically useful in glomerular diseases to promote and maintain PGC-1α expression and consequently podocyte integrity.
10-Pacher et al, 2008	Animal experimental study	To assess the effect of TGF-β on the ER-mitochondrial Ca^{2+}, at first $[Ca^{2+}]$ c and mitochondrial matrix Ca^{2+} ($[Ca^{2+}]$) m	TGF-β Pretreatment decreased both the $[Ca^{2+}]$ c and $[Ca^{2+}]$ m responses evoked by angiotensin II or endothelin.	TGF-β causes uncoupling of mitochondria from the ER Ca^{2+} release. Since both positive and negative

		signals in preglomerular afferent arteriolar smooth muscle cells (PGASMC).	More depression and delay of [Ca^{2+}] m signal than the [Ca^{2+}] c signal. In permeabilized cells, TGF-β pretreatment attenuated the rate but not the magnitude of the IP3-induced [Ca^{2+}] c rise, yet caused massive depression of the [Ca^{2+}] m responses. ER Ca^{2+} storage and mitochondrial uptake of added Ca^{2+} were not affected by TGF-β.TGF-β had not effect on mitochondrial distribution and on the ER-mitochondrial contacts. Downregulation of IP3R1 and IP3R3 was found in TGF-β treated PGASMC.	mitochondrial feedback effects on the IP3Rs have been described in various cell types, it is likely that suppression of the mitochondrial Ca^{2+} uptake may have marked effects on ER Ca^{2+} mobilization. The impaired of these mechanisms can be relevant in VSMCs, where regulation of the vascular tone depends on spatially and temporally coordinated local interactions between IP3Rs and mitochondria and Ca^{2+}-activated K^+ channels.
11-Hacki et al, 2000	Animal experimental study	To uncover a hitherto unrecognized apoptotic crosstalk between the ER and mitochondria that is controlled by BCl-2 Rat 6 (R6) embryo fibroblasts expressing the retroviral vector pMV12 (controls) or the vector containing mouse Bcl-2 were generated and cultured. R6 derivatives expressing the ER-targeted Bcl-2/cb5 were produced by transfecting the Bcl-2/cb5/pcDNA3 plasmid in the presence of superfect followed by antibiotic selection on geneticin. A clone expressing Bcl-2 in R6-Bcl-2#9 was used for further studies. The various	After triggering massive ER dilation due to an inhibition of secretion, the drug brefeldin A (BFA) induces the release of cytochrome c from mitochondria in a caspase-8 and Bid-independent manner. Then activation of caspase-3 and DNA-nuclear fragmentation does. Cytochrome c release by BFA is not only blocked by wild-type Bcl-2 but also by a Bcl-2 variant that is exclusively targeted to the ER (Bcl-2/cb5). Similar findings were obtained with tunicamycin, an agent interfering with N-linked glycosylations in the secretory system.	Apoptotic agents perturbing ER functions induce a novel crosstalk between the ER and mitochondria that can be interrupted by ER-based Bcl-2.

		cell lines were either treated with 5μg/ml BFA and 1μg/ml cycloheximide or 5 μg/ml tunicamycin or 250 nM staurosporine in the presence or absence of 100μM of the general caspase inhibitor ZVAD.fmk Human JILY B-lymphoblast were cultured and exposed to anti-CD95 antibody. To creat the Bcl-2/cb5 fusion gene the DNA fragment corresponding to the hydrophobic C-terminus of rat cytochrome b5 by PCR.		
12-Gomez et al, 2016	Animal experimental study	To investigate role of GSK3β in the Ca^{2+} transfer from SR/ER to mitochondria at reperfusion. Cell fractionation was performed by differential ultracentrifugation. Ventricular cardiomyocyte were isolated using enzymatic digestion.to monitor mitochondrial Ca^{2+}, isolated adult cardiomyocytes were loaded with 2.5μM rhod-2/AM.	Localization of a fraction of GSK3β protein to the SR-ER and mitochondria-associated ER membranes (MAMs) in the heart and that GSK3β specifically interacted with the IP3Rs Ca^{2+} channeling complex in MAMs. Both pharmacological and genetic inhibition of GSK3β decreased protein interaction of IP3R with the Ca^{2+}channelling complex, impaired SR/ER Ca^{2+} release and reduced the histamine-stimulated Ca^{2+} exchange between SR/ER and mitochondria in cardiomyocytes. During hypoxia reoxygenation, cell death is associated with an increased of GSK3β activity and IP3R phosphorylation, which leads to	Inhibition of GSK3β at reperfusion diminishes Ca^{2+} leak from IP3R at MAMs in the heart, which limits both cytosolic and mitochondrial Ca^{2+}overload and subsequent cell death.

			enhanced transfer of Ca^{2+} from SR/ER to mitochondria. Inhibition of GSK3β at reperfusion reduced both IP3R phosphorylation and ER/SR Ca^{2+}which consequently diminished both cytosolic and mitochondrial Ca^{2+} concentrations as well as sensitivity to apoptosis.	
13-Diwan et al, 2009	Animal experimental study	Mice with inducible cardiac myocyte-specific expression of Nix, germline ablation of Nix, and cardiac specific Gq overexpression were considered. HEK cells were transfected with N-terminal FLAG-tagged mouce Nix and subcellular fractionation was performed. Immunoblotting was performed with antibodies FLAG, COX IV, calnexin and GAPDH.	NIX localized both to the mitochondria and to the ER/SR calcium stores are proportional to the Endogenous cardiac NIX and recombinant level of expressed NIX. Wherease NIX ablation was protective in a mouse model of apoptotic cardiomyopathy, genetic correction of the decreased SR calcium content of Nix-null mice restored sensitivity to cell death and reestablished cardiomyopathy. Nix mutant specific to ER/SR or mitochondria activated caspases and were equally lethal, but only ER/SR –Nix caused loss of the mitochondrial loss of the mitochondrial membrane potential.	Nix is as an integrator of transcriptional and calcium-mediated signals for programmed cell death.
14-Naon et al, 2016	Animal experimental study	To investigate of critical re-evaluation of mitofusin's (Mfn) role in ER-mitochondria cross-talk Juxtaposition is mediated by protein structures that can be visualized in electron microscopy and electron tomography	Electron microscopy and fluorescence-based probes of organelle proximity confirmed that ER-mitochondria juxtaposition was reduced by constitutive or acute Mitofusin 2 deletion. Functionally mitochondrial uptake of Ca^{2+} released from the ER was reduced following	Mfn2 stands as a bona fide ER-mitochondria tether whose ablation decreases interorganellar juxtaposition and communication.

		studies.	acute Mitofusin 2 ablation as well as in Mfn$^{-/-}$cells overexpressing the mitochondrial calcium uniporter. Mitochondrial Ca2+ uptake rate and extent were normal in in isolated Mfn $^{-/-}$ liver mitochondria, consistent with the finding that acute or chronic Mfn2 ablation or overexpression did not alter mitochondrial calcium uniporter complex component levels.	
20-Hwang et al, 2012	Animal experimental study	Male catalase wild type (WT) & catalase knock out (CKO) C57BL/6 J mice were used. Six-week-old mice were divided into four groups: nondiabetic and diabetic WT mice, nondiabetic and diabetic CKO mice DM was induced was induced by low-dose streptozocin	Despite equivalent hyperglycemia, parameters of DN, along with markers of oxidative stress in diabetic CKO mice than in diabetic WT mice up to 10 weeks of diabetes. CKO mice and murine mesangial cells showed impaired peroxisomal/mitochondrial biogenesis and FFA oxidation. Catalase deficiency increased mitochondrial ROS and fibronectin expression in response to FFAs which were effectively restored by catalase overexpression or N-acetylcystein.	FFA-induced peroxisomal dysfunction exacerbates DN and that endogenous catalase plays in important role in protecting the kidney from diabetic stress through maintaining peroxisomal and mitochondrial fitness.
21-Ivashchenko et al, 2011	Animal experimental study	To monitor the peroxisomal redox state at the single cell level under basal and stress conditions by employing a redox sensitive variant of enhanced green fluorescent protein (roGFP2-PTS1)	This study showed that intraperoxisomal redox status is strongly influenced by environmental growth conditions. Disturbances in peroxisomal redox balance may trigger its degradation. Disturbances in mitochondrial redox balance in catalase-deficient cells and upon generation of	This study suggests a potential role for the peroxisome in cellular aging and the initiation of age-related degenerative disease.

			excess ROS inside peroxisomes. Peroxisomes are found to resist oxidative stress generated elsewhere in the cell but are affected when the burden originates within the organelle.	
17-Abuaita et al, 2018	Animal experimental study	To find the MDVs deliver the mitochondrial peroxide-generating enzyme SOD_2 into the bacteria-containing phagosome, controlling bacterial burden To test extensive crosstalk between ER and mitochondrial stress pathways, they hypothesized that IRE1α-dependent antimicrobial activity might rely on mROS.	1. Induction of mROS by IRE1-α promotes macrophages bactericidal function. 2. Mitochondrial peroxide accumulation in phagosomes is TLR dependent 3. Bacterial infection triggers parkin-dependent generation of MDVs 4. Parkin controls phagosomal mH2O2 accumulation and promotes bactericidal function 5. SOD2 is required for generation of bactericidal mH2O2 and is delivered to bacteria-containing phagosomes 6. $SOD2^+$ vesicles define a distinct population of MDV	Methicillin-resistant staphylococcal aureus (MRSA) infection also stimulates the generation of MDVs, which require the mitochondrial stress response factor parkin, and contributes to mH2O2 accumulation in bacteria-containing phagosomes. Accumulation of phagosomal H2O2 requires toll-like receptor signalling and the mitochondrial enzyme superoxide dismutase- 2 (SOD-2) which is delivered to phagosomes by MDVs.
18-Fernandez-Sanz et al, 2014	Animal experimental study	Young adult (5-6 months) and old (> 20 months) C57BL/6 mice were used for in situ functional analysis (echocardiography) and for the obtention of myocardial tissue, isolated cardiomyocytes and mitochondria. LVEF, LVEDD, LVESD, SWT, PWT were measured in the M-mode recordings at the level of papillary muscle. NMR spectroscopy was performed.	1. Aging is associated with altered sarcoplasmic reticulum ryanodine (SR RyR) gating properties. 2. Advanced age depresses SR-mitochondria calcium transfer and NADPH regeneration. 3. Aged cardiomyocytes have less glutathione and increased mitochondrial ROS production. 3. Spatial proximity between mitochondria and SR decreases with aging. 4. Increased oxidation of mitochondrial	Defective SR-mitochondria communication underlies inefficient interorganelle Ca2+ exchange that contributes to energy demand/supply mismatch and oxidative stress in the aged heart.

			respiratory proteins in aged hearts. 5. Disruption of SR-mitochondria connection in young cardiomyocytes mimics age-induced alterations in calcium handling.	
19-Sala-Vila et al, 2016	Animal Experimental Study	12 week old male C57BL/6WJT and CAV1KO MEFs were enrolled in this research. 1. To assess a comprehensive list of proteins of WT hepatic MAMs by proteomics. 2. To explore of the CAV1on MAMs revealing a mechanistic link that explains why VLDL synthesis is impaired in CAVKO mice. 3. To explore mechanistic link between CAV1-dependent functions and MAM integrity.	1. CAV1 is a MAM resident protein of liver. 2. This analysis highlights lipid metabolism, energy management and as steroid anabolism as major regulated targets of MAM functions. 3. CAV1 is as a novel potential key modulator of both the physical integrity and the function of ER-mitochondria interactions.	This study has implications in complex metabolic phenotypes in caveolinopathies and disease e.g. DM, obesity, hepatosteatosis and cancer.

[Ca^{2+}] c, cytosolic calcium; [Ca^{2+}] m, matrix calcium; CAV1, caveolin; DM, diabetes mellitus; DN, diabetic nephropathy; ER, endoplasmic reticulum; FFAs, free fatty acids; IF, immunofluorescence; IRE1α, inositol requiring transmembrane kinase/endonuclease-1α; IP3R1, inositol triphosphate receptor 1; [Ca^{2+}]m, intracellular Ca^{2+} release channel; KO, knock down; LVEF, left ventricle ejection fraction; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; MAMs, mitochondria-associated membranes; MDVs mitochondrial-derived vesicles; MEFs, mouse embryonic fibroblasts; mROS, mitochondrial reactive oxygen species; NADPH, nicotinamide-adenine dinucleotide phosphate; PWT, posterior wall thickness; RyR, ryanodine receptor; SOD, superoxide dismutase; SR, sarcoplasmic reticulum; SWT, septum wall thickness; TGF-β, transforming growth factor- β; TLR, toll like receptor; VLDL, very low density lipoproteins; VSMCs, vascular smooth muscle cells.

Appendix 3b. Human and combined animal-human studies of interorganelle communication (mitochondria with other organelles) in health and kidney diseases.

Ref/Author/Year	Study design	Study method	Results	Conclusion
7-Raharijaona et al, 2009	Human experimental study	Role of nitric oxide in PRC-regulated mitochondrial biogenesis and determined its action in the control of the phosphorylation status of the mitogen-activated protein kinase pathway. PRC-regulated pathways were explored in a cell-line model derived from mitochondrial-rich tumors with an essentially oxidative metabolism and specifically high PRC expression. Comparison of functional status of mitochondria with results of microarray analysis. Expression levels of the genes and proteins involved in the oxidative phosphorylation process were studied by RT-QPCR and western blotting.	Nitric oxide rapidly influences PRC expression at the transcriptional level. Focusing on mitochondrial energetic metabolism, PRC differentially controls respiratory chain complexes and coupling efficiency in a time-dependent manner to maintain mitochondrial homeostasis.	This study highlights the key role of PRC in the rapid modulation of metabolic functions in response to the status of the cell cycle.
15-Garofalo et al, 2016	Human experimental study	Primary human skin cultured fibroblast were obtained from biopsies of sun-protected forearm skin according to standard culture methods. Evaluation of autophagy was performed by using a Cyto-ID Autophagy Detection Kit. To characterize lipid rafts in MAMs and to decipher their possible implication in the autophagosome formation.	The presence of lipid microdomains in MAMs has been detected and in these structures a molecular interaction of the ganglioside GD3, a paradigmatic brick of lipid rafts with core-initiator proteins of autophagy such as AMBRA1 and WIPI1was revealed. This association seems to take place in the early phases of autophagic process in which	This experimental condition results in fact in the impairment of the ER-mitochondria crosstalk and the subsequent hindering of the autophagosome nucleation. This paper hypothesize that MAMs raft-like microdomains could be pivotal in the initial organelle scrambling activity that finally leads

			MAMs have been hypothesized to play a key role.	to the formation of autophagosome
23-Ghavami et al, 2010	Human experimental study	Human neutrophils were prepared from leukocyte-rich blood fractions (buffy coat), S100A8/A9 was purified. Cytotoxicity of S100A8/A9 was determined by MTT assays. Apoptosis was measured by flow cytometry. Luminescence caspase activity assays, Measurement of ROS production, mitochondrial membrane potential assay, immunocytochemistry, were performed and confocal imaging, electron microscopy were used.	1. S100A8/A9 induces apoptosis in various cell lines. 2. S100A8/A9 induces autophagy in apoptotic cells 3. S100A8/A9-induced cell death is partially reversed by inhibition of PI3-kinase or vacuolar H+-ATPase pump, cathepsin inhibitors and ATG5 shRNA 4. ΔTM-BNIP3 overexpression partially inhibits S100A8/A9-induced cell death, ROS production, and lysosomal activation.	1. S100A8/A9 induces both apoptosis and autophagy. 2. S100A8/A9-induced cell death involves BNIP3 and increase of ROS production by mitochondria, subsequently followed by mitochondrial damage and lysosomal activation. 3. They suggest ROS as the critical factor that integrates S100-induced mitochondrial and lysosomal death pathways.
8-Safiedeen, et al, 2017	Human & animal cohort study	Total 30 patients with metabolic syndrome were enrolled in this study.	Both types of MPs increased expression of ER stress markers XBP1, p-eIF2alpha, CHOP and nuclear translocation of ATF6 on human aortic endothelial cells. MPs decreased in vitro NO release by human aortic endothelial cells whereas in vivo MP injection into mice impaired the endothelium-dependent relaxation induced by acetylcholine. With ER stress inhibition, these effects were prevented, suggesting that ER stress is implicated in the endothelial effects induced by MPs.	Endothelial dysfunction triggered by MPs involves cross-talk between ER and mitochondria with respect to spatial regulation of ROS via the neural sphingomyelinase and interaction of MPs with Fas and/or LDL receptor. Providing a novel molecular insight into the manner MPs mediate vascular dysfunction and allow identification of potential therapeutic targets to treat vascular

			MPs affected mitochondrial function and evoked sequential increase of cytosolic and mitochondrial ROS.	complications associated with metabolic syndrome.
9-Kawakami, et al, 2017	Animal and human experimental study	Mice containing LoxP sites inserted in the ATG5 And ATG7 loci. Human biopsy specimens with primary idiopathic FSGS and human control biopsy with no pathologic alterations were identified. Study performed with SDS-PAGE and western blotting, urine and plasma analysis, histologic analysis (EM&IF), epithelial cell culture and assays and quantitative RT-PCR.	1. Mutation of ATG5 in kidney epithelium results in FSGS, tubulointerstitial disease, loss of organ function, and death,↑ ROS generation, ER stress and mitochondrial dysfunction 2. Podocyte foot process effacement precedes FSGS in mice with mutation of ATG5 in kidney epithelium 3. ATG7 mutation in kidney epithelium resulting in FSGS 4. Patients with FGSG have mitochondrial abnormalities	Mitochondrial dysfunction and ER stress due to impaired autophagic organelle turnover in podocytes and tubular epithelium are sufficient to cause many of the manifestations of FSGS in mice.
22-Fernandez-Mosquera et al, 2015	Animal and human experimental study	At first, wild-type mouse embryonic fibroblasts (MEF) to a mitochondrial respiratory chain (RC) complex I inhibitor, rotenone (250 nM) were selected. Then, observed that the transcript levels of several lysosomal genes are rapidly increased upon RC complex I inhibition, and eventually return to baseline levels after 12 h treatment.	1. Lysosomal biogenesis is differentially regulated by acute and chronic mt dysfunction. 2. Induction of lysosomal biogenesis by acute mitochondrial stress is TFEB/MITF- dependent 3. AMPK signaling is necessary for lysosomal biogenesis induced by acute mitochondrial stress.	1. mt respiratory chain impairments elicit a stress signalling pathway that regulates lysosomal biogenesis via the microphthalmia transcription factor family. 2. The effect of mitochondrial stress over lysosomal biogenesis depends on the timeframe of the stress elicited: 2.1. While RC inhibition with

				rotenone or uncoupling with CCCP initially triggers lysosomal biogenesis, the effect peaks after few hours and returns to baseline. 2.2. Long-term RC inhibition by long-term treatment with rotenone, or patient mutations in fibroblasts and in a mouse model result in repression of lysosomal biogenesis. 3. The induction of lysosomal biogenesis by short-term mitochondrial stress is dependent on TFEB and MITF, requires AMPK signalling and is independent of calcineurin signalling.
24-Baixuali et al, 2015	Animal and human experimental study	Naïve CD4+T-cells were obtained by negative selection using the auto-MACS pro Separator. Human fibroblasts from control and patients by skin biosy were obtained. T-cell differentiation, proliferation and intracellular staining were performed. A mouse model with defective mitochondrial function in CD4+ T-lymphocytes by genetic deletion of the mitochondrial transcription factor A (Tfam)	1.Tfam depletion impairs respiratory-chain function in T-cells 2.respiration-impaired cells increase lysosomal compartment through TFEB(transcription factor EB) 3. Mitochondrial dysfunction promotes lysosomal disorder and sphyngolipidosis 4.Tfam deficiency exacerbates inflammatory responses 5.Mitochondrial dysfunction deviates T-cell differentiation towards proinflammatory	1. Mitochondrial respiration deficiency impairs lysosomal function, promotes p62 and sphingomyelin accumulation and disrupts endolysosomal trafficking pathways and autophagy, thus linking a primary mitochondrial dysfunction to a lysosomal storage disorder. 2. The impaired lysosomal function in Tfam deficient cells subverts T-

			Th1 subsets 6. Increasing intracellular NAD+ content boosts lysosomal function and dampens Th1 responses in respiration-impaired cells.	cell differentiation toward proinflammatory subsets and exacerbates the in vivo inflammatory response. 3. Restoration of NAD+ levels improves lysosome function and corrects the inflammatory defects in Tfam deficient T-cells.
25-Brahimi-Hornet al, 2015	Human and animal experimental study	Ten patients who underwent surgery for lung adenocarcinoma were selected. Protein and microRNA were extracted from the same tissue sample using an All Prep DNA/RNA/protein kit.	1. Cleavage of voltage-dependent anion channel 1(VDAC1) is regulated by TP53 2. TP53 regulation of VDAC1 cleavage occurs through mitochondrial Mieap and is dependent on the endolysosomal pH. 3. Truncation of VDAC1is dependent on BNIP3 and mitochondrial fusion but not on the mitochondrial membrane potential. 4. Mitochondria make contact with endolysosomal compartments with hypoxia 5. VDAC1is C-terminally truncated at asparagine 214 by endolysosomal asparagine endopeptidase. 6. Truncated VDAC1is present in tumor tissue from patients with wild-type TP53 lung adenocarcinomas and enlarged mt made contact with endolysosomes	1. truncation was dependent of mitophagy 2. Local microfusion between mt and endolysosomes in hypoxic cells in culture and in patients' tumor tissues. 3. Hypoxic cell metabolism and cell survival through mitochondrial-endolysosomal microfusion regulated by hypoxia-inducible factor 1and TP53.
16-Basso et al,	Human and	Human fibroblasts from skin biopsy from PD	1. Parkin regulates ER-mitochondria	1. Significant increase in ER-

2018	animal experimental study	patient obtained (n=50000 cells). Mitofusin 2 (Mfn2) knockout (KO) mouse embryonic fibroblasts provided. To assess post-translational modification e.g. a parkin dependent ubiquitination plays an indispensable role in the formation of ER-mitochondria contacts sites via Mfn2. To demonstrate that in vivo manipulation of ER-mitochondria tethering by expressing an ER-mitochondria synthetic linker is sufficient to rescue the locomotor deficits associated to an in vivo drosophila model of PD. To investigate degree of tethering between ER and mitochondria upon parkin downregulation in a condition dMfn ubiquitination is impaired. Then performed electron microscopy analysis on control and parkin downregulating cells and measured the average distance between mitochondria and the juxtaposing ER.	contacts 2. CMT type 2A disease-associated MFN mutants are not ubiquitinated and are incompetent in promoting ER-mitochondria interaction. 3. Ubiquitination of lysine 416 in the HR1 Mfn2 domain control physical and functional ER-mitochondria interaction. 4. ER-mitochondria physical and functional interaction is impaired in parkin mutant fibroblasts. 5. Expression of ER-mitochondria synthetic tether rescues the locomotor defect of a drosophila model of parkinson's disease.	mitochondria distance (MERCs width) in parkin deficient S2R+ cells and an overall decrease in the average number of ER-mitochondria contacts per mitochondria compared to control cells. 2. Manipulation of ER-mitochondria tethering by expressing an ER-mitochondria synthetic linker is sufficient to rescue the locomotor deficit associated to an in vivo Drosophila model of PD.

ATF6, activating transcription factor 6; CHOP, CCAAT/enhancer binding homologous protein; EM, electron microscopy; ER, endoplasmic reticulum; FSGS, focal segmental glomerulosclerosis; IF, immunofluorescence; LDL, low density lipoprotein; MAMs, mitochondria-associated membranes; MERCs, mitochondrial ER contact sites; MPs, microparticles; NO, nitric oxide; p-eIF2α; p-eukaryotic translation initiation factor 2alpha; PRC, PGC-1 related coactivator; ROS, reactive oxygen species; RT-PCR, real time-polymerase chain reaction.

Appendix 4. Investigated variables in mitochondria-nucleus crosstalk in renal disease.

Reference	**ROS levels**	**Caspase activity**			**RC cytochrome c release**	**Apop**	**Urinary F2-isoprostan levels**	**MMP**	**pod**	**Neph**	**Malondialdehyde levels**	**ATP levels**	**Mt morphology**	**Mt DNA copy number**
		3	8	9										
Yuan et al, 2012	↑	70 %	0 %	35 %	100 nmol/l	65%	↑	↓	↓25 %	↓35 %	↑	↓	Disorganized & fragmented cristae, swollen mitochondria	↓

Apop, apoptosis; ATP, adenosine triphosphate; Mt morphology, mitochondrial morphology; Mt DNA copy number, mitochondrial deoxyribonucleic acid; MMP, mitochondrial membrane potential; nmol/l, nanomole per liter; Neph, nephrin; Pod, podocin; RC, respiratory chain; ROS, reactive oxygen species.

Appendix 5a. Existing data of mitochondrial-nucleus crosstalk in metabolic disease.

Reference	**NO in XTC.UC1 cell lines**				**SOD2 induction with SNAP treatment in XTC.UC1**				**NRF1 , ND5, PRC induction with SNAP treatment in XTC.UC1**				**NRF1 , ND5, PRC induction with SNAP treatment in BCPAP**			
	T0	T48	T72	T96	T0	T48	T72	T96	T0	T48	T72	T96	T0	T48	T72	T96
Raharijaona, 2009	↑4.2					+				+		+ ND5				-

B-CPAP, human papillary thyroid cancer cells; ND5, nicotinamide-adenine dinucleotide **(**NADH) dehydrogenase, subunit 5 (complex I); NO, nitric oxide; NRF-1, nuclear respiratory factor-1; PRC, Peroxisome proliferator-activated receptor-ϒ coactivator1a (PGC-1) related coactivator; SOD2, superoxide dismutase -2; SNAP, S-nitroso-N-acetyl-D, L-Penicillamine; XTC.UC1, human hurtle cell carcinoma line.

Appendix 5b2. Nitric oxide concentration, SOD2, NRF1, ND5, PRC induction with SNAP treatment in two cell lines.

Ref	**NO in XTC.UC1 cell lines**				**SOD2 induction with SNAP treatment in XTC.UC1**				**NRF1 , ND5, PRC induction with SNAP treatment in XTC.UC1**				**NRF1 , ND5, PRC induction with SNAP treatment in BCPAP**			
	T0	T48	T72	T96	T0	T48	T72	T96	T0	T48	T72	T96	T0	T48	T72	T96
Raharijaona et al, 2009	↑4.2					+		+		+		+ ND5				-

B-CPAP, human papillary thyroid cancer cells; ND5, nicotinamide-adenine dinucleotide (NADH) dehydrogenase, subunit 5 (complex I); NRF-1, nuclear respiratory factor-1; PRC, Peroxisome proliferator-activated receptor-ϒ coactivator1a (PGC-1) related coactivator; SOD2, superoxide dismutase -2; SNAP, S-nitroso-N-acetyl-D,L-Penicillamine; XTC.UC1, human hurtle cell carcinoma line. ND5, nicotinamide-adenine dinucleotide **(**NADH) dehydrogenase, subunit 5 (complex I).

Appendix 5b3. PRC mRNA expression level with different treatments.

Ref	**PRC mRNA expression level with 20% serum treatment**				**PRC mRNA expression level with SNAP treatment**				**PRC mRNA expression level with PRC SiRNA treatment**					**PRC mRNA expression level with PRC SiRNA + SNAP treatment**				
	T0	T48	T72	T96	T0	T48	T72	T96	T0	T6	T48	T72	T96	T0	T6	T48	T72	T96
Raharijaona et al, 2009						↑ 2.2		+		3.5 ± 0.4	↓ (70%)		+ ND5		5.6 ± 0.6	↑ 1.4		-

mRNA, messenger ribonucleic acid; ND5, ND5, nicotinamide-adenine dinucleotide (NADH) dehydrogenase, subunit 5 (complex I); PRC, Peroxisome proliferator-activated receptor-ϒ coactivator1a (PGC-1) related coactivator; SiRNA, small interfering ribonucleic acids; SNAP, S-nitroso-N-acetyl-D,L-Penicillamine.

Appendix 5b4. PRC SiRNA gene expression with different treatments in control group.

Ref	**PRC expression level, NRF, TFAM, COX5B in PKG inhibitor XTC.UC1 cell lines**	**PRC SiRNA gene expression with SiRNA treatment**					**PRC SiRNA gene expression with SiRNA treatment in control group**				**PRC SiRNA gene expression and without control group during 20% serum induction**
		T0	T12	T24	T48	T96	T0	T12	T24	T48	8 cluster of genes during 48 hr. Clusters of 2,8 in mt functions were enriched and 2, 5 were enriched in cell functions. A pearson's correlation of 90% microarray analysis and real-time RT-PCR
Raharijaona et al, 2009	↓2.2 ± 0.1 to 0.8 ± 0.1(P≤0.05)	↓ 42%	↓ 42%	70%	74%				>80%		

PRC, Peroxisome proliferator-activated receptor-ϒ coactivator1a (PGC-1) related coactivator; SiRNA, small interfering ribonucleic acid or short interfering RNA or silencing RNA.

Appendix 5c. Mitochondrial RC functions in mitochondrial-nucleus crosstalk in metabolic disease.

Ref	**Complex I with PRC inhibition**			**Complex II with PRC inhibition**			**Complex III with PRC inhibition**			**Complex IV with PRC inhibition**			**Complex V with PRC inhibition**			**SOD2**		
Raharijaona et al, 2009	T 12	T24	T48	T12	T24	T48	T12	T24	T48	T12	T24	T48	T12	T24	T48	T12	T24	T48
RC concentration		↓	↓			↓		↓			↑	↓						
Expression of selected genes coding complex IV subunits											↓COII							
Expression of nuclear genes coding complex IV subunits (↑COX15,↓COX5B)										↑	COX15 (↑1.8)	(↓8%)						↔
OXPHOS			↓			↓			↔			↓			↔			

OXPHOS, oxidative phosphorylation; PGC, Peroxisome proliferator-activated receptor-ϒ coactivator1a (PGC-1) related coactivator ; RC, respiratory chain; SOD2, superoxide dismutase -2.

Appendix 6a1. Raw data existing in mitochondrial-endoplasmic reticulum crosstalk in metabolic syndrome.

Ref/Safiedeen et al, 2017	**PERK**	**IRE1α**	**ATF6**	**eIF2α**	**mRNA**	**Protein CHOP**	**XBP1**	**NO**	**EDR**	**eNOS**
Substance concentration	↑		↑	↑	↑	↑	↑	↓	↓	
TUDCA	↓		↓	↓	↓	↓	↓	↑	↑	
Tunicamycin	↑	↑	↑					↓	↓	
Treatment of ECs by MPs				↑ for 24hr						
Neutral SMase silensing with SiRNA after 24 hr Tx with MPs				↓						
Neutral SMase inhibitor GW4869 or SiRNA by phospho-Ser eNOS/phosphoThr eNOS ratio										↑

ATF6, activating transcription factor 6; CHOP, C/EBP homologous protein; XBP1, x-box binding protein 1; ECs, endothelial cells; EDR, endothelium-dependent relaxation in response to acetylcholine; eIF2a, eukaryotic translation initiation factor 2 alpha; eNOS, endothelial nitric oxide synthase; IRE1a, inositol -requiring enzyme-1 alpha; MP, microparticles; mRNA, messenger ribonucleic acid; NO, nitric oxide; PERK, pancreatic endoplasmic reticulum kinase; SMase, sphigomyelinase; SiRNA, small interfering ribonucleic acid or short interfering RNA or silencing RNA.

Appendix 6a2. ROS levels after microparticle and TUDCA treatments. ROS, reactive oxygen species; TUDCA, tauroursodeoxycholic acid.

Ref/ Safiedeen et al, 2017	**Cytosolic ROS**			**MitoSox fluorescent**			**Mitochondrial ROS**	**MP induced P47Phox**		
Time	T2	T4	T24	T2	T4	T24			T4	T24
MP treatment	↑	↑	-	-	-	↑				
TUDCA	↓	↓	↓							
SMase Silencing									↓	

ROS, reactive oxygen species; TUDCA, tauroursodeoxycholic acid; SMase, sphingomyelinase.

Appendix 6b. Existing data of mitochondrial-endoplasmic reticulum crosstalk in metabolic syndrome.

Ref/ Safiedeen et al, 2017	**PERK**	**IRE1α**	**ATF6**	**eIF2α**	**mRNA**	**Protein CHOP**	**XBP1**	**NO**	**EDR**	**eNOS**	**Cytosolic ROS**			**MitoSox fluorescent**			**Mt ROS**	**MP induced P47Phox**		
											T2	**T4**	**T24**	**T2**	**T4**	**T24**		**T2**	**T4**	**T24**
MP treatment	↑		↑	↑	↑	↑	↑	↓	↓		↑	↑	-	-	-	↑				
TUDCA	↓		↓	↓	↓	↓	↓	↑	↑		↓	↓	↓							
Tunicamycin	↑	↑	↑					↓	↓											
Treatment of ECs by MP				↑ for 24hr																
Neutral SMase with SiRNA after 24 hr Tx with MP				↓																
Neutral SMase inhibitor GW4869 or SiRNA by phospho-Ser eNOS/phospho Thr eNOS ratio										↑										
SMase silencing																			↓	

ATF6, activating transcription factor 6; CHOP, C/EBP homologous protein; ECs, endothelial cells; EDR, endothelium-dependent relaxation; eIF2α,eukaryotic translation initiation factor 2α; eNOS, endothelial nitric oxide synthase; IRE-1a, inositol requiring transmembrane kinase/endonuclease-1a; MPs, microparticles ; mRNA, messenger ribonucleic acid; NO, nitric oxide; PERK, protein-kinase- RNA-like-ER kinase; mt ROS, mitochondrial reactive oxygen species; SMase, sphingomyelinase; TUDCA, tauroursodeoxycholic acid; XBP1, X-box binding

Appendix 7a. Data of original study of mitochondrial-endoplasmic reticulum crosstalk in renal disease.

Ref	Mt content	Mt morphometry	Podocyte cell		tubules	Anti-LC3	Anti-P62	p-eIF2α	GADD34	CHOP	BiP	CREB/2ATF4	OAT1	DRP-1	SDH	ATPA5	MnSOD	MPV17L	Actin	p-P42/44	p-JNK	p-P38	UAlb	pAlb	BUN/Cr	TG/Chol	LPF/FFA
			Mt number	Mt diameter	diameter																						
Kawakami, 2015					↑at 2 months,↓length, patchy loss of cristae in mt-focal dilated cisternae in ER			↑	↔				Down-regulated	Down-regulated at 2 months of age			Down-regulated later			↔	↔	↑	↓	↓		↑	

BiP, binding immunoglobulin protein; BUN/Cr, blood urea nitrogen/creatinin; CHOP, C/EBP homologous protein; CREB/2ATF4, (cAMP) response element binding protein/2 activating transcription factor 4; DRP1, dynamin-related protein-1; LC3, light-chain microtubule-associated protein-3; MnSOD, manganese superoxide dismutase; OAT1, organic anion transporter 1; p-eIF2a, p-eukaryotic translation initiation factor 2 alpha; p-JNK, p-Jun-N-terminal kinase; TG/Chol, triglyceride/cholesterol.

Appendix 7b. Existing data of mitochondrial-endoplasmic reticulum crosstalk in FSGS.

Ref	**PERK**	**BiP/Grp78**	**ATF4/CREB-2**	**C/EBP**	**TRB3**	**MAPK**	**Glomerular cells & tubular ROS**	**Nonmitochondrial ROS**	**α-cyclophilin-D**	**Electron transport enzymes**
Kawakami, 2015	↑	Up-regulated	Up-regulated	Up-regulated	Up-regulated	↑	↑	↑	Down-regulated	Up-regulated or ↔

ATF4/CREB-2, (cAMP) response element binding protein/2 activating transcription factor 4; BiP/Grp, binding immunoglobulin protein/glucose-related protein78; C/EBP, CCAAT/enhancer binding protein ; MAPK, mitogen-activated protein kinase; PERK, pancreatic endoplasmic reticulum kinase; ROS, reactive oxygen species; TRIB3, tribbles-related protein 3.

Appendix 8. Existing data about mitochondrial-endoplasmic reticulum communication (crosstalk) in vascular pathophysiology.

Ref/ Pacher,2008		**AII-induced [Ca2+]c**	**[Ca2+]c**	**Total Ca2+ storage in ER & nonacidic Ca2+ pools**	**[Ca2+]m**	**[Ca2+]c + [C2+]m in PGASMC cells by AII & ET**		**[Ca2+]m in response to AII**	**$CaCL_2$**		**IP3R1-induced Ca^{2+}**	**IP3R3-induced Ca^{2+}**
						AII	**ET**		**$[Ca^{2+}]c$**	**$[Ca^{2+}]m$**		
TGF-β pretreated PGASMC with fura2		Absent or ↑↑ delayed or attenuated	↑(delayed)									
Naïve cells		↑	↑(100%)									
Gradual decay of naïve cells		↑										
Supramaximal dose of AII (100nM)			↑									
Combined naïve PGASMC plus TGF-β pretreated cells	**Naïve PGSMC**	↑100% to 2nM AII	↑(93.3%)									
	TGF-β pretreated cells	↑92.8% to 100 nM AII	↑ 51%									
TGF-β pretreatment			↑in 41 of 42 control									

by ET(n=41)			↑ in 16						
TGF-β pretreatment by thapsigargin (Tg) 2 μM			↑ in 100% of both control plus pretreated PGASMC cells						
TGF-β pretreatment by Ionomycin			↑in control plus pretreated TGF	↔					
TGF-β pretreatment measured by rhod$_2$							↑		
IP3-induced in naïve cells			↑(rapid)		↑(slow)				
IP3-induced in permeabilized PGASMC					↑				
Naïve permeabilized PGASMCs								42.5±8%	↑
Naïve permeabilized PGASMCs (30μM CaCl$_2$)									28.6±3.1% /s

TGF-β permeabilized PGASMCs (30μM $CaCl_2$)									30.6±6.7%/s		
TGF-β permeabilized PGASMCs										40%↓of mRNA	↓

AII, angiotensin II; ET, endothelin; IP3R, inositol 1,4,5-triphosphate receptors; mRNA, messenger ribonucleic acid; PGASMCs, preglomerular afferent smooth muscle cells; TGF-ß, transforming growth factor-ß.

Appendix 9. Existing data about Mitochondrial-endoplasmic reticulum crosstalk in questionable cancer and aging.

Ref/ Hacki, 2000	**Low dose CHX**	**CHX+BFA-induced apoptosis**		**Tunicamycin-induced apoptosis**	**BFA**	**Staurosporine**
		6 h	**24 h**			
Bcl-2			Massive ER dilation			
Caspase-3 activation						
Caspase-8 activation						
COX for mitochondria						
Calnexin for microsome /ER						
Lamp-1 for						

lysosome/peroxisome						
Lamin B1 for nuclei						
Bcl-2/cb5)						
Induction of apoptosis	NA				+	
Vacuolarization of the ER/Golgi network		+				
Nuclear condensation/DNA fragmentation		-	> 70%			
Cytochrome c oxidase						
P17& DEVDase activity			detected			

Bcl2, B-cell lymphoma-2; BFA, brefeldin A; CHX, cycloheximide; COX, cytochrome c oxidase; CHX, cycloheximide; DNA, deoxyribonucleic acid; ER, endoplasmic reticulum.

Appendix 10a. Existing data of mitochondria-endoplasmic reticulum crosstalk in myocardial ischemic-reperfusion injury.

Ref/ Gomez, 2016	**IP3R**	**Grp75**	**VDAC**	**CypD**	**RyR2**	**ANT**	**IP3R-mediated Ca2+ transfer from SR/ER to mt**	**Caffeine-induced Ca2+ transfer from SR/ER to mt**	**Mt Ca2+ amplitude**	**Ca2+ transfer into mt**	**Ca2+ transfer into mt**
GSK3β inhibitors	↓	↓	↓	↓					↓the amplitude ofCa2+ into mt averaging 0.36±0.01 vs. 1±0.1-fold with SiC (P<0.05)		Not modified
SB216763	interaction	↓	↓	↓					Did not modulate induced by caffeine (P=NS),↓Ca2+ transfer under histamine stimulation in H9c2 cells		
GSK3β inhibition by SB21							0.6±0.06 vs. 1±0.07 fold vs. control (p <0.05)	Did not modify (P=NS)			
Overexpression of GSK3β in H9c2 cells										↑ compared with its control averaging 1.52±0.07 vs. 1±0.04 in the pcDNA	

										(P<0.05)	

5-triphosphate receptors; mt, mitochondria; RyR2, ryanodine receptors; SR/ER, sarcoplasmic reticulum/endoplasmic reticulum; VDAC, voltage dependent anion channels.

Appendix 10b. Existing data of mitochondrial-endoplasmic reticulum crosstalk.

Ref/ Gomez**, 2016**	**Reticular (ER) Ca efflux**	**Cytosolic**	**IP3-mediated Ca2+ transfer from SR/ER to mitochondria**	**Mt Ca2+ homeostasis after HR**	**Cell death**
HR					4h hypoxia followed by 2h reoxygenation averaging 50.4±2.9% vs. 7.4±0.5% (P<0.05)
SB21at reoxygenation	↑ averaging 2.19±0.1 vs. 1.44±0.11% in HR group	0.3±0.02 vs. 0.38±0.01 in HR group (P<0.05)			↓by half-averaging 25.9±1.8% vs. 50.4±2.9% in HR group
Thapsigargin	↑by 2.5-fold higher in the HR+SB21 group was higher in comparison with the HR group				
GSK3β inhibition at R group	↑ steady-state [Ca2+] in ER lumen during HR	Abolished averaging 1.05±0.02 vs. 1.1±0.03 in the HR group (P<0.05)			

GSK3β, glycogen synthase kinase-3β; HR, hypoxia reoxygenation; SR/ER, sarco/endoplasmic reticulum.

Appendix 10c. Existing data of mitochondrial-endoplasmic reticulum crosstalk in myocardial ischemic-reperfusion injury.

Ref/ Gomez, 2016	**Cell death**	**Phosphorylation of GSK3β at tyrosine 216**	**GSK3β with IP3R**	**Infarct size after prolonged IR**
HR	65.3±3.2% vs. 13.6±0.7%	1.82±0.08 vs.1±0.05-fold in basal group (P<0.05)	Doubled;2.23±0.23 vs. 1±0.19-fold in basal group	
SB21	↓ (50%)	1.18±0.1 vs. 1.82±0.08 in HR group	↓interaction at reoxygenation averaging 0.74±0.1 vs. 2.23±0.23(P<0.05)	
IR+SB21		↓	↓	↓averaging 31±0.6% vs. 44.6±1.7%

GSK3ß, glycogen synthase kinase-3β; HR, hypoxia reoxygenation; IR, ischemia reperfusion injury.

Appendix 11a. Existing data of mitochondrial-endoplasmic reticulum crosstalk in cardiovascular disease.

Ref/ Diwan, 2009	**Caffeine-induced cytosolic calcium release (SR calcium content)**	**Immunoreactive SERCA levels**	**Phospholamban (PLN)**	**Ryanodine receptor(RYR)**	**Na/Ca2+ exchanger (NCE)**	**Calsequestrin (CSQN)**	**Inward calcium current (Ica2+)**	**NCE current**	**Calcium cycling during phasic electrical stimulation**
Overexpressed NIX	25% ± 5% greater than controls								
Genetically ablated NIX	28% ± 4% lower than controls	↔	↔	↔	↔	↔			
Nix-KO mice							The same	The same	↓
WT heart							The same	The same	
Nix-KO mice combined PLN ablation									restore
PLN-KO mice									

DKO, double knockout mice; KO, knockout; SERCA, SR calcium ATPase.

Appendix 11b. Existing data of mitochondrial-endoplasmic reticulum crosstalk.

Ref/ Diwan, 2009	**Aggressive apoptotic cardiomyopathy (CMP)**	**Periportal mortality**	**Left ventricular dysfunction (LVD)**	**Cardiac performance**	**Salutary effects of Nix ablation on ventricular dilation & contractile performance**	**Peripartum lethality**	**Cardiomyocyte necrosis (form of dystrophic calcification)**
Gq-Nix-KO	↓	↓	prevented	Improved		Protective (1st postpartum week)	Not appeared
Gq-Nix/PLN-DKO							
Gq mice	50% died within 2 wks						In 2/3 appeared

DKO, double knockout ; PLN, Phospholamban.

Appendix 11c. Existing data of mitochondrial-endoplasmic reticulum crosstalk.

Ref/ Diwan, 2009	**ER/SR Ca2+-mt signalling**	**Ca-mediated programmed cell death**	**ER/SR calcium content**	**Lethality of mitochondria-associated NIX**	**Lethality of SR-associated NIX**	**Cytosolic proteins**	**Mt proteins**	**ER-rich proteins**	**ER proteins**	**Cell viability (death)**	**TUNEL positivity**	**Caspase activation**	**MTP activation**	**apoptosis**	**Mt mm potential (PTP opening)**
Nix-ActA cofractionated with COXIV(mt marker)										+ (2 fold or more)	+	+		+	didnot
NIX-cb5 cofractionated with calnexin(marker for ER)										+	+	+		-	Loss of mm potential
NIX-WT (NIX-wild type)										+	+	+		+	Loss of mm potential

COXIV, cytochrome c oxidase IV; ER/SR, endoplasmic reticulum/sarcoplasmic reticulum.

Appendix 12a. Existing data about Mitochondria-endoplasmic reticulum in Alzheimer's disease.

Ref/ Garofalo, 2016	**BECN1**	**CANX**	**TOMM20**	**VDAC1,2**	**PIK3C3**	**P4HB**	**AMBRA1+WIPI1**	**ATG16l+WIPI2**	**GD3**
MAMs fraction		+	-	+		-	↑	-	+
Pure mt fraction		**+**	VDAC1						
PtdIns3P									**+**

AMBRA1, autophagy/Beclin 1 regulator 1; ATG 14, autophagy related 14; BECN1,beclin 1, autophagy related; CANX, calnexin; MAMs, mitochondria-associated membranes; P4HB, prolyl 4-hydroxylase subunit β; PIK3C3, phosphatidylinositol 3-kinase catalytic subunit type 3; PtdIns3P, phosphatidylinositol 3-phosphate; TOMM20, translocase of outer mitochondrial membrane 20 homolog; VDAC1,2, voltage dependent anion channel 1; WIPI 1, WD repeat domain, phosphoinositide interacting 1.

Appendix 12b1. Existing data of mitochondrial-endoplasmic reticulum in Alzheimer's disease.

REF/ Garofalo, 2016	**WIPI1**	**UVRAG**	**Ganglioside GD3**	**AMBRA1**	**AMBRA2**	**ANTI-LC3**	**LC3-II**	**P-ULK1**	**ATG14**	**BECN1**	**GREEN FLUORESCENCE**	**FRACTION 4&6 (Raft fraction)**	**Fraction 6&7 corresponding to raft-like microdomains**	**PIK3C3/VPS34**
CALNEXIN	+	+	weak association after HBSS	+					+	+		↑	↑	+
AUTOPHAGIC FLUX	+			+	+						↑($P < 0.01$)			
Western blot analysis							+	↓						
VDAC1												↑		
MAMs			+											
SEL1L			+											

ATG14, autophagy-related 14; BECN1, Beclin 1, autophagy related ; GD3, aNeu5Ac(2-8)aNeu5Ac(2-3)bDGalp (1-4)bDGlcp(1-1) ceramide; MAMs, mitochondrial associated membranes; p-ULK1, phosphorylated-unc-51 like autophagy activating ; PIK3C3, phosphatidylinositol 3-kinase catalytic subunit type 3; VDAC1, voltage dependent anion channel.

Appendix 12b2a. Existing data about mitochondria-endoplasmic reticulum crosstalk in Alzheimer's disease.

Ref/ Garofalo, 2016	**ST8S1A1 siRNA**	**MFN2 siRNA**
CANX-AMBRA1	no increase	↓
CANX-BECN1	Lower than in scrambled siRNA-transfected cells after autophagic triggering by HBSS	
MFN2		↓
MFN2 knockdown		↓

MFN2, mitofusin 2; ST8SIA1/GD3 synthase, ST8 α-N-acetyl-neuraminide α-2, 8-sialyltransferase 1; MFN2 siRNA, mitofusin 2 small interfering ribonucleic acid.

Appendix 12b2b. Existing data of mitochondrial-endoplasmic reticulum in Alzheimer's disease.

REF/ Garofalo**, 2016**	**SEL1L IN UNTREATED CELLS & SEL1L in HBSS-treated cells**	**SEL1L & GD3 association**	**WIPI after treatment with HBSS**	**PIK3C3 after treatment with HBSS**	**BECN1 after treatment with HBSS**	**ATG14 after treatment with HBSS**	**UVRAG after treatment with HBSS**	**WIPI 1**	**IMMUNOPERCIPITATES**	**WIPI 2**	**AMBRA1+WIPI1**
GD3	weakly association ($p<0.02$)	NOT INFLUENCED BY AUTOPHAGIC INDUCTION									+
CALNEXIN			+ association	+	+	+	+				
ATG16L1										+	
									NO BANDS corresponding to AMBRA1, WIPI1,ATG16L1 or WIPI2 were detected		

For abbreviated words be referred to related reference.

Appendix 12b3. Existing data of mitochondrial-endoplasmic reticulum in Alzheimer's disease.

REF/ Garofalo**, 2016**	**AMBRA1+WIPI1**	**AMBRA1**	**AMBRA1+GD3**	**WIPI1**	**CALNEXIN**
FGD3		↑Association		↑Association	↑Association
CALNEXIN		↑Association after autophagic induction			
WIPI1		PRESENT Association			
ATG16L1+WIPI2			undetectable in AMBRA1 immunoprecipitates either from untreated or HBSS-treated cells		
WIPI2		NOT ASSOCIATION			

For abbreviated words be referred to related reference.

Appendix 13. Existing data about mitochondria-endoplasmic reticulum in cardiomyocyte neurons.

Ref/ Naon, 2016	**Mfn1**	**Mfn2**	**Combined double mfn1, mfn2**	**Mt surface-ER juxtaposition**	**ERMICC**	**ddGFP+**	**dsRED+**	**ddGFP fluorescence**	**ER-mt tethering**	**MCU**	**MICU 1**	**MICU 2**	**IO tethering**
MEF1			~ 20% ↑in the distance between two organelles										
MEF2				↓10-15%									
Mfn2 ablation					~ > 70%	↑ER-mt distance		↓contact coefficient of ERMICC	↓	Not affected	Not affected	Not affected	
Acute Mfn2 deletion													↓

ERMIC,endoplasmic reticulum-mitochondria contact coefficient; MEF, mouse embryonic fibroblasts; Mfn2, mitofusin 2; MCU, mitochondrial Ca2+ uniporter.

Appendix 14. Raw data of parkin regulation in ER-mitochondria contacts in the present research.

Ref/ Basso et al 2018	**Parkin SiRNA**	**Scamble SiRNA (Ctrl RNAi)**	**Monoubiquitinated forms of dMFN (PINK1/Parkin dependent)**	**Multiubiquitinated Forms of dMFN (PINK1/Parkin dependent)**	**Unmodified dMfn**	**Steady state levels of dMfn (absence of PINK1 or Parkin)**	**Volume rendered 3d reconstruction of z-axis stacks of confocal images of fluorescent tagged mt and ER (Manders' coefficient)**	**Electron microscopy**	**FRET ratio (ΔR/R) by FEMP probe**	**Anti-Mfn2 Ab by WB**	**Coimmunopercipitation analysis**	**Climbing assay**
S2R+ Drosophila cells			Upper molecular weight bands by western blotting	Upper band by western blotting	Smaller molecular weight bands	increased	Mutant $dMfn^{k416R}$					
Parkin deficient S2R+ fly cells								↑↑in ER-mt distance (MERCs width), overall↓ in average number of ER-mt contact per mt				
MEFs transfected with parkin siRNA							Degree of tethering (n=8, 12-15 cells per experiment (clear ↓ in ER-mt contacts), p-value=0.0005					
MEFs transfected with Scamble siRNA (Control RNAi)												
Parkin MEFs transfected with pcDNA 3.1 (Ctrl)												
Parkin MEFs transfected with pcDNA 3.1-Cre							↓ ER-mt tethering		N=4, p-value=0.0485			

(CRE)												
Mfn2										Single band	Partially decreased upon parkin deletion	
Mfn2 ubiquitination in Mfn2 KO MEFs							Wild type CMT2A(R94Q) or MFN2 p251A and MFN2R280H			Single band of Mfn2	Clear reduction of Mfn2-Ub in all CMT type 2A disease-asssociated Mfn2 mutants, reduction in ER-mitochondria contacts with Mfn251A or Mfn2R280A	
Mfn2 ubiquitination in Mfn2 KO MEF indicated plasmids+HA-Ub							Yellow spots: area of organelle tethering (scale bar:20 μm) N=4,15 cells per experiment, p-value <0.0001) Mfn2 vs. Mfn2p251A (p value=0.0003) Mfn2 vs Mfn2R280H(p value=0.0001) Inputs and IP eluate:2-100% of the protein lysates (n=4, p value=0.0029) Peak [Ca2+] mit in 9 independent experiments (p-value=0.0186)			Cells were lysed subjected to immunoprecipitation, WB by α-HA antibody and α-Mfn2:inputs represents 10% of the protein lysates, IP shows 100% of protein lysates		
Mfn2 KO MEFs with Myc-tagged form of wild type Mfn2 and Mfn2^{K416R} and HA-Ub										Single band of Mfn	↓ ubiquitinated forms in non-ubiquitinitable mutant Mfn2^{K416R} Mfn2 KO cells expressing Mfn2^{k416R}: ↓mt Ca^{2+} uptake	
TM in wild type												P value< 0.0001
TM in PINK1 mutant[B9]												P value< 0.0001

CMT2A, Charcot-Marie-Tooth neuropathy type 2A; ER, endoplasmic reticulum; FEMP, FRET-based indicator of ER-mitochondria proximity; MEFs, mouce embryonic fibroblasts; Mfn, mitofusin; pcDNA, polyclonal deoxynucleic acid.

Appendix 15. Raw data of mitochondria to ER crosstalk in the present research.

Ref/ Abuaita et al, 2018	**mROS**	**MitoPY1 fluorescence intensity**	**Difference in MFI of MitoPY1 by flow cytometry**	**MRSA killing in macrophages**	**mH2O2 spatial localization**	**IF analysis by HRCM**	**Tom20 +MDVs**	**MitoPY1 in phagosomes**	**mH2O2 levels**	**Bactericidal capacity**	**↑ caspase-3/7 activation or alter activation of AMPK or SOCS**	**TEM**	**Immunogold labelling using anti-Tom20 antibody**	**Spacial distribution of SOD2 by confocal IF microscopy**	**Anti-SOD2 Ab or Anti-LAMP Ab**	**SOD2 vesicle accumulation**	**mH2O2 induction upon MRSA infection**	**Confocal IF microscopy**	**Citate synthase and mt IMP of complex I**
Exogenous H2O2		increased																	
RAW264.7 cells transfected mcherry-Mito-7&loaded with MitoPY1																			
MRSA infection		Increased at 4 hr post infection																	
IRE-α deficient RAW264.7 macrophages by CRISPR/Cas 9				Significant decrease in macrophage killing, suppressed ability of MRSA-infected macrophages to induce mH2O2															
Wild-type control cells				Not decreased															

NOX-2 deficient macrophages																			
NecroX-5		Lower MitoPY1 fluorescence and decreased capacity to kill MRSA																	
Live cells with viable MRSA, killing MRSA, latex beads					mH2O2 increased with lived or fixed MRSA but not with beads, ↑mH2O2 levels in MRSA-containing phagosomes														
Time-lapse imaging of infected macrophages preloaded with MitoPY1					By 10 min pi, mitoPY1 signal in mitochondrial work had increased														

WT&TLR2/4/9-deficient bone marrow-derived macrophages during MRSA infection		↑overall mH2O2																
TLR2/4/9-deficient macrophages				Failed to kill MRSA&↓ MitiPY1 accumulation in MRSA-containing phagosomes vs. Wild type macrophages														
MDVs induced by MRSA infection						Infection stimulated ↑small particles positive for mOMP Tom20 vs. bead-containing macrophages												
MRSA-Infected park2$^{-/-}$ BMDM				Less capable in killing MRSA			Lower numbers vs. wild type											
Infected parkin deficient macrophages vs. wild type macrophages								Minimal accumulation in	↑↑		Not stimulated							

Pink1-deficient BMDM vs. wild type										↓									
DRP1 knock down macrophages				Killed MRSA															
WT or parkin-deficient macrophages with NEMO inhibitor				Not affect MRSA killing															
Quantified MDV induction in infected macrophages treated with Bafilomycin (BafA1)				↑			Increased in MRSA infection	↑											
MRSA-infected macrophages with or without bafilomycinA1												MRSA-containing phagosomes containing double membrane bound vesicles	Observation of Tom20+ particles in close proximity to the bacterial surface within the phagosome space							
Untreated macrophages														SOD2 localized to mt network					

Infected macrophages or beads															Large SOD2+mt network objects juxtaposed with phagosomes	Bacteria-containing phagosome: more SOD2 MDVs			
SOD2- KD RAW264.7macrophages				impaired													SOD2 KD cells fail to induce mH2O2 but higher level of mitochondrial superoxide production, not caspase 3/7 activation or host cell death		
WT BM derived infected macrophages																		Exhibited SOD2+/TOM20+ MDVs and relatively few SOD2+/TOM20+vesicl*es* observed	

SOD2+/Tom 20+MDVs required parkin/pink1																SOD2 MDVs controlled by mt stress machinery			
SOD2+/Tom 20+ MDVs																			Generation of all MDVs: parkin dependent but with Tom20+: SOD2 vesicles distinct from CS^+ and complex I^+ vesicles

BM, bone marrow; ER, endoplasmic reticulum; IF, immunofluorescence analysis; HRCM, high resolution confocal microscopy; MDVs, mitochondrial derived vesicles; MFI, mean fluorescence intensity; mOMP, mitochondrial outer membrane protein; mROS, mitochondrial reactive oxygen species; MRSA, methicillin-resistant staphylococcus aureus; TEM, transmission electron microscopy; WT, wild type.

Appendix 16. Raw data of sarcoplasmic reticulum/endoplasmic reticulum to mitochondria crosstalk in the present research.

Fernandez-Sanz et al, 2014	**Ventricular wall**	**LVEDV**	**EF**	**Lysosomal vesicles**	**Lipofuscin Pigment**	**β –galactosidase activity**	**Age-dependent differences in mt pool by mitotracker red staining**	**Citrate synthase activity**	**Total cardiac mitochondrial yield**	**Myocardial ATP to PC ratio**	**O2 consumption at rest and after ADP stimulation**	**RCR (complex I, III)**	**SR Ca2+ transient, rate Ca2+ rise**	**SR Ca2+ content as mx caffeine-induced Ca2+release**	**SR sparks, ↓Ca2+diffusion**	**Mitochondrial Ca^{2+} uptake**	**Net NADPH consumption due to field stimulation**	**Total GSH levels**	**GSSH levels**	**Short-term mitochondrial ROS production**	**Cytosolic ROS levels**	**Proximity ligation assay**	**Expression of main proteins to tether two organelles**	**SR-mt interaction**	**RyR-VDAC immunocolocalization**	**Manders coefficient analysis of SR&mt immunolabelling**	**ATP/PC ratio by NMR spectroscopy, $\Delta\Psi m$**
Aging phenotype	thin	↑	↓	↑	↑	↑	No difference	No difference	No difference																		
Young mice group										↓				similar			Not						Not reduction			>75%	
Old mice group										↓	Largely preserved in subsarcolemmal mt	↓	↓, ↓	similar	↑, ↓	After caffeine induction, SR Ca^{2+} release,	Not but slight ↑in young cells	↓		↑	↑		Not reduction			<60%	preserved

																severely depression in cardiomyocytes										
Dissociation effect of age																						≤40 nm				
Accerelation of electrical pacing in both groups																	Decay in NADPH/NADP^{+} in cardiomyocytes in old group		↑							
Positive amplification fluorescent spots																						↓SR RyR juxtaposed with mt VDAC				
Treatment with																						↓number of amp		Partial disrupti	decreased	

colchicine																						lification clusters		on			

ADP, adenosine diphosphate; ATP, adenosine triphosphate; EF, ejection fraction; LVEDV, left ventricle end-diastolic volume; NADP, nicotinamide-adenine dinucleotide; NADPH, nicotinamide-adenine dinucleotide phosphate; NMR, ; PC, phosphocreatine; RCR, respiratory control rate; ROS, reactive oxygen species; RyR, ryanodine; SR, sarcoplasmic reticulum; VDAC, voltage-dependent anion channel. ↑ mark shows elevated and ↓ declined amount.

Appendix 17. Raw data of interorganelle crosstalk between ER-mt in the present research.

Sala-Vila et al, 2016	**Quantitative mass spectrometry**	**acyl-CoA synthetase long chain 4 (ACSL4/FACL4)**	**Calreticulin**	**Associated with lipid droplet protein 1 (ALDI)**	**ACSL1 and ACSL4**	**TOMM20 (outer membrane)**	**Cytochrome C (intermembrane space)**	**Mitochondrial inner membrane proteins such as cytochrome C oxidase subunit 1(Cox 1/Mtco1)**	**Cis-Golgi protein GM130**	**Transferrin receptor & flotillin in MAM fraction**	**Annexin-6**	**CAV1**	**Transmission electron microscopy**	**Total mitochondrial mass**	**Superresolution microscopy of ER or Mitochondrial network**	**FRET signal by flow cytometry**	**Opera automated microscopy**	**Cholesterol level in MAM**	**Purified MAM**
Henceforth Wild type													More extensive ER-mt contacts (70±11.8%),absolute length: 28.1±3.2 nm	Modestly higher			Differential average distribution of mitochondria	ER: 7.2±0.5 vs. 4.8±1.5 mg cho/mgprotein <0.01 mg chol/	ER: x1.8 Mt: x2.6

																		mg protein	
CAV1-deficient mice													53±13%, 11.5±2.6 nm (p-value <0.05)	-	Apparent aberrancies	Lower FRET signal	Differential average distribution of mitochondria	↑mt: 9.5±1.1 vs. 6.7±1.7 mg chol/ mg protin <0.01	↑ER: x2.8
MAMs					↑↑														
Bulk of ER					-														
MAMs fraction						Not detectable	Not detectable	Not detectable	Not	Absence, ↑									
MAMs											↑	↑							
HMG-CoA reductase inhibitor (lovastatin)																Did not rescue FRET signal in CAV1			

																KO cells			
Differential protein compositions (WT vs.CAV1 KO cells)	Zq≥1.5																		

CAV1, caveolin; ER, endoplasmic reticulum; KO, knock down; HMG-CoA reductase, methyhydroxy glutaryl-Coenzyme A reductase; MAM, mitochondria-associated membrane; mt, mitochondria; WT, wild type.

Appendix 18. Existing data of mitochondrial-peroxisome crosstalk in renal disease and aging-related disorders.

Ref/ Hwang, 2012	**Diabetic WT mice**	**Nondiabetic WT mice**	**Diabetic CKO mice**	**Nondiabetic CKO mice**	**Diabetic WT mice& diabetic CKO mice difference**	**Renal expression**	**Catalase knock-down cells**
Blood glucose							
Mean blood pressure (BP)	↑ since5 wks		Little difference between diabetic CKO mice & diabetic WT mice				
Urinary protein & albumin excretion							
Plasma creatinin levels							
Glomerular volume & FMA	↑upto 10 wks		↑upto 10 wks	↑GV&FMA vs. age-matched nondiabetic WT mice	↑glomerular volume & FMA vs. diabetic WT mice at both 4-10 wks		
Urinary creatinine							
Body weight	up to 10 wks after low dose STZ maintained		up to 10 wks after low dose STZ maintained		No		

Kidney weight	↓in 4-10 wks		↑ in 4-10 wks				
TGF-β1			↑ in 4-10 wks	upregulated			
CTGF			↑in 10 wks	upregulated			
α-SMA				upregulated			
BMP7				downregulated			
E-cadherin mRNA			↓ in 4-10 wks	downregulated			
FN mRNA			in 4-10 wks ↓ (10wk>4wks)	upregulated			
Protein expression			in 4-10 wks ↓ (10wk>4wks)				
GPx1	nonupregulated		upregulated			Lower in diabetic CKO mice than in diabetic WT mice	
Prx1	nonupregulated		upregulated	higher			
Prx5				higher		Lower in diabetic CKO mice than in diabetic WT mice	
SOD1	nonupregulated		upregulated			Lower in diabetic CKO mice than in diabetic WT mice	
SOD2	nonupregulated		upregulated			Lower in diabetic CKO mice than in diabetic WT mice	

Sulfiredoxin-1	nonupregulated		upregulated			Lower in diabetic CKO mice than in diabetic WT mice	
NOX4			↑at 4wks then upto wks				
Urinary LPO			↑at 4wks then upto wks				
Renal nirotyrosine			↑at 4 wks then upto 10 wks				
PEX11-α	↑at 4 wks but at 10 wks		↓at 4-10 wks				
ABCD3	↑ at 4 wks but at 10 wks		↓at 4-10 wks				
Mt SOA levels using MitoSOX							↑
Cytochrome b mRNA level	↑at 4 wks but ↓at 10 wks		↓At 4-10 wks				
CPT-1α			↓At 4-10 wks				
Lipid droplets			↑				
ACO			Upregulated by PhA with or without HG				

ABCD3, ATP binding cassette member 3; ACO, acyl-CoA oxidase; α-smooth muscle chain ; BMP7, bone morphogenic protein 7; CKO, catalase null mice; CPT-1α, carnitine palmitoyltransferase; CTGF, connective tissue growth factor; FMA, fractional mesangial area; GPx1, glutathione peroxidase-1; LPO, urinary lipid peroxide; NOX, NADPH oxidase; Prx1, peroxiredoxin-1; SOD, superoxide dismutase; WT, wild type.

Appendix 19. Existing data of mitochondrial-peroxisome crosstalk in aging and age-related disorders.

Ref/ Ivashchenko**,** 2011	**Peroxisomal (roGFP2-PTS1)[pex14p]**	**Cytosolic roGFP2(c-roGFP2)**	**Mt roGFP2 proteins**	**MM redox state**	**killerRed proteins (relative fluorescence intensities of the photosensitizer per unit area)**			**p-value**
					P (KR-PTS1)	**Cytosolic (c-KR)**	**Mitochondrial (mt-KR)**	
Control mouse fibroblasts (5+/+WT)	Expressed, ↓excitation ratio				Expressed protein			
Pex5p-deficient mouse fibroblasts					Expressed protein			
Treating the cells with Aldrithiol-4	↑oxidation state of roGFP2-PTS1							

↓Cu^{2+} or Zn^{2+} levels	Not affect the redox state of PM					
Redox state	↑↑	↑	↑↑↑			
Redox state differences						(N=73, p<0.0001)
Peroxisomal pH-mt pH [(6.9-8.2)-(7.8-8)]						Redox state of p-redox state of mt=pH value of P-pH value of mt
Excitation ratio of cytosolic & peroxisomal roGFP2	↑	↑↑	↑↑ ↑			Small but significant changes
Oxidation state of roGFP2 in human fibroblasts lacking peroxisomes (mutated PEX16 gene)						No significant difference
Mt & c-roGFP2-treated with Aldrithiol-4	Rapidly returned to basal levels	Rapidly returned to basal levels	Rapidly returned to basal levels			p<0.001
GSTK1						

COS-7/H-cat cells vs. COS-7 cells or immortalized wild-type MEFs	Excitation ratio is higher in COS-7/H-cat cells					p<0.0001
Influence of cell passage number on the redox balance of peroxisomes, cytosol & mt in primary HuFs	↑↑		↑↑			P < 0.0001
Percentage of peroxisomes a 400/480 excitation ratio larger than the mean plus the SD of control						↑ over time
Redox state of roGFP2 in late-passage cells	↑	↑↑	↑			p<0.005
Number of peroxisomes per cell in late-passage cells	↑,↓ capacity to import the roGFP2-PTS1 reporter protein					
Immortalized wild type		↔				
Catalase-deficient MEFs	↔		↑redox state			

Acute catalase inhibition by 3-AT	↔		↑			
p-derived oxidative stress		↑				
Mt-derived oxidative stress		↑↑				
Cytosol-derived oxidative stress		↓		↑↑↑mt fragmentation		

Appendix 20a. Existing data of mitochondria-lysosome in neurodegenerative disorders.

Ref/ Fernandez-Mosquera, 2015		**GSE35642**	**GSE4773**
rotenone 5nM) & (Rotenone (50 nM)	**One week after Tx**	Higher number of up-regulated lysosomal genes (↑in lysosomal biogenesis), high	The number of up- and down-regulated was similar after one wk treatment
			Amount of down-regulated genes progressively at 2 and 4 wks of treatment

		number of lysosomal genes down-regulated	
	Four wk after Tx	Effect reversed	
Rotenone (50 nM)		Four genes not down-regulated after 1 wk but significant	

	down-regulation after 4 wks T*x*	
	↑ 23 transcripts after 1 wk, ↓ 9 transcripts ; 22 of 23 transcripts increased at 1 wk down-regulated after 4	

	wks; 9 transcripts down-regulated at 1 wk and up-regulated after 4 wks	

Appendix 20b. Existing data of mitochondria-lysosome crosstalk in aging and age-related disorders.

Ref/ Fernandez-Mosquera,2015	**TFEB**	**MITF**	**TFEC**	**TFE3**	**Lysosomal genes**	**Mt inner mm potential (Δψm)**	**Cellular Ca2+ homeostasis**	**Overall activity of RC (O2 consumption)**	**LAMP1**	**GAA**	**CTSD**	**AMPK-p**	**CTSF**
Mt RCCI inhibitor-treated wild type MEFs (rotenone)	Rapid up-regulation then	Rapid up-regulation then return to	↓	Rapid up-regulation then return to	↑ and return to baselines after 12 h treatm	Small effect							

	return to the baseline		the baseline	ent									
Mt RCCI inhibitor-treated wild type MEFs (rotenone) for 5 days									↓	↓	↔		↓
Chronic respiratory chain									↓	↓	↓		↓

deficiency													
Coq9R^{239x} MEFs									↓	↓	↓		↓
Coq9R239x in heart mice									↓	↓	↓		↓
Mt CCCP treated wild type MEFs	Rapid up-regulation then return to	Rapid up-regulation then return to the baseline	↓	Rapid up-regulation then return to the baseline	↑rapidly and return to baselines after few hours	Strongly affect							

	the baseline												
Mt RC & OXPHOS perturbation					Rapid up-regulation followed by baseline levels after few hours								

Rotenone-treated Hela cells	Rapid up-regulation then return to the baseline												

CCCP-treated Hela cells	Rapid up-regulation then return to the baseline				↑in number of lysosomal genes after 4 treatment								

Knock-down TFEB in Hela cells													
MITF Knock-down (qPCR) in Hela cells	↔								↓	↔			
TFEB knock-down in Hela cells													
Double TFEB/MITF knock-down in scrambled cells with									↑	↑			

CCCP treatment													
AMPK with CCCP treatment												↑	
mTORC1 inhibitor	inhibit												
AMPK with CCCP treatment in Hela cells									↑	↑	↑		↑
AMPK inhibitor (dorsomorph									↓	↓	↓		↓

in)													
AMPK activator(A769662) in hela cells									↔	↔	↔		↔
Treated cells with CCCP plus (AMPK-calcineurin inhibitor mTORC1 axis)	↔												

CCCP, carbonyl cyanide 3-chlorophenyl hydrazine; RCCI, respiratory chain complex inhibitor; TFEB, transcription factor EB; AMPK, AMP-associated protein kinase.

Appendix 21a. Existing data of mitochondria-lysosome crosstalk in DM, aging and CNS disease

Ref/ Ghavami, 2010	**Beclin-1 expression**	**Atg12-Atg5 formation**	**NADPH oxidase**	**BNIP3**	**ROS**	**MCF7 cells**	**SHEP cells**	**L929 cells**			**HEK-293 cells**		
Time								**12 h ≥ 100 μg/ml**	**24 h ≥ 60**	**36 h ≥60**	**12h 60 μg/ml**	**24 h ≥ 40μg/ml**	**36 h ≥40 μg/ml**
S100A8/A9-treated cells								toxic					
PCD I (apoptosis)													
PCD-II (autophagy)													

ATG5, autophagy protein 5; HEK cells, human embryonic cells; NADPH, nicotinamide dinucleotide phosphate; ROS, reactive oxygen species.

Appendix 21b. Existing data of mitochondria-lysosome crosstalk in diabetes mellitus, aging and central nervous disease.

Ref/Ghavami, 2010	**Caspase-8 activation in MCF7 & SHEP cells**	**BID**	**PARP-1 cleavage in SHEP cells**	**CASP activation in MCF7 cells**	**LC3-I**	**Class III PI3-kinase inhibition 3-MA**	**LC3-II**	**Lysosomal hydrogen pump inhibitor (bafilomycin-A1)**	**ATG12-ATG5**	**Beclin-1**	**Bcl2**	**ATG5 expression**	**Volume & frequency of cytoplasmic granules staining with LTR**
S100A8/A9-triggered cell death	-		CASP 7 activation	Not CASP 3 activation									
S100A8/A9 in MCF-7 cells						suppressed		suppressed		↑	↑	inhibited	
S100A8/A9 in SHEP cells						suppressed	inhibited	suppressed		↑	↑		

S100A8/A9 treated Baf-A1 in SHEP cells							inhibited						
S100A8/A9 treated in L929 cells													↑($p < 0.001$)
Autophagy co-treated NAC plus S100A8/A9 in MCF7 cells							inhibited		inhibited				

ATG5, autophagy protein 5; HEK cells, human embryonic cells; NADPH, nicotinamide dinucleotide phosphate; ROS, reactive oxygen species.

Appendix 21c. Existing data of mitochondria-lysosome crosstalk in DM, aging and CNS disease.

Ref/ Ghavami, 2010	**Cath B inhibitor (CA-074-ME)**	**Cath L inhibitor (z-FF-FMK)**	**MTR**	**BNIP3**	**ΔTM-BNIP3**	**Lysosomal activation**	**ΔTM-BNIP3 vs. WT cells**	**ROS**	**Δψm using DHR-123**
S100A8/A9-induced cell death in MCF7 cells	inhibited	Inhibited (P< 0.001)			Resistant to cell death				
S100A8/A9-induced cell death in SHEP cells									
S100A8/A9-induced cell death in L929 cells							Resistant to cell death (P < 0.05)	↑	↓
S100A8/A9-induced cell death in HEK-293 cells							Resistant to cell death (P < 0.05)		
ΔTM-BNIP3-L929								↓	↓
ΔTM-BNIP3-MCF7 cells								↓	↓
S100A8/A9-induced apoptosis in HT29/219&SW742 colon carcinoma cells									
MCF7 cells treated with S100A8/A9									
MCF7 cells treated with S100A8/A9 plus NAC for 4 h						↓			
Wt L929 cells after treatment with S100A8/A9									

ΔTM-BNIP3 after L929 cells overexpressing treatment with S100A8/A9 vs. wt controls						blocked			

Appendix 22a1. Existing data of mitochondria-lysosome crosstalk in cancer, metabolic disease and neurodegenerative disorders.

Ref/ Baixuali, 2015	**Mt DNA**	**Mt respiration**	**Anaerobic glycolysis**	**FAO**	**Lysosomal ca mobilization**	**Lysosomal degradation capacity**		**mRNA of Tfam in $CD4^+$ & $CD8^+$ T naïve lymphocytes**	**CD4+ & CD8+ T-cells**	**Tfam levels**	**Mt ROS**
						Sphingomyelin accumulation	**P62**				
Tfam deficient cells	Below - normal levels	↓	↑	impaired		T-cell differentiation		↓			Below normal
Respiration-impaired cells					↓	impaired					
Spleen& peripheral LN									↓percentage		
Lymphoblast differentiation										suppressed	

Mt DNA, mitochondrial deoxyribonucleic acid; FAO, oxidation of fatty acids; mRNA, mitochondria ribonucleic acid.

Appendix 22a2. Existing data of mitochondria-lysosome crosstalk in cancer, metabolic disease and neurodegenerative disorders.

Ref/ Baixuali, 2015	**Mt ATP generation**	**Survival in galactose medium**	**oligomycin**	**Mt mm potential**	**Total cellular ATP content**	**ECAR**	**OXPHOS**	**OCR**	**EEA1**	**HRS**	**LBPA**	**LAMP1**
Tfam deficient T cells				Reversal F1F0ATPase function resulting impaired electron transport chain function	Phosphorylation level of the metabolic sensor AMPK did not differ between Tfam deficient T cells vs. controls	↑	↓	↓				abundant
WT cells			Transient hyperpolarization									
Primary CD4+ Tfam-/- T cells					Was comparable vs. controls							
Jurkat shTfam T cells												
Respirator chain impaired cells									No substantial differences	↑	↑	

Mt ATP, mm, membrane; ECAR, extracellular acidification rate; OXPHOS, oxidative phosphorylation; OCR, oxygen consumption rate; EEA1, early endocrine marker-1;HRS, late endocrine marker; LBPA, lysobisphosphatidic acid.

Appendix 22a3. Existing data of mitochondria-lysosome crosstalk in cancer, metabolic disease and neurodegenerative disorders.

Ref/ Baixuali, 2015	**LAMP1**	**TFEB**	**PGC1α**	**ATP6V0**	**FABP3**	**CD36**	**Acacb**	**Cyp4a10**	**Calevels**	**Bafilomycin A1**	**Lysosomal pH**	**Cathepsin B**	**Lipid profile**	**Acid phosphatase activity**
↑ autophagy		↑												
Lysosomal biogenesis		↑												
Tfam depleted cells			upregulated	upregulated	upregulated	upregulated	upregulated	upregulated	weaker			↓	Altered(↑)	No difference
Respiration-Impaired Tfam-/- cells		TFEB activation							↓		↓		↓ SM & ,TAGs↓ ASM	

FABPs, fatty acid binding protein; LAMP1, lysosomal associated membrane protein-1; PGC1a, peroxisome proliferator-activated receptor-ϒ coactivator1a; TFEB, transcription factor EB.

Appendix 22a4. Existing data of mitochondria-lysosome crosstalk in cancer, metabolic disease and neurodegenerative disorders.

Ref/ Baixuali, 2015	**Lysosomal Ca levels**	**SM**	**LC3 GFP-RFP**	**GFP fluorescence**	**RFP-positive puncta number**	**CCCP**	**Lipidated form of LC3**	**P62**	**Lipid trafficking**	**Ca mobilization**	**Mt DNA levels**	**Flow cytometry**	**IFN-ϒ&T-bet producing cell**
Respiration-impaired cells	↓	Abnormal SM accumulation	↓	↓				Slower with cyclohexamide					
rapamycin					↑								
Tfam deficient cells					↓	Larger GFP aggregates	↑	↑	abnormal	altered	↑ Tfam expression →↑mt DNA	↓proliferation	↑

CCCP, carbonyl cyanide 3-chlorophenyl hydrazine; Mt DNA, mitochondrial deoxyribonucleic acid; SM, sphingomyelin.

Appendix 22a5. Existing data of mitochondria-lysosome crosstalk in cancer, metabolic disease and neurodegenerative disorders.

Ref Baixuali/**2015**	**IL-6 mRNA**	**IL-1α mRNA**	**IL-1β mRNA**	**INF-ϒm RNA**	**IFN-ϒ secretion**	**IL-6 secretion**	**IL-4 mRNA**	**IL-4**	**IL-10**	**IL-17**	**Mt mass**	**mROS**	**ATP**	**OCR**
Tfam deficient cells	↑	↑	↑	↑	↑	↑	Below-nl	Below-nl	Below-nl	↓				
Respiration-impaired cells				↑										
TASM cells											Not mt alterations	Not mt alterations	Not mt alterations	Not mt alterations

ATP, adenosine triphosphate; mRNA, messenger ribonucleic acid; mROS, mitochondrial reactive oxygen species; OCR, oxygen consumption rate.

Appendix 22b1. Existing data of mitochondria-lysosome crosstalk in cancer, metabolic disease and neurodegenerative disorders.

Ref/ Baixuali, 2015	**Mt DNA**	**Mt respiration**	**Anaerobic glycolysis**	**FAO**	**Lysosomal ca mobilization**	**Lysosomal degradation capacity**		**mRNA of Tfam in $CD4^+$ & $CD8^+$ T naïve lymphocytes**	**CD4+& CD8+ T-cells**	**Tfam levels**
						Sphingomyelin accumulation	**P62**			
Tfam deficient cells	Below-normal levels	↓	↑	impaired		T-cell differentiation		↓		
Respiration-impaired cells					↓	impaired				
Spleen& peripheral LN									↓percentage	
Lymphoblast differentiation										suppressed
Tfam levels	Close relationship									

CD4, cluster determination; FAO, oxidation of fatty acids; Mt DNA, mitochondrial deoxyribonucleic acid; mRNA, messenger ribonucleic acid.

Appendix 22b2. Existing data of mitochondria-lysosome crosstalk in cancer, metabolic disease and neurodegenerative disorders.

REf/ Baixuali,2015	**mtDNA-encoded subunits of mt CI, III, IV,V mRNA**	**Nuclear-encoded subunits**	**mtDNA-encoded subunits of I&IV**	**Nuclear-encoded subunit of II**	**Mt content**	**Electron microscopy**	**Electron transport**	**EEA1**	**HRS**	**LBPA**	**LAMP1**	**IF analysis**
Tfam deficiency	↓	Not affected	Below normal	Not affected	↑		Stronger impairment of electron transport from NADH than from FADH2	No substantial difference			↑	Enlargement of late endosome
Tfam-/- CD4+ T cells						Severely aberrant mt morphology, impaired cristae organization & loss of mt electron density						
BNGE extracts of						Sever loss of complexes						

from Tfam-silenced cells						I,III, not II, alterations in mt supercomplex assembly						
RC impaired cells									↑	↑		

Appendix 23a1. Existing data of mitochondria-lysosome crosstalk in lung adenocarcinoma.

Ref/ Brahimi-Horn, 2015	**Functional mitochondria**	**VDAC1-ΔC**	**HIF-1α**			**Cell death**	**TP53-specific siRNA**	**Cell survival**
CCL39	Enlarged functional mt	↑ resistance to STS-induced apoptosis						
LS174	Enlarged functional mt	↑ resistance to STS-induced apoptosis					STS-induced apoptosis in hypoxia	
LS174 cells transfected with TP53-specific siRNA			↑	↓				

A549	Enlarged functional mt	↑ resistance to STS-induced apoptosis						
786-O	Enlarged functional mt	↑ resistance to STS-induced apoptosis						
HeLa cell lines	Enlarged functional mt	↑ resistance to STS-induced apoptosis					WT for TP53:↓	
MEF cell lines	Enlarged functional mt	↑ resistance to STS-induced apoptosis		Wild type TP53:↑ null for TP53:↔				
PC3	Nl tubular mt network & sensitive to							

	apoptosis							
SKMel								
MDA-MB								
HT29 cell lines								
Hypoxic cells								
DMOG					Stabilize in normoxia	High concentrations of DMOG induced cell death		
DMGO treatment in hypoxia			Rapid VDAC1 processing					
Normoxia				Not detected or minimally				

				detected				
TP63&TP73 in HeLa cells			Promote VDAC cleavage and protection from induced apoptosis, ↓↓TP63 levels					
TP63siRNA in hypoxic Hela cells				↔				
siRNA against TP73				↓ & ↑sensitivity to STS-induced				

				cell death				
Silencing of TP53 or HIF-1α in hypoxic LS174 cells								↓
Silencing of TP53 plus HIF-1α								↓ In presence of STS

DMOG, dimethyl-oxalylglycine; HIF-1, hypoxia-inducible factor-1; VDAC1, voltage dependent anion channel-1.

Appendix 23a2. Existing data of mitochondria-lysosome crosstalk in lung adenocarcinoma.

Ref/ Brahimi-Horn, 2015	**STS-induced cell death in hypoxia**	**Truncation of VDAC1**	**VDAC1 cleavage to VDAC1-ΔC**	**Drug-induced cell death**
Mieap	↑	↓		
siRNA against Lamp1 or Lamp2		↔		
Bafilomycin A1or chloroquine			inhibited	↑

SiRNA, small interfering ribonucleic acid; STS, staurosporine; VDAC, voltage dependent anion channel.

Appendix 24. Investigated variables in mitochondrial crosstalk with other organelles in included studies.

Study of publication (Communication type	**First author, Journal**	**Country**	**Ca homeostasis**	**Apoptosis & autophagy**	**ROS levels (ROS generation)**	**ATP levels (ATP generation)**	**Redox state**	**Lipid metabolism**	**RC dysfunction**
Mt-nucleus crosstalk	Yuan et al, KI	China		65%	↑	↓			
Mt-nucleus crosstalk	Raharijoana et al, PLOS ONE	France			↑				CI, II, IV↓
Mt-ER crosstalk	Garofalo et al, Autophagy	Italy		+				+	
Mt-ER crosstalk	Kawakami et al, J Am Soc Nephrol	Colombia		+	+				
Mt-ER crosstalk	Diwan et al, J	USA	+	+					

	Clin Invest								
Mt-ER crosstalk	Gomez et al, Cell Death Differentiation	France	+	+					
Mt-ER crosstalk	Hacki et al, Oncogene	Germany		+					
Mt-ER crosstalk	Pacher et al	USA	+						
Mt-ER crosstalk	Safiedeen et al, Antioxidant Redox Signaling	France			+				
Mt-ER crosstalk	Naon et al, PNAS	Italy	+						
Mt-ER crosstalk	Basso et al, Pharmacol	Italy	+						

	Res								
Mt-ER crosstalk	Abuaita et al, Cell host Microbe	USA			+				
Mt-SR/ER	Fernandez-Sanz, Cell Death Dis	Spain			+	+			
Mt-ER	Sala-Vila et al, Sci Rep	Spain						+	
Mt-PO crosstalk	Ivashencko et al, Mol Biol Cell	Belgium			+		+		
Mt-PO crosstalk	Hwang et al, Diabetes	Korea			+				
Mt-Lysosome crosstalk	Bauxali et al, Cell Metab	USA	+					+	

Mt-Lysosome crosstalk	Ghavami et al, Cell Res	Canada		+	+				
Mt-Lysosome crosstalk	Fernandez et al, Sci rep	Germany		+			+		
Mt-Lysosome crosstalk	Brahimi et al, Mol Cell Biol	France		+					

Note: Positive sign means the mentioned function is identified function of two organelle communication (crosstalk).

Appendix 25. Proportion, relative risk and odds ratio of two variables of increased oxidative stress and apoptosis in the present research.

Statistical analysis / IOC	**Proportion of ROS levels and CI of Proportion**	**Proportion Difference and CI of proportion difference**	**p-value of proportions**	**Relative risk of ROS levels**	**Odds ratio of ROS levels**	**P-value**	**Proportion of Apoptosis and CI of Proportion**	**Proportion Difference and CI of proportion difference**	**p-value of proportions**	**Relative risk of Apoptosis**	**Odds ratio of Apoptosis**	**P-value**
Mt-ER	33.3% (0.0992-0.6511)	29.2 (-13.0074-59-9860)	0.21	0.53 (0.2035-1.3978)	0.32 (0.0463-1.9426)	0.20	41.6% (0.1517-0.7233)	8.4% (-30.4287-445830)	0.77	0.83 (0.318-	0.7 (10.1181 to 4.3187)	0.71
Mt-Nuc	100% (0.15-1)	36.4% (-31.7619-59.1116)	0.31	0.02			50% (0.0126-0.9874)	30% (-16.5479-72.3741)	0.35	1.13 (0.2299-4.3492)	1.25 (0.0672-23.26)	0.88
Mt-PO	100% (0.15-1)	36.4% (-31.7619-59.1116)	0.31	0.02								
Mt-Lys	25% (0.0063-0.859)	25% (-25.0325 to 55.0311)	0.38	0.5 (0.0854-2.9258)	0.33 (0.0283 to 3.9262)	0.38	75% (0.1941-0.9937)	15% (-34.0671 - 46.2058)	0.58	2 (0.8559-4.6732)	5 (0.4190-59.6601)	0.2032

Appendix 26. Raw data of interorganelle crosstalk effect on variables of elevated reactive oxygen species and apoptosis in the present research.

↑ROS levels / Effect of IOC of Mt-ER	+	-	Sum
+	4 (a)	8 (b)	12 (n1)
-	5 (c)	3 (d)	8 (n0)
Sum	m1	m2	20 (N)

↑ROS levels / Effect of IOC Of Mt-Nuc	+	-	Sum
+	2	0	2 (n1)
-	7	11	18 (n0)
Sum	m1	m2	20 (N)

↑ROS levels / Effect of IOC Of Mt-Nuc & Mt-PO	+	-	Sum

+	2	0	2 (n1)
-	7	11	18 (n0)
Sum	m1	m2	20 (N)
Effect of IOC Of Mt-Lys	+	-	Sum
+	5	7	12 (n1)
-	4	4	8 (n0)
Sum	m1	m2	20 (N)
Apoptosis Effect of IOC Of Mt-ER	+	-	Sum
+	5	7	12 (n1)
-	4	4	8 (n0)

Sum	m1	m2	20 (N)
Apoptosis Effect of IOC Of Mt-Nuc	+	-	Sum
+	1	1	2 (n1)
-	8	10	18 (n0)
Sum	m1	m2	20 (N)
Apoptosis Effect of IOC Of Mt-PO	+	-	Sum
+	0	2	2 (n0)
-	0	9	9 (n1)
Sum	m1	m2	11 (N)

Apoptosis / Effect of IOC Of Mt-Lys	+	-	Sum
+	3	1	4 (n1)
-	6	10	16 (n0)
Sum	m1	m2	20 (N)

the first group; n1, number in the second group; PO, peroxisome; ROS, reactive oxygen species. Plus sign shows presence of effect or variable and negative sign is indicative of absence of them.

Appendix 27. Outcome of clinical entity in mitochondrial crosstalk with other organelles.

Disease / **Type of Interorganellar Communication /Author/Ref**	**Renal disease (Glomerular disease,…)**	**Cardiovascular disease**	**Metabolic syndrome**	**Cancer**	**Aging & Age-related disorders (DM, Alzheimer's diseases)**	**Metabolic disease or disorders**	**CNS disease**	**Inflammation**
Mitochondrial-nucleus/Yuan et al/6	Aldosterone-induced podocyte injury							
Mitochondria-nucleus/ Raharijaona et al/7						+		
Mitochondria-ER/ Safiedeen et al/8			+					
Mitochondria-ER/Kawakami et	FSGS							

al/9								
Mitochondria-ER/Pacher et al/10		Vascular pathophysiology						
Mitochondria-ER/Hacki et al/11				?	?			
Mitochondria-ER/ Gomez et al/12		Myocardial IR injury						
Mitochondria-ER/Diwan et al/13		Heart failure, CMP						
Mitochondria-ER/ Naon et al/14		cardiomyocyte					neurons	
Mitochondria-ER/Garofalo et al/15							Alzheimer's disease	
Mitochondria-ER/Basso et al/16							PD	
Mitochondria-ER/Abuaita et al/17								Methicillin-resistant staphylococcus infection

Mitochondria-SR/ER, Fernandez-Sanz/18		Aged myocardium			+			
Mitochondria-ER, Sala-Vila et al/19							+	
Mitochondria-PO/Hwang et al/20	Diabetic nephropathy			+				
Mitochondria-PO/Ivashchenko et al /21					+			
Mitochondria-lysosome/ Fernandez-mosquera et al/22							Neurodegenerative disorders (parkinson disease)	
Mitochondria-lysosome/Ghavami et al/23			DM		+		+	

Mitochondria-lysosome/ Baixauli et al/24				+	+		Neurodegenerative disorders	+
Mitochondria-lysosome/ Brahimi-Horn et al/25				Lung adenocarcinoma			+	

CMP, cardiomyopathy; CNS, central nervous system; DM, diabetes mellitus; FSGS, focal segmental glomerulosclerosis; PD, parkinson disease; PO, peroxisome; IR injury, ischemic reperfusion injury; Positive sign means creation of disease is due to involving mechanisms of two organelles communication (crosstalk) or resulting action of two organelle crosstalk in cells of mentioned organ. Question mark means insufficient data or absence of mentioned entity in text precisely but clinical entities of cancer and aging are according to author's opinion.

Appendix 28. Outcome of pharmacological inhibition in mitochondrial crosstalk with other organelles.

Communication type	**Reference**	**Country**	**Signalling pathway or molecule**	**Pharmacologic inhibition**
Mt-nucleus	Yuan et al, 2012	China	SIRT1/PGC-1α pathway	Resveratrol
Mt-nucleus	Raharijoana et al, 2015	France	eNOS/PRC pathway	-
Mt-ER	Garofalo et al, 2016	Italy	GD3-MBRA1 pathway, WIPI1	-
Mt-ER	Kawakami et al, 2015	Colombia	ATG5, ATG7	-
Mt-ER	Diwan et al, 2009	USA	NIX	-
Mt-ER	Gomez et al, 2016	France	GSK3β	SB216763
Mt-ER	Hacki et al, 2000	Germany	Bcl-2	Brefeldin A
Mt-ER	Pacher et al,	USA	TGF-β	Thapsigargine,

	2008			Ionomycin
Mt-ER	Safiedeen et al, 2017	France	SMase route	MPs
Mt-ER	Naon et al, 2016	Italy	Mitofusin 2	-
Mt-ER	Basso et al, 2018	Italy	By parkin via Mfn2	
Mt-ER	Abuaita et al, 2018	USA	Parkin	Bafilomycin A1
Mt-SR/ER	Fernandez-Sanz et al, 2014	Spain	RyR/IP3-VDAC	-
Mt-ER	Sala-Vila et al, 2016	Spain	Caveolin-1	-
Mt-PO	Ivashencko et al, 2011	Belgium	roGFP2-PTS1mt pathway	-
Mt-PO	Hwang et al, 2012	Korea	Catalase	N-acetylcysteine
Mt-Lysosome	Bauxali et al, 2015	USA	Tfam	cycloheximide
Mt-Lysosome	Ghavami et al, 2010	Canada	BNIP3	N-acetylcysteine
Mt-Lysosome	Fernandez et al,	Germany	TFEB	Rotenone

	2015			
Mt-Lysosome	Brahimi et al, 2015	France	TP53-induced Mieap	Bafilomycin Chloroquine

ATG5, autophagy related gene 5 ; ATG7, autophagy related gene 7 ; B-cl2, B-cell lymphoma 2 ; BNIP3, B-cl2 and adenovirus E1B19 KDa interacting protein-3 ; eNOS/PRC, endothelial nitric oxide synthase/ peroxisome proliferator-activated receptor-ϒ coactivator1a (PGC-1) related coactivator ; GD3-MBRA1, ganglioside 3-autophagy/Beclin1 regulator 1 ; GSK3ß, glycogen synthase kinase-3β; ER, endoplasmic reticulum; MPs, microparticles ; Mt, mitochondria; NIX, NIP3-like protein 3 that is known BNIP3L; PO, peroxisome; SB216763, a moderate autophagic agonist and GSK3 inhibitor; SMase, sphingomyelinase; Tfam, mitochondrial transcription factor A; roGFP2-PTS1mt, redox-sensitive variant of enhanced green fluorescent protein; SIRT1/PGC1a, sirtuin 1/ peroxisome proliferator-activated receptor-ϒ coactivator1a; TFEB, transcription factor EB; TGF-ß, transforming growth factor-ß ; USA, United States of America; WIPI1, WD repeat domain, phosphoinositide interacting 1.