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Supplementary information

Mitochondrial control of inflammation

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Table 1 | **Dysregulated mtDAMP signalling in disease***

Disease	DAMP	PRR	Effect	Mechanistic evidence	Patient data	Note(s)	Ref.
Acute kidney injury	mtDNA	cGAS	Detrimental	Yes	Yes	Reduced inflammation and kidney injury driven by cisplatin in *Sting1*$^{-/-}$ mice	1
	ROS	n.d.	Detrimental	Yes	No	Mitophagy inhibition imposed by *Pink1* and/or *Prkn* deletion aggravated ischemic kidney injury	2
Acute liver failure	mtDNA *N*-formyl peptides	cGAS FPR1	Detrimental	Yes	Yes	Pathological FPR1 and TLR9 activation in mice and high circulating levels of mtDNA in both mice and patients	3
Alzheimer's disease	n.d.	n.d.	Detrimental	Yes	Yes	Impaired mitophagy due to cholesterol accumulation in mice and patients with Alzheimer's disease	4
	ROS	NLRP3	Detrimental	Yes	Yes	Pharmacological mitophagy activation ameliorates biochemical and behavioural defects in nematodes and mice	5
Amyotrophic lateral sclerosis	mtDNA	cGAS	Detrimental	Yes	Yes	mtDNA release mechanistically linked to biochemical marker of amyotrophic lateral sclerosis and increased cGAMP levels in spinal cord samples form patients	6
ARDS	mtDNA	NLRP3	Detrimental	Yes	No	Reduced lung injury in mice upon inhibition of mtDNA synthesis with metformin	7
	N-formyl peptides	FPR1	Detrimental	Yes	Yes	High levels of *N*-formyl peptides in patients with ARDS and FPR1-dependent lung injury in mice	8
Breast cancer	ATP	NLRP3	Beneficial	Yes	No	Mechanistic link between ATP release by cancer cells and tumour-targeting immunity in mice, and correlation between loss-of-function *P2RX7* allele and poor disease outcome in patients	9
	mtDNA	cGAS	Beneficial	Yes	Yes	Cytosolic accumulation of mtDNA in irradiated cells (under tonic inhibition by autophagy) mechanistically linked to anticancer immunity in mice, and signature of autophagy proficiency correlated with limited type I interferon signalling and immunity in patient samples	10
	mtDNA	cGAS	Beneficial	Partial	Yes	Apoptotic caspase activation in cancer cells mechanistically linked to poor type I interferon signalling in mice, and signatures of apoptotic proficiency correlated with poor disease outcome in patients	11
Chronic kidney disease	mtDNA	cGAS	Detrimental	Yes	Yes	*Tfam* deletion from renal tubules is sufficient to drive kidney injury upon mitochondrial dysfunction	12
Colorectal cancer	ATP	n.d.	Beneficial	Yes	No	Mechanistic link between autophagy activation in dying cancer cells and ATP release driving anticancer immunity in mice	13
	mtDNA	cGAS	Beneficial	Yes	No	CASP9 activation linked to inhibited mtDNA-driven cGAS signalling in cancer cells and consequent antitumour immunity in mice	14
	n.d.	n.d.	Beneficial	Yes	No	Activation of apoptotic caspases linked to inhibition of MOMP-elicited NF-κB-dependent tumour-targeting immunity in mice	15

COPD	mtDNA	cGAS NLRP3	Detrimental	Partial	Yes	Increased circulating levels of mtDNA in patients with COPD and mice exposed to cigarette smoke	16
	ROS	n.d.	Detrimental	Yes	Yes	Signs of mitochondrial dysfunction in mice exposed to ozone and patients with COPD	17
Crohn's disease	n.d.	n.d.	Detrimental	Yes	Yes	Genetic inactivation of mitophagy promotes mitochondrial defects and Paneth cell dysfunction	18
	ROS	NLRP3	Detrimental	Yes	No	Genetic inactivation of mitophagy promotes mitochondrial dysfunction and ROS generation	19
Diabetic nephropathy	ROS	NLRP3	Detrimental	No	Yes	Reduced OPTN levels in patients, negatively correlating with inflammatory markers in urine	20
Flu	mtDNA	cGAS	Beneficial	Yes	No	Virus-driven MAVS-dependent mtDNA release ignites antiviral type I interferon responses via cGAS	21
H. pylori infection	SMAC	NIK	Detrimental	No	Partial	Correlation between SMAC levels and signs of inflammation in biopsies from patients with gastritis positive for *H. pylori*	22
Heart failure	mtDNA	TLR9	Detrimental	Yes	No	Defective autophagic clearance of mtDNA exacerbates pressure overload-driven myocarditis	23
Hepatocellular carcinoma	mtDNA	TLR9	Detrimental	Yes	Yes	Mitochondrial fission mechanistically linked to TLR9-dependent CCL2 secretion and establishment of immunosuppression in mice	24
	mtDNA	TLR9	Detrimental	Partial	Yes	HMGB1-bound mtDNA mechanistically linked to TLR9-dependent cancer cell proliferation driven by hypoxia in immunodeficient mice	25
Interstitial lung disease	mtDNA ROS	cGAS NLRP3	Detrimental	Yes	Yes	Increased dsDNA in sputum and STING activation in lungs from patients with silicosis	26
Intracerebral haemorrhage	Haem	TLR4	Detrimental	Partial	No	Evidence of a TLR4-dependent pathogenic mechanism driven by haemorrhage and aggravated by exogenous haemin administration	27
Lowe syndrome	mtDNA	TLR9	Detrimental	No	Yes	Mitophagy defects in cells from patients with Lowe syndromes bearing *OCRL* mutations	28
Melanoma	ROS	n.d.	Detrimental	Partial	No	Mitochondrial dysfunction linked to ROS-driven pro-inflammatory cytokine secretion in support of cancer immunoevasion in mice	29
Nonalcoholic fatty liver disease	mtDNA	AIM2	Detrimental	Yes	No	Pathological AIM signalling in mice exposed to a high-fat diet, correlating with mitochondrial dysfunction	30
	ROS	NLRP3	Detrimental	Yes	No	Mitophagy impairment in mice exposed to a high-fat diet, correlating with NLRP3 inflammasome activation	31
Obesity	mtDNA	cGAS	Detrimental	Yes	No	Mechanistic link between cGAS activation driven by mtDNA and obesity-related insulin resistance in mice	32
	ROS	n.d.	Detrimental	Yes	No	Defective mitophagy in *Fundc1*$^{-/-}$ mice aggravates obesity-related insulin resistance	33
Ovarian cancer	mtDNA	n.d.	Detrimental	No	Yes	mtDNA levels in ascites inversely correlate with progression-free survival	34
P. aeruginosa infection	mtDNA	NLRC4	Detrimental	Partial	No	Pathogenic NLRC4 activation under tonic inhibition by autophagy in a mouse model of intraperitoneal infection	35
Pancreatic cancer	ROS	AIM2	Detrimental	Yes	Yes	Mitophagy dysfunction accelerates spontaneous pancreatic oncogenesis in mice via mitochondrial iron accumulation and AIM2	36

Parkinson's disease	mtDNA	cGAS	Detrimental	Yes	Yes	STING1-dependent loss of dopaminergic neurons from the substantia nigra in mice with *Prkn* deletion, and high cytokine levels in humans with *PRKN* mutations	37
	mtDNA	n.d.	Detrimental	No	Yes	Increased cytokine and mtDNA levels in patients with biallelic or heterozygous *PRKN* or *PINK1* mutations	38
	n.d.	n.d.	Detrimental	Partial	No	Mitochondrial dysfunction in the brain of *Prkn*$^{-/-}$ mice correlating with hindlimb defects and neuronal loss	39
	n.d.	NLRP3	Detrimental	Yes	Partial	Accrued NLRP3 activation in mice and patients bearing PRKN or PINK1 defects	40
Rhabdomyolysis	mtDNA	TLR9	Detrimental	No	Partial	Signs of dysfunctional mitophagy in primary myoblasts from patients with recurrent rhabdomyolysis	41
Rheumatoid arthritis	mtDNA	cGAS	Detrimental	Yes	No	TNF blocks PINK1-dependent mitophagy hence promoting type I interferon secretion via cGAS	42
	Cytochrome *c*	TLR4	Detrimental	Partial	Partial	Pathogenic effects of intra-articular cytochrome *c* administration but paradoxical reduction of circulating and intra-articular cytochrome *c* levels in patients with rheumatoid arthritis	43
SARS-CoV-2	mtDNA	cGAS	Detrimental	Yes	Yes	Pathogenic cGAS activation in mice and human lung tissues with extensive damage from infection	44
	mtDNA	TLR9	Detrimental	Yes	Yes	Increased levels of circulating mtDNA in patients with COVID-19, and pathogenic TLR9 signalling in mice	45
Septic shock	mtDNA ROS	NLRP3	Detrimental	Yes	Yes	Autophagy defects linked to accrued NLRP3 activation and mortality in mice, and increased IL-18 levels in septic vs non-septic patients admitted to the ICU	46
	N-formyl peptides	FPR1	Detrimental	No	Yes	High circulating levels of *N*-formyl peptides are associated with increased risk for secondary infection and mortality	47
SFTS	mtDNA	NLRP3	Detrimental	Yes	Yes	Pathogenic NLRP3 signalling in mice and correlation between BAK1 levels and disease outcome in patients	48
Sickle cell disease	Haem	TLR4	Detrimental	Yes	No	Evidence of haem-driven TLR4-dependent and TLR4-independent vaso-occlusion in mice	49
SIRS	mtDNA *N*-formyl peptides	TLR9 FPR1	Detrimental	Yes	Yes	Evidence of lung injury in rats administered with mitochondrial DAMPs and elevated blood levels of mtDNA in patients with SIRS	50
Systemic lupus erythematosus	mtDNA	AGER TLR9	Detrimental	No	Yes	Extracellular TFAM- or HMGB1-bound mtDNA linked to exacerbated inflammation	51
	mtDNA	cGAS	Detrimental	No	Yes	Dysfunctional mitophagy leads to pathogenic mitochondrial accumulation in red blood cells	52
	mtDNA ROS	cGAS	Detrimental	Yes	Yes	Mitochondrial ROS and oxidized mtDNA promote NET extrusion by neutrophils	53
	mtDNA	n.d.	Detrimental	Partial	Yes	Pathogenic role for mtDNA released from platelets	54
	mtDNA	n.d.	Detrimental	No	Yes	Oxidized mtDNA escaping degradation and accumulating in the extracellular environment promotes neutrophil activation	55
	mtDNA	n.d.	Detrimental	Yes	Yes	VDAC dependent mtDNA release and ROS production support pathogenic NETosis	56

*Limited to studies providing mechanistic evidence *in vivo* or patient data.

AGER, advanced glycosylation end-product specific receptor; AIM2, absent in melanoma 2; ARDS, acute respiratory distress syndrome; BAK1, BCL2 antagonist/killer 1; CASP9, caspase 9; cGAMP, cyclic GMP–AMP; cGAS, cyclic GMP–AMP synthase; COPD, chronic obstructive pulmonary disease; DAMP, damage-associated molecular pattern; FPR1, formyl peptide receptor 1; FUNDC1, FUN14 domain-containing protein 1; HMGB1, high mobility group box 1; ICU, intensive care unit; MAVS, mitochondrial antiviral signalling protein; MOMP, mitochondrial outer membrane permeabilization; mtDAMP, mitochondrial DAMP; mtDNA, mitochondrial DNA; n.d., not determined; NET, neutrophil extracellular trap; NIK, official name mitogen-activated protein kinase kinase kinase 14 (MAP3K14); NLRC4, NLR family CARD containing 4; NLRP3, NLR family, pyrin domain containing 3; OPTN, optineurin; PINK1, PTEN-induced putative kinase 1; PRKN, parkin RBR E3 ubiquitin protein ligase; PRR, pattern recognition receptor; ROS, reactive oxygen species; SIRS, systemic inflammatory response syndrome; SFTS, severe fever with thrombocytopenia syndrome; SMAC, official name diablo IAP-binding mitochondrial protein (DIABLO); STING1, stimulator of interferon response cGAMP interactor 1; TFAM, transcription factor A, mitochondrial; TLR, Toll-like receptor; TNF, tumour necrosis factor; VDAC, voltage-dependent anion channel.

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