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THE LINK BETWEEN MITOCHONDRIA AND INFLAMMATION: A BRIEF REVIEW

D. MARTINELLI

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Division of Metabolic Diseases, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

Corresponding Author
Diego Martinelli, MD, PhD; e-mail: diego.martinelli@opbg.net

ABSTRACT **–** Inflammation plays a central role in various diseases, including autoimmune disorders and viral infections, and can worsen conditions caused by non-inflammatory stressors. Mitochondria, with their bacterial-like properties, are involved in regulating inflammation. Damaged mitochondria release components such as mtDNA into the cytosol, triggering innate immune responses. The DNA sensor cGAS activates the STING pathway, leading to a type I-IFN response and inflammasome activation. MtDNA is also a key activator of the NLRP3 inflammasome via a reactive oxygen species (ROS)-dependent mechanism. Mitochondrial ROS and mtDNA act as damage-associated molecular patterns (DAMPs), which are critical for inflammasome activation and regulate regulated cell death (RCD). Mitochondrial components such as cytochrome c, cardiolipin, and N-formyl peptides can trigger inflammatory responses through various receptors like TLR9 and RAGE. Excessive mtDAMP signaling is tightly regulated to prevent unwarranted inflammation, with mechanisms like apoptosis and autophagy modulating immune responses. Dysregulated mtDAMP signaling contributes to diseases such as Systemic Lupus Erythematosus, Crohn's disease, and Parkinson's disease, and can affect viral infections and cancer progression. Mitochondrial dysfunctions play a significant role in abnormal innate immune responses. Although mitochondrial-targeting therapies for inflammation are largely unexplored, they present a potential avenue for treatment, especially given the limited pharmacological options available. In conclusion, while mitochondria are key regulators of inflammation, further research is needed to fully understand their role and develop effective therapeutic strategies to address mitochondrial dysfunction and its connection to various inflammatory diseases.

Keywords: Mitochondria, Inflammation, cGAS-STING, Inflammasome.

INTRODUCTION

Numerous human diseases, including autoimmune disorders and viral infections, are linked to dysregulated inflammatory responses[1-4]. Conversely, unregulated inflammation may exacerbate the progression, severity and duration of diseases induced by non-inflammatory stressors[5]. The activation of adaptive immunity leads to a robust inflammatory response, contributing to the beneficial effects seen in various cancer treatments[6-10]. Additionally, several elements of the molecular pathways that trigger inflammation play a role in embryonic and postembryonic development[11]. Immune and non-immune cells possess pattern recognition receptors (PRRs), which are generally activated to initiate inflammation[12]. Endogenous molecules known as damage-associated molecular patterns (DAMPs) can activate pattern recognition receptors (PRRs) alongside microbial components linked to infection, the so-called pathogen-associated molecular patterns (PAMPs)[12]. DAMPs generally cannot activate PRRs signaling in normal physiological conditions because they have restricted access to the subcellular regions containing PRRs[13]. However, during cellular stress or death, alterations in the permeability of cellular compartments enable DAMPs to engage PRRs, initiating inflammatory responses[13].

Several lines of evidence suggest the involvement of mitochondria in the regulation of inflammatory pathways. Firstly, a variety of mitochondrial and bacterial proteins exhibit numerous similarities[14]. Se-

condly, mitochondrial genome, circular and lacking histone association, is closely related with bacterial genomes[15]. Mitochondria possess two membranes that help separate mitochondrial DAMPs (mtDAMPs) from specific PRRs: the inner mitochondrial membrane (IMM) and the outer mitochondrial membrane (OMM)[15]. Finally, both necrotic and apoptotic regulated cell death (RCD) are primarily governed by irreversible mitochondrial permeabilization[16]. When adaptation to cellular stress is unsuccessful, mitochondria serve as a distinct platform for inflammation, PRRs signaling, and DAMPs redistribution, which is associated with the initiation of regulated cell death (RCD)[16]. After damage, mitochondria release their inner components including mtDNA into the cytosol eliciting innate immune cascades[17]. The nucleic acid or its components are detected into the cytosol by the DNA sensor cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS), which triggers a potent type I-Interferon (type I-IFN) response, through the stimulator of the interferon genes protein (STING). This, in turn, promotes the expression of interferon-stimulated genes (ISGs)[18]. MtDNA is also able to activate the inflammasome pathway. Moreover, oxidative stress with production of reactive oxygen species (ROS) has been found to regulate both positively and negatively the IFN response. Aim of this review is to briefly summarize the existing evidence and the molecular bases of mitochondria control on inflammations and the relevance for human diseases.

MATERIALS AND METHODS

This review was created investigating PUBMED databases using the following terms: mitochondria AND inflammation OR mitochondria AND apoptosis OR mitochondria AND caspases OR mitochondria AND inflammasome OR mitochondria and autophagy. A total of 1313 papers were selected. The resulting list of publications was disposed of all articles without information relevant to the outcomes of interest by screening of abstracts. In total, 115 publications were included in the qualitative data analysis.

cGAS-STING SIGNALING PATHWAY

Among the mitochondrial DAMPs, mtDNA leaked into the cytosol can function as endogenous ligand for cGAS and induce cGAS-STING signaling-mediated inflammation[18]. Mitochondrial RNA species in cytosol can lead to IFN induction as well, through the activation of the mitochondrial antiviral-signaling protein (MAVS): therefore, outside the mitochondrion, nucleic acids can be the cause of various inflammation-related diseases[19]. MtDNA enters the cytosol due to mitochondrial outer membrane permeabilization (MOMP) or other mitochondrial dysfunctions[20,21]. Apoptotic caspases, however, significantly inhibit this process[22-24] (Figure 1, panel A).

MtDNA, naked double-strand (ds) DNA, and dsDNA associated with proteins that induce specific curvature – such as high mobility group box 1 (HMGB1) and TFAM, a mitochondrial transcription factor – are potent activators of cGAS: in contrast, histone-bound nuclear dsDNA exhibits weak activation of cGAS[25,26]. These findings indicate a system that prevents unnecessary activation of cGAS under normal conditions while remaining able to start inflammatory reactions in critical situations[27,28]. Intracellular viral infections frequently lead to mitochondrial dysfunction and/or MOMP, ultimately resulting in the release of mtDNA, which is particularly relevant in the context of pathogen virulence[29-33]. Two proteins, BAX1 and BAK1, are usually responsible for triggering the release of mtDNA during MOMP, leading to a loss of soluble electron transport chain components like cytochrome c[34,35]. This affects mitochondrial respiration and hampers the maintaining of metabolic balance across the IMM[36]. In this context, the pores formed by BAX and BAK1 in the OMM cause the expulsion of the IMM into the cytosol, resulting in its degradation and the release of mtDNA[34,35]. A considerable amount of mtDNA that exits mitochondria seems to remain associated with the permeabilized organelles rather than circulating freely in the cytoplasm[34]. Recent research indicates that the relative levels of BAK1 and BAX significantly regulate the rate of mtDNA release during MOMP[36,37]. A variety of physiological and pathological contexts have documented “minority MOMP,” in which only a few mitochondria of the cell experience MOMP and there is no involvement of RCD[38,39]. The activation of DNA fragmentation factor subunit-β (DFFB)[38] induces DNA damage, while mtDAMPs[40,41] facilitate inflammatory responses. Additionally, mitochondrial fusion resulting from BCL-2 redistribution[42] actively inhibits this type of MOMP and this may additionally stimulate inflammatory pathways. Recent reports indicate that mtDNA release may occurs independently of BAK1/BAX, for example through execution of large macropores at the mitochondrial membrane by voltage-dependent anion channel (VDAC) oligomers[43,44] (Figure 1, panel B).

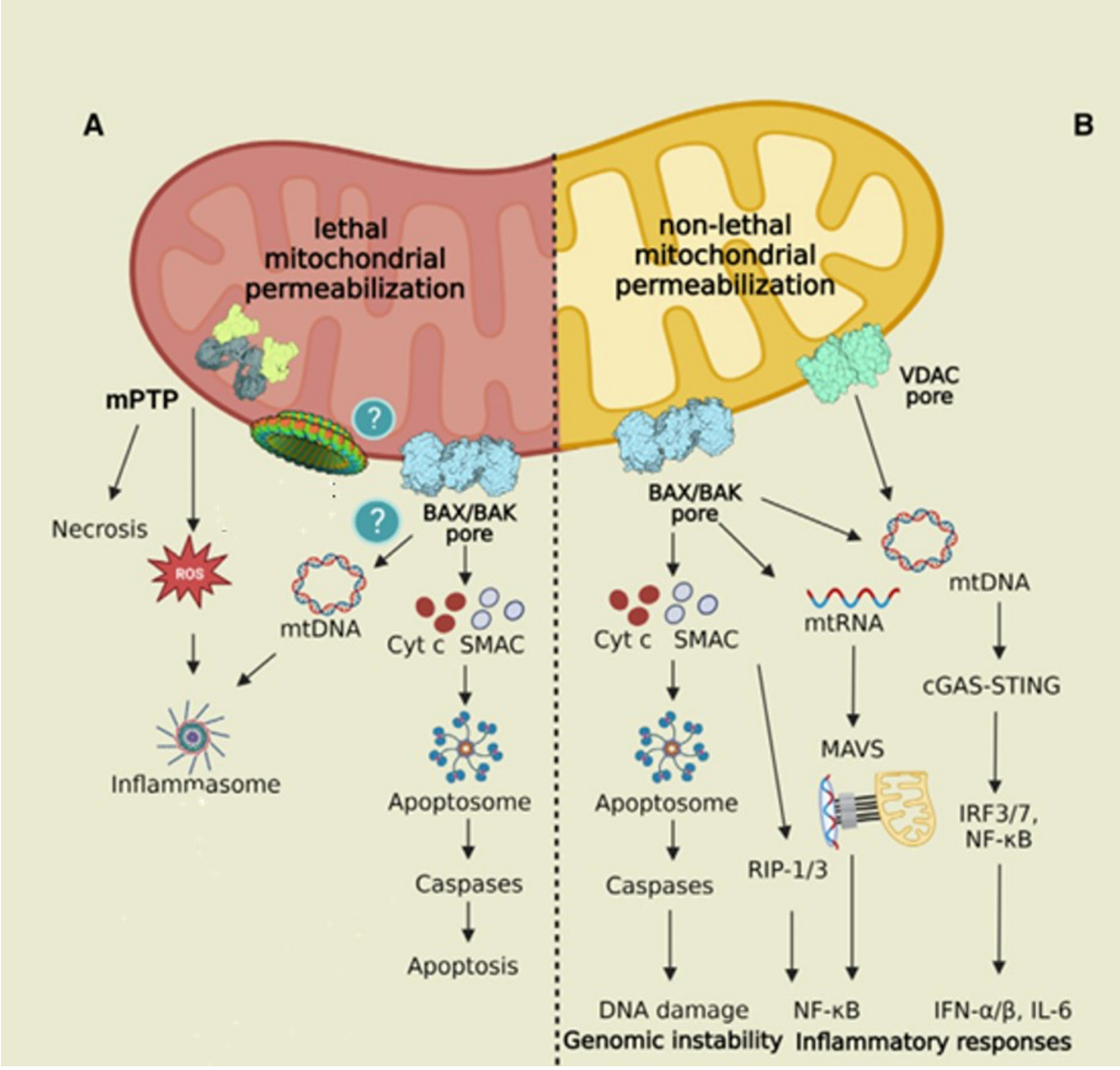

Figure 1. Mitochondrial permeabilization in cell death and inflammation.
When mitochondrial pores open, mitochondrial contents enter the cytosol, which can cause cell dismissal (A) or non-lethal inflammatory signaling (B). BAX and BAK help generate persistent protein-lipid holes at mitochondria during apoptosis, releasing apoptogenic substances.
Caspase activation, along with mtDNA, is involved in the cGAS/STING pathway and inflammasome activation. The release of cytochrome c from mitochondria through a mechanism that remains inadequately characterized, potentially establishing a positive feedback loop that enhances apoptosome activation and the caspase cascade. mPTP disrupts electron transport, leading to increased reactive oxygen species (ROS) production, ATP depletion, and subsequent necrotic cell death. In the context of non-lethal mitochondrial permeabilization, mitochondrial content resulting from BAX/BAK-mediated minority mitochondrial outer membrane permeabilization (MOMP) can initiate various pathways, including (1) prooncogenic DNA damage through cytochrome c and sublethal caspase activation; (2) activation of the NF-kB pathway and maturation of IL-1b, an inflammatory response mediated by released SMAC; (3) release of mtRNA, which can activate MAVS on the mitochondrial surface, subsequently activating MDA5, leading to TBK1 activation and inflammation; and (4) release of mtDNA in the absence of caspase activation, resulting in robust STING pathway activation for cytokine production and inflammation.

This is particularly true for mild mitochondrial stress, unable to cause MOMP and RCD. The notion that mitochondrial permeability transition pore (MPT) contributes to mtDNA leakage is supported by evidence indicating that various VDAC isoforms modulate MPT-induced regulated necrosis[45]. DsDNA can diffuse through pores of at least 3 nm in diameter[46] while MPT generates pores ranging from 1.5 to 3

nm[47]. The presence of 1 to 9 open MPT complexes per mitochondrion suggests that MPT functions efficiently. Conversely, the estimated count of BAX-BAK1 oligomers involved in MOMP exceeds 20[48]. Both MPT and MOMP may, therefore, contribute to mtDNA release. In conclusion, the activation of cGAS/STING1 can elicit strong inflammatory responses triggered by mtDNA, especially when the activation of apoptotic caspases is restricted[49].

INFLAMMASOME SIGNALING

Inflammasomes, which are supramolecular complexes that activate caspases (CASP) 1, 4, and 5, can also be stimulated by cytoplasmic mtDNA, a potent cGAS agonist[50]. Various chemical patterns associated with microorganisms consistently activate the inflammasome, particularly through NLRP3 sensing component[51]. MtDNA released during mitochondrial dysfunction is recognized as a key activator of the NLRP3 inflammasome, mainly through ROS-dependent mechanisms[51]. For optimal NLRP3 inflammatory signaling, traditional activators such as lipopolysaccharides (LPS) and ATP need the neo synthesis of mtDNA[52]. Experimental methods that reduce mtDNA also impact oxidative phosphorylation by diminishing the levels of specific electron transport chain components[53]. This indicates that the inhibition of NLRP3 signaling following mtDNA depletion may be occasionally attributed to intracellular ATP deficiency, or at a minimum, may worsen it. Recent studies have shown that the activation of BAX and BAK1 enhances the degradation of the inhibitor of apoptosis protein (IAP), subsequently promoting CASP8-dependent NLRP3 inflammasome activation[54,55]. Additionally, they initiate a supramolecular complex known as the ripoptosome, which operates independently of NLRP3 and results in the maturation of IL-1β[55].

In summary, mitochondrial ROS and mtDNA serve as essential DAMPs for inflammasome activation, generating a signal cascade able to regulate the molecular mechanisms of RCD.

ADDITIONAL PRO-INFLAMMATORY MOLECULES

Other cellular PRRs include Toll-like receptor 9 (TLR9) and the advanced glycosylation end product-specific receptor (AGER, or RAGE)[56,57]. Both free and protein-bound mtDNA effectively activate these receptors. Unbound mtDNA acts primarily as an agonist for TLR9, due to its close resemblance to bacterial DNA (the typical TLR9 activator) and the low methylation of CpG islands in the mitochondrial genome[58,59]. When mtDNA is associated with HMGB1 or TFAM, it exhibits immunostimulatory properties upon interacting with TLR9 or AGER[60]. In response to various stressors, including the onset of inflammation, proteins are translocated from the nucleus to the cytoplasm[61]. Recombinant TFAM has been found to enhance cytokine release from primary microglial cells and cultured human monocytes. To activate these pathways, mtDNA must be released into the extracellular space, whether in a protein-bound or unbound form. In lasmacytoid dendritic cells, the activation of endosomal TLR9 have been shown to respond to the accumulation of cytoplasmic mtDNA evocated by slight mitochondrial dysfunction[61].

Four additional mitochondrial components – cytochrome c, cardiolipin, N-formyl peptides, and SMAC – have the potential to trigger inflammatory responses. In cultured human microglial cell models, extracellular cytochrome c demonstrates immunostimulatory effects that are dependent on TLR4[62]. It has been suggested that recombinant cytochrome c may induce arthritis in mice through mechanisms involving neutrophils and monocytes[63]. Also, ATP[64] and haem[65], produced by mitochondria, have been associated with various immunomodulatory effects when released extracellularly, including the activation of endothelial cells and microglia, as well as the release of IL-1β by macrophages[66]. These processes are mediated by NLRP3-dependent CASP1 activation, alongside NLRP3-independent activation of CASP4 and CASP5, in conjunction with regulated cell death (RCD)[67]. Haem functions as an agonist for TLR4 and AGER[65].

Cardiolipin is generally found in the mitochondrial matrix, while N-formyl peptides are in the IMM. Structural disruption caused by late-stage RCD results in cellular fragments that retain mitochondria. These fragments persist in degrading within the extracellular environment until they are internalized by specialized phagocytes[68]. Extracellular cardiolipin interacts with specific T cells, causing expression of the MHC class I-like molecule CD1d on antigen-presenting cells[69,70]. When released extracellular due to end-stage RCD, N-formyl peptides activate neutrophils by binding to formyl peptide receptor 1[56]. SMAC (diablo IAP-binding mitochondrial protein) plays a role in triggering antitumor immune responses and can directly alter T cell immunological responses[71].

REGULATION OF EXCESSIVE mtDAMP SIGNALING

Regulation of mtDAMP signaling is critical due to the involvement of MOMP in cellular differentiation, embryonic and postembryonic development, tissue homeostasis[28]. Consequently, multiple mechanisms have evolved to mitigate unwarranted inflammation triggered by mitochondria.

Apoptosis

During apoptosis, extensive MOMP leads to the formation of a cytosolic supramolecular platform that includes CASP9. CASP9 in turn activates CASP3, CASP6, and CASP7, playing a relevant role in regulating the kinetic of RCD and immunological manifestations[19,72].

Additionally, caspases trigger the externalization of phosphatidylserine on the surfaces of dying cells, which stimulate phagocytosis and the clearance of these cells[73,74]. Without an active phagocytic system and with inactive caspases, the shift from MOM to cell death is delayed[75]. This postponement may create an extended timeframe for the production and release of pro-inflammatory factors following MOMP[75].

Autophagy

The sublethal MOMP induces mitophagy, facilitating the clearance of permeabilized or dysfunctional mitochondria via lysosomes[76,77]. This process diminishes the availability of mitochondrial components, such as mtDNA and ROS for PRRs signaling or release into the extracellular environment during RCD. Mitophagy is able to either completely or partially suppress the cGAS signals generated by MOMP[78]. Increased cytosolic mtDAMP availability is frequently associated with genetic or pharmacological methods that suppress autophagy or diminish lysosomal degradation, mediated by enhanced signaling through TLR9, cGAS, and the inflammasome[79]. Experimental methods aimed at specifically inhibiting mitophagy, rather than autophagy broadly, have yielded comparable results. Active inflammasome signaling has been shown to trigger an NF-κB-dependent response that facilitates the autophagic removal of inflammasomes and the mitophagic removal of permeabilized mitochondria, likely serving as components of an adaptive pathway aimed at restoring inflammatory and cellular homeostasis[80]. Activation of the effectors of STING1 cascade is reported to enhance mitophagy through a comparable mechanism, particularly in the initial stages[81,82]. The key mitophagy gene PRKN has been shown to facilitate the ubiquitylation-dependent deactivation of BAK1, thereby contributing to the restoration of cellular homeostasis during sublethal MOMP[83,84]. Mitophagy inactivation occurs alongside significant inflammatory responses resulting from irreversible mitochondrial dysfunction, partially due to CASP1-dependent cleavage of PRKN triggered by intense inflammasome activity[85]. The packaging of mtDAMPs into mitochondria-derived vesicles (MDVs), released during mitochondrial quality control, may be inhibited by PRKN-dependent mitophagy, preventing potential inflammatory responses in adjacent cells[86]. These processes necessitate the suppression of mitophagy to proceed unregulated, potentially involving a feedforward loop that links significant mitochondrial dysfunction to substantial inflammasome activation and CASP1-dependent PRKN degradation[87]. During immunogenic cell death, autophagy is essential for effective ATP secretion and subsequent immunostimulation. This is primarily because effective autophagic responses can sustain intracellular ATP levels instead of directly affecting mitochondria. Apoptosis and autophagy represent molecular systems that have facilitated the retention of potentially harmful inflammatory signals during the co-evolution of mitochondria and host cells. Eukaryotic cells, however, manage inflammatory responses initiated by mitochondria through alternative mechanisms, such as the apparent mutual inhibition of cGAS and inflammasomes[88,89].

EXCESSIVE mtDAMP SIGNALING IN HUMAN DISEASES

Patients with systemic lupus erythematosus (SLE) exhibited increased blood levels of oxidized mtDNA with activation of type I interferon responses[90]. A greater risk of Crohn's disease is associated with pathogenic variants in *ATG16L1* gene, encoding a vital component of the autophagy machinery. This aligns with the role of ATG16L1 protein in preventing inflammation and the build-up of damaged mitochondria, which contributes to the function of Paneth cells[91]. Individuals diagnosed with Crohn's disease

exhibit dysfunction in Paneth cells within their ileal tissue[92], as confirmed in mice models[93,94]. Patients diagnosed with silicosis or interstitial lung disease exhibit elevated levels of CXCL10, a chemokine stimulated by type I interferon signaling[95]. Additionally, there are increased levels of STING1 and phosphorylation of its associated effectors, TBK1 and IRF3[95]. Chronic obstructive pulmonary disease is associated with elevated levels of circulating mtDNA, inflammatory cytokines and ROS overproduction[96]. Patients with acute kidney injury show hyperactivation of STING1 in their renal tubules[97]. In chronic kidney disease, lower levels of TFAM expression correlate with CGAS and STING1 overexpression[98]. The co-deletion of Pink1 and Prkn disrupts mitophagy, worsening acute renal injury induced by ischemia in mice[99]. Missense mutations in *PINK1* and *PRKN* cause familial Parkinson's disease and are associated with elevated blood levels of inflammatory cytokines and mtDNA[100]. Microglial cells that ingest mtDNA from deceased neurons trigger inflammatory responses associated with Alzheimer's disease[100]. Furthermore, post-mortem cerebral tissues from patients with Alzheimer's disease show signs of mitophagy suppression and accumulation of damaged mitochondria. Stimulation of mitophagy has been shown to mitigate the progression of the disease in a rat model of Alzheimer's disease[101]. These findings strongly suggest a potential link between mitochondrial dysfunction and various inflammatory diseases.

For primary mitochondrial diseases, mutations in *PNPT1* gene, involved in mitochondrial double stranded RNA suppression, causes a neurodegenerative disorder characterized by the accumulation of these RNA species in patients' fibroblasts, resulting in an enhanced type I-IFN response[102]. These species subsequently activate the RLR melanoma differentiation-associated protein 5 (MDA5; also referred to as IFIH1) through BAX-BAK1-mediated MOMP[102].

Recently, defects in ATAD3A, a mitochondrial protein involved in mtDNA maintenance, and dysfunction in TOP1MT, a regulator of mtDNA, have been reported to produce an enhanced interferon response[103,104].

INADEQUATE mtDAMP SIGNALING

Dysfunctional mtDAMP signaling affects the pathophysiology of viral infections and cancer. Inhibition of MOMP or the inflammatory responses induced by MOMP leads to an increase in viral persistence and tumor growth[105]. Hyperactivation of autophagy in cancer cells or the production of viral proteins can inhibit several components of cGAS/STING pathway[106]. For example, ICP27, a component of HSV-1 pathogenicity, inhibits STING1 and TBK[105]. The ability of the latter to activate NF-κB, rather than IRF3, is essential for the regulation of infection in mice[107]. Additionally, the X protein produced by Hepatitis B virus causes degradation of cellular cGAS[108]. Under these conditions, the quantitative measurement of mtDAMP signaling's role in promoting pathogen control through the induction of inflammatory responses remains unassessed. Autophagic anomalies resulting in decreased ATP secretion during immunogenic cell death promote malignant transformation, a process closely regulated by immunosurveillance, in various immunocompetent mouse models of early oncogenesis[109]. The observed anomalies are associated with of myeloid cells dysfunction within the tumor microenvironment, which further facilitates tumoral cells resistance to various chemotherapeutic agents that induce antitumor immunity, such as oxaliplatin and anthracyclines[110].

THERAPEUTIC PROSPECTIVE

The overall incidence of primary mitochondrial disease is uncertain but has been estimated to be as frequent as 1 in 5,000 births, causing debilitating, often fatal, diseases and placing a significant financial burden on healthcare and social support services. There is currently no cure for these diseases. Moreover, mitochondrial dysfunctions are increasingly recognized to have important roles in abnormal innate immune responses, and research on this field has expanded dramatically in the last years. Despite an increasing number of studies has highlighted the relationship between secondary mitochondrial dysfunction and inflammation in different pathological conditions (Alzheimer, Multiple Sclerosis, Parkinson and cancer), whether inflammation suppresses or exacerbates disease pathology is still unclear[111]. Primary inflammatory disorders such as SLE are usually treated with drugs targeting PRRs or cGAS-STING cascade (for example STING1 agonists), or blocking the effector phase of inflammation (cytokine-neutralizing drugs). However, as novel mitopathogenic mechanisms are being uncovered across several medical disciplines, an increasing knowledge of the link between mitochondria and innate immune response

and inflammation may also provide new opportunities for diagnosis, therapy, prevention in various domains of medicine. The potential application of mitochondrial-targeting medications for inflammation reduction has in fact been minimally explored. The limited availability of pharmacological treatments targeting mitochondrial functions, such as MOMP and MPT, may be attributed to the nascent stage of research in this field. Research is being conducted on BAX inhibitors as cytoprotective agents to prevent cardiovascular diseases[112,113]. Pharmacological BAX inhibitors are expected to limit mitochondrial outer membrane permeabilization (MOMP) and consequently mitigate mitochondria-driven inflammatory responses[112,113]. However, recent studies indicate that these inhibitors may accelerate MOMP-driven mtDNA release, particularly in BAK1-competent cancer cells, without substantially affecting the kinetics of caspase activation. This may offer an opportunity to initiate cGAS signaling before the caspase-dependent cleavage and subsequent inactivation of cGAS[114]. Cyclosporine A in humans, a medication targeting PPIF with significant MPT-inhibitory properties, is commonly utilized as an immunosuppressive agent for the treatment of autoimmune disorders and the prevention of transplant rejection. Cyclosporine A binds the PPIF-like cytosolic protein PPIA, which subsequently inhibits calcineurin to reduce lymphocyte activity[115]. However, part of the pharmacological effect of this drug may be related to MPT inhibition, preventing mtDNA leakage and inflammatory cascade.

CONCLUSIONS

In conclusion, while mitochondria are recognized as key regulators of inflammation, further research is necessary to address unresolved issues and overcome existing challenges, with the primary objective of modulating inflammatory responses in patients through the focus on mitochondrial processes.

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ORCID ID
Diego Martinelli - 0000-0002-9324-2871

REFERENCES

1. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, Kaser A, Peyrin-Biroulet L, Danese S. Crohn's disease. Nat Rev Dis Prim 2020; 6: 22.
2. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol 2022; 22: 657-673.
3. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. Nat Rev Cardiol 2021; 18: 666-82.

4. Basso PJ, Andrade-Oliveira V, Camara NOS. Targeting immune cell metabolism in kidney diseases. Nat Rev Nephrol 2021; 17: 465-80.
5. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol 2011; 29: 235-71.
6. Mantovani A, Ponzetta A, Inforzato A, Jaillon S Innate immunity, inflammation and tumour progression: double-edged swords. J Intern Med 2019; 285: 524-32.
7. Galluzzi L, Humeau J, Buqué A, Zitvogel L, Kroemer G. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. Nat Rev Clin Oncol 2020; 17: 725-41.
8. Marchi S, Guilbaud E, Tait SWG, Yamazaki T, Galluzzi L. Mitochondrial control of inflammation. Nat Rev Immunol 2023; 23: 159-173.
9. Petroni G, Buqué A, Coussens LM, Galluzzi L. Targeting oncogene and non-oncogene addiction to inflame the tumour microenvironment. Nat Rev Drug Discov 2022; 21: 440-62.
10. Rodriguez-Ruiz ME, Vitale I, Harrington KJ, Melero I, Galluzzi L. Immunological impact of cell death signaling driven by radiation on the tumor microenvironment. Nat Immunol 2020; 21: 120-34.
11. Zengeler KE, Lukens JR. Innate immunity at the crossroads of healthy brain maturation and neurodevelopmental disorders. Nat Rev Immunol 2021; 21: 454-68.
12. Kroemer G, Galassi C, Zitvogel L, Galluzzi L. Immunogenic cell stress and death. Nat Immunol 2022; 23: 487-500.
13. Vanpouille-Box C, Hoffmann JA, Galluzzi L. Pharmacological modulation of nucleic acid sensors - therapeutic potential and persisting obstacles. Nat Rev Drug Discov 2019; 18: 845-67.
14. Roger AJ, Muñoz-Gómez SA, Kamikawa R. The origin and diversification of mitochondria. Curr Biol 2017; 27: R1177-R1192.
15. Harapas CR, Idiiatullina E, Al-Azab M, Hrovat-Schaale K, Reygaerts T, Steiner A, Laohamonthonkul P, Davidson S, Yu CH, Booty L, Masters SL. Organellar homeostasis and innate immune sensing. Nat Rev Immunol 2022; 22: 535-549.
16. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, Annicchiarico-Petruzzelli M, Antonov AV, Arama E, Baehrecke EH, Barlev NA, Bazan NG, Bernassola F, Bertrand MJM, Bianchi K, Blagosklonny MV, Blomgren K, Borner C, Boya P, Brenner C, Campanella M, Candi E, Carmona-Gutierrez D, Cecconi F, Chan FK, Chandel NS, Cheng EH, Chipuk JE, Cidlowski JA, Ciechanover A, Cohen GM, Conrad M, Cubillos-Ruiz JR, Czabotar PE, D'Angiolella V, Dawson TM, Dawson VL, De Laurenzi V, De Maria R, Debatin KM, DeBerardinis RJ, Deshmukh M, Di Daniele N, Di Virgilio F, Dixit VM, Dixon SJ, Duckett CS, Dynlacht BD, El-Deiry WS, Elrod JW, Fimia GM, Fulda S, García-Sáez AJ, Garg AD, Garrido C, Gavathiotis E, Golstein P, Gottlieb E, Green DR, Greene LA, Gronemeyer H, Gross A, Hajnoczky G, Hardwick JM, Harris IS, Hengartner MO, Hetz C, Ichijo H, Jäättelä M, Joseph B, Jost PJ, Juin PP, Kaiser WJ, Karin M, Kaufmann T, Kepp O, Kimchi A, Kitsis RN, Klionsky DJ, Knight RA, Kumar S, Lee SW, Lemasters JJ, Levine B, Linkermann A, Lipton SA, Lockshin RA, López-Otín C, Lowe SW, Luedde T, Lugli E, MacFarlane M, Madeo F, Malewicz M, Malorni W, Manic G, Marine JC, Martin SJ, Martinou JC, Medema JP, Mehlen P, Meier P, Melino S, Miao EA, Molkentin JD, Moll UM, Muñoz-Pinedo C, Nagata S, Nuñez G, Oberst A, Oren M, Overholtzer M, Pagano M, Panaretakis T, Pasparakis M, Penninger JM, Pereira DM, Pervaiz S, Peter ME, Piacentini M, Pinton P, Prehn JHM, Puthalakath H, Rabinovich GA, Rehm M, Rizzuto R, Rodrigues CMP, Rubinsztein DC, Rudel T, Ryan KM, Sayan E, Scorrano L, Shao F, Shi Y, Silke J, Simon HU, Sistigu A, Stockwell BR, Strasser A, Szabadkai G, Tait SWG, Tang D, Tavernarakis N, Thorburn A, Tsujimoto Y, Turk B, Vanden Berghe T, Vandenabeele P, Vander Heiden MG, Villunger A, Virgin HW, Vousden KH, Vucic D, Wagner EF, Walczak H, Wallach D, Wang Y, Wells JA, Wood W, Yuan J, Zakeri Z, Zhivotovsky B, Zitvogel L, Melino G, Kroemer G. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018. Cell Death Differ 2018; 25: 486-541.
17. Bader V, Winklhofer KF. Mitochondria at the interface between neurodegeneration and neuroinflammation. Semin Cell Dev Biol 2020; 99: 163-71.
18. Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science 2013; 339: 786-91.
19. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. Nat Rev Immunol 2021; 21: 548-69.
20. Li XD, Wu J, Gao D, Wang H, Sun L, Chen ZJ. Pivotal roles of cGAS-cGAMP signaling in antiviral defense and immune adjuvant effects. Science 2013; 341: 1390-4.
21. Civril F, Deimling T, de Oliveira Mann CC, Ablasser A, Moldt M, Witte G, Hornung V, Hopfner KP. Structural mechanism of cytosolic DNA sensing by cGAS. Nature 2013; 498: 332-7.
22. White MJ, McArthur K, Metcalf D, Lane RM, Cambier JC, Herold MJ, van Delft MF, Bedoui S, Lessene G, Ritchie ME, Huang DC, Kile BT. Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. Cell 2014; 159: 1549-62.
23. Rongvaux A, Jackson R, Harman CC, Li T, West AP, de Zoete MR, Wu Y, Yordy B, Lakhani SA, Kuan CY, Taniguchi T, Shadel GS, Chen ZJ, Iwasaki A, Flavell RA. Apoptotic caspases prevent the induction of type I interferons by mitochondrial DNA. Cell 2014; 159: 1563-77.
24. West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, Bestwick M, Duguay BA, Raimundo N, MacDuff DA, Kaech SM, Smiley JR, Means RE, Iwasaki A, Shadel GS. Mitochondrial DNA stress primes the antiviral innate immune response. Nature 2015; 520: 553-7.
25. Andreeva L, Hiller B, Kostrewa D, Lässig C, de Oliveira Mann CC, Jan Drexler D, Maiser A, Gaidt M, Leonhardt H, Hornung V, Hopfner KP. cGAS senses long and HMGB/TFAM-bound U-turn DNA by forming protein-DNA ladders. Nature 2017; 549: 394-8.
26. Zierhut C, Yamaguchi N, Paredes M, Luo JD, Carroll T, Funabiki H. The cytoplasmic DNA sensor cGAS promotes mitotic cell death. Cell 2019; 178: 302-15.e323.
27. 27 Li T, Huang T, Du M, Chen X, Du F, Ren J, Chen ZJ. Phosphorylation and chromatin tethering prevent cGAS activation during mitosis. Science 2021; 371: eabc5386.
28. Fuchs Y, Steller H. Live to die another way: modes of programmed cell death and the signals emanating from dying cells. Nat Rev Mol Cell Biol 2015; 16: 329-44.
29. Domizio JD, Gulen MF, Saidoune F, Thacker VV, Yatim A, Sharma K, Nass T, Guenova E, Schaller M, Conrad C, Goepfert C, de Leval L, Garnier CV, Berezowska S, Dubois A, Gilliet M, Ablasser A. The cGAS-STING pathway drives type I IFN immunopathology in COVID-19. Nature 2022; 603: 145-51.

30. Wiens KE, Ernst JD. The mechanism for type I interferon induction by mycobacterium tuberculosis is bacterial strain-dependent. PLoS Pathog 2016; 12: e1005809.
31. Sun B, Sundström KB, Chew JJ, Bist P, Gan ES, Tan HC, Goh KC, Chawla T, Tang CK, Ooi EE. Dengue virus activates cGAS through the release of mitochondrial DNA. Sci Rep 2017; 7: 3594.
32. Zhou CM, Wang B, Wu Q, Lin P, Qin SG, Pu QQ, Yu XJ, Wu M. Identification of cGAS as an innate immune sensor of extracellular bacterium Pseudomonas aeruginosa. iScience 2021; 24: 101928.
33. Moriyama M, Koshiba T, Ichinohe T. Influenza A virus M2 protein triggers mitochondrial DNA-mediated antiviral immune responses. Nat Commun 2019; 10: 4624.
34. McArthur K, Whitehead LW, Heddleston JM, Li L, Padman BS, Oorschot V, Geoghegan ND, Chappaz S, Davidson S, San Chin H, Lane RM, Dramicanin M, Saunders TL, Sugiana C, Lessene R, Osellame LD, Chew TL, Dewson G, Lazarou M, Ramm G, Lessene G, Ryan MT, Rogers KL, van Delft MF, Kile BT. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. Science 2018; 359: eao6047.
35. Riley JS, Quarato G, Cloix C, Lopez J, O'Prey J, Pearson M, Chapman J, Sesaki H, Carlin LM, Passos JF, Wheeler AP, Oberst A, Ryan KM, Tait SW. Mitochondrial inner membrane permeabilisation enables mtDNA release during apoptosis. EMBO J 2018; 37: e99238.
36. Bock FJ, Tait SWG. Mitochondria as multifaceted regulators of cell death. Nat Rev Mol Cell Biol 2020; 21: 85-100.
37. Cosentino K, Hertlein V, Jenner A, Dellmann T, Gojkovic M, Peña-Blanco A, Dadsena S, Wajngarten N, Danial JSH, Thevathasan JV, Mund M, Ries J, Garcia-Saez AJ. The interplay between BAX and BAK tunes apoptotic pore growth to control mitochondrial-DNA-mediated inflammation. Mol Cell 2022; 82: 933-49.e939.
38. Ichim G, Lopez J, Ahmed SU, Muthalagu N, Giampazolias E, Delgado ME, Haller M, Riley JS, Mason SM, Athineos D, Parsons MJ, van de Kooij B, Bouchier-Hayes L, Chalmers AJ, Rooswinkel RW, Oberst A, Blyth K, Rehm M, Murphy DJ, Tait SWG. Limited mitochondrial permeabilization causes DNA damage and genomic instability in the absence of cell death. Mol Cell 2015; 57: 860-72.
39. Galluzzi L, Kepp O, Trojel-Hansen C, Kroemer G. Non-apoptotic functions of apoptosis-regulatory proteins. EMBO Rep 2012; 13: 322-30.
40. Brokatzky D, Dörflinger B, Haimovici A, Weber A, Kirschnek S, Vier J, Metz A, Henschel J, Steinfeldt T, Gentle IE, Häcker G. A non-death function of the mitochondrial apoptosis apparatus in immunity. EMBO J 2019; 38: e100907.
41. Tigano M, Vargas DC, Tremblay-Belzile S, Fu Y, Sfeir A.Nuclear sensing of breaks in mitochondrial DNA enhances immune surveillance. Nature 2021; 591: 477-81.
42. Cao K, Riley JS, Heilig R, Montes-Gómez AE, Vringer E, Berthenet K, Cloix C, Elmasry Y, Spiller DG, Ichim G, Campbell KJ, Gilmore AP, Tait SWG. Mitochondrial dynamics regulate genome stability via control of caspase-dependent DNA damage. Dev Cell 2022; 57: 1211-25.e1216.
43. McArthur K, Whitehead LW, Heddleston JM, Li L, Padman BS, Oorschot V, Geoghegan ND, Chappaz S, Davidson S, San Chin H, Lane RM, Dramicanin M, Saunders TL, Sugiana C, Lessene R, Osellame LD, Chew TL, Dewson G, Lazarou M, Ramm G, Lessene G, Ryan MT, Rogers KL, van Delft MF, Kile BT. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. Science 2018; 359: eaao6047.
44. Kim J, Gupta R, Blanco LP, Yang S, Shteinfer-Kuzmine A, Wang K, Zhu J, Yoon HE, Wang X, Kerkhofs M, Kang H, Brown AL, Park SJ, Xu X, Zandee van Rilland E, Kim MK, Cohen JI, Kaplan MJ, Shoshan-Barmatz V, Chung JH. VDAC oligomers form mitochondrial pores to release mtDNA fragments and promote lupus-like disease. Science 2019; 366: 1531-6.
45. Xian H, Watari K, Sanchez-Lopez E, Offenberger J, Onyuru J, Sampath H, Ying W, Hoffman HM, Shadel GS, Karin M. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. Immunity 2022; 55: 1370-85.e8.
46. Kruglov AG, Kharechkina ES, Nikiforova AB, Odinokova IV, Kruglova SA. Dynamics of the permeability transition pore size in isolated mitochondria and mitoplasts. FASEB J 2020; 34: 8762-70.
47. Huang R, Ning Q, Zhao J, Zhao X, Zeng L, Yi Y, Tang S. Targeting STING for cancer immunotherapy: From mechanisms to translation. Int Immunopharmacol 2022; 113: 109304.
48. Xu Q, Xing J, Wang S, Peng H, Liu Y. The role of the cGAS-STING pathway in metabolic diseases. Heliyon 2024; 10: e33093.
49. Danthi P. Viruses and the Diversity of Cell Death. Annu Rev Virol 2016; 3: 533-553.
50. Ross C, Chan AH, von Pein JB, Maddugoda MP, Boucher D, Schroder K. Inflammatory caspases: toward a unified model for caspase activation by inflammasomes. Annu Rev Immunol 2022; 40: 249-69.
51. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ, Vergnes L, Ojcius DM, Rentsendorj A, Vargas M, Guerrero C, Wang Y, Fitzgerald KA, Underhill DM, Town T, Arditi M. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 2012; 36: 401-14.
52. Zhong Z, Liang S, Sanchez-Lopez E, He F, Shalapour S, Lin XJ, Wong J, Ding S, Seki E, Schnabl B, Hevener AL, Greenberg HB, Kisseleva T, Karin M. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. Nature 2018; 560: 198-203.
53. Billingham LK, Stoolman JS, Vasan K, Rodriguez AE, Poor TA, Szibor M, Jacobs HT, Reczek CR, Rashidi A, Zhang P, Miska J, Chandel NS. Mitochondrial electron transport chain is necessary for NLRP3 inflammasome activation. Nat Immunol 2022; 23: 692-704.
54. Vince JE, De Nardo D, Gao W, Vince AJ, Hall C, McArthur K, Simpson D, Vijayaraj S, Lindqvist LM, Bouillet P, Rizzacasa MA, Man SM, Silke J, Masters SL, Lessene G, Huang DCS, Gray DHD, Kile BT, Shao F, Lawlor KE. The mitochondrial apoptotic effectors BAX/BAK activate caspase-3 and -7 to trigger NLRP3 inflammasome and caspase-8 driven IL-1β activation. Cell Rep 2018; 25: 2339-53.e4.
55. Chauhan D, Bartok E, Gaidt MM, Bock FJ, Herrmann J, Seeger JM, Broz P, Beckmann R, Kashkar H, Tait SWG, Müller R, Hornung V. BAX/BAK-induced apoptosis results in caspase-8-dependent IL-1β maturation in macrophages. Cell Rep 2018; 25: 2354-68. e5.
56. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser CJ. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010; 464: 104-7.

57. Tian J, Avalos AM, Mao SY, Chen B, Senthil K, Wu H, Parroche P, Drabic S, Golenbock D, Sirois C, Hua J, An LL, Audoly L, La Rosa G, Bierhaus A, Naworth P, Marshak-Rothstein A, Crow MK, Fitzgerald KA, Latz E, Kiener PA, Coyle AJ. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol 2007; 8: 487-96.
58. Mangelinck A, Mann C. DNA methylation and histone variants in aging and cancer. Int Rev Cell Mol Biol 2021; 364: 1-110.
59. Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, Matsumoto M, Hoshino K, Wagner H, Takeda K, Akira S. A Toll-like receptor recognizes bacterial DNA. Nature 2000; 408: 740-5.
60. Tian J, Avalos AM, Mao SY, Chen B, Senthil K, Wu H, Parroche P, Drabic S, Golenbock D, Sirois C, Hua J, An LL, Audoly L, La Rosa G, Bierhaus A, Naworth P, Marshak-Rothstein A, Crow MK, Fitzgerald KA, Latz E, Kiener PA, Coyle AJ. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol 2007; 8: 487-96.
61. Liu Y, Yan W, Tohme S, Chen M, Fu Y, Tian D, Lotze M, Tang D, Tsung A. Hypoxia induced HMGB1 and mitochondrial DNA interactions mediate tumor growth in hepatocellular carcinoma through Toll-like receptor 9. J Hepatol 2015; 63: 114-21.
62. Gouveia A, Bajwa E, Klegeris A. Extracellular cytochrome c as an intercellular signaling molecule regulating microglial functions. Biochim Biophys Acta Gen Subj 2017; 1861: 2274-81.
63. Pullerits R, Bokarewa M, Jonsson IM, Verdrengh M, Tarkowski A. Extracellular cytochrome c, a mitochondrial apoptosis-related protein, induces arthritis. Rheumatology 2005; 44: 32-9.
64. Kepp O, Bezu L, Yamazaki T, Di Virgilio F, Smyth MJ, Kroemer G, Galluzzi L. ATP and cancer immunosurveillance. EMBO J 2021; 40: e108130.
65. Lin S, Yin Q, Zhong Q, Lv FL, Zhou Y, Li JQ, Wang JZ, Su BY, Yang QW. Heme activates TLR4-mediated inflammatory injury via MyD88/TRIF signaling pathway in intracerebral hemorrhage. J Neuroinflamm 2012; 9: 46.
66. Ghiringhelli F, Apetoh L, Tesniere A, Aymeric L, Ma Y, Ortiz C, Vermaelen K, Panaretakis T, Mignot G, Ullrich E, Perfettini JL, Schlemmer F, Tasdemir E, Uhl M, Génin P, Civas A, Ryffel B, Kanellopoulos J, Tschopp J, André F, Lidereau R, McLaughlin NM, Haynes NM, Smyth MJ, Kroemer G, Zitvogel L. Activation of the NLRP3 inflammasome in dendritic cells induces IL-1β-dependent adaptive immunity against tumors. Nat Med 2009; 15: 1170-8.
67. Bolívar BE, Brown-Suedel AN, Rohrman BA, Charendoff CI, Yazdani V, Belcher JD, Vercellotti GM, Flanagan JM, Bouchier-Hayes L. Noncanonical roles of caspase-4 and caspase-5 in heme-driven IL-1β release and cell death. J Immunol 2021; 206: 1878-89.
68. Boada-Romero E, Martinez J, Heckmann BL, Green DR. The clearance of dead cells by efferocytosis. Nat Rev Mol Cell Biol 2020; 21: 398-414.
69. Leslie DS, Dascher CC, Cembrola K, Townes MA, Hava DL, Hugendubler LC, Mueller E, Fox L, Roura-Mir C, Moody DB, Vincent MS, Gumperz JE, Illarionov PA, Besra GS, Reynolds CG, Brenner MB.. Serum lipids regulate dendritic cell CD1 expression and function. Immunology 2008; 125: 289-301.
70. Dieudé M, Striegl H, Tyznik AJ, Wang J, Behar SM, Piccirillo CA, Levine JS, Zajonc DM, Rauch J. Cardiolipin binds to CD1d and stimulates CD1d-restricted γδ T cells in the normal murine repertoire. J Immunol 2011; 186: 4771-81.
71. Rizk J, Kaplinsky J, Agerholm R, Kadekar D, Ivars F, Agace WW, Wong WW, Szucs MJ, Myers SA, Carr SA, Waisman A, Bekiaris V. SMAC mimetics promote NIK-dependent inhibition of CD4+ TH17 cell differentiation. Sci Signal 2019; 12: eaw3469.
72. Galluzzi L, López-Soto A, Kumar S, Kroemer G. Caspases connect cell-death signaling to organismal homeostasis. Immunity 2016; 44: 221-31.
73. Segawa K, Kurata S, Yanagihashi Y, Brummelkamp TR, Matsuda F, Nagata S. Caspase-mediated cleavage of phospholipid flippase for apoptotic phosphatidylserine exposure. Science 2014; 344: 1164-8.
74. Fadok VA, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM. Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. J Immunol 1992; 148: 2207-16.
75. Buqué A, Rodriguez-Ruiz ME, Fucikova J, Galluzzi L. Apoptotic caspases cut down the immunogenicity of radiation. Oncoimmunology 2019; 8: e1655364.
76. Lindqvist LM, Frank D, McArthur K, Dite TA, Lazarou M, Oakhill JS, Kile BT, Vaux DL. Autophagy induced during apoptosis degrades mitochondria and inhibits type I interferon secretion. Cell Death Differ 2018; 25: 784-96.
77. Galluzzi L, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cecconi F, Choi AM, Chu CT, Codogno P, Colombo MI, Cuervo AM, Debnath J, Deretic V, Dikic I, Eskelinen EL, Fimia GM, Fulda S, Gewirtz DA, Green DR, Hansen M, Harper JW, Jäättelä M, Johansen T, Juhasz G, Kimmelman AC, Kraft C, Ktistakis NT, Kumar S, Levine B, Lopez-Otin C, Madeo F, Martens S, Martinez J, Melendez A, Mizushima N, Münz C, Murphy LO, Penninger JM, Piacentini M, Reggiori F, Rubinsztein DC, Ryan KM, Santambrogio L, Scorrano L, Simon AK, Simon HU, Simonsen A, Tavernarakis N, Tooze SA, Yoshimori T, Yuan J, Yue Z, Zhong Q, Kroemer G. Molecular definitions of autophagy and related processes. EMBO J 2017; 36: 1811-36.
78. Yamazaki T, Kirchmair A, Sato A, Buqué A, Rybstein M, Petroni G, Bloy N, Finotello F, Stafford L, Navarro Manzano E, Ayala de la Peña F, García-Martínez E, Formenti SC, Trajanoski Z, Galluzzi L. Mitochondrial DNA drives abscopal responses to radiation that are inhibited by autophagy. Nat Immunol 2020; 21: 1160-71.
79. Oka T, Hikoso S, Yamaguchi O, Taneike M, Takeda T, Tamai T, Oyabu J, Murakawa T, Nakayama H, Nishida K, Akira S, Yamamoto A, Komuro I, Otsu K. Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure. Nature 2012; 485: 251-5.
80. Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, He F, Boassa D, Perkins G, Ali SR, McGeough MD, Ellisman MH, Seki E, Gustafsson AB, Hoffman HM, Diaz-Meco MT, Moscat J, Karin M. NF-κB restricts inflammasome activation via elimination of damaged mitochondria. Cell 2016; 164: 896-910.
81. Richter B, Sliter DA, Herhaus L, Stolz A, Wang C, Beli P, Zaffagnini G, Wild P, Martens S, Wagner SA, Youle RJ, Dikic I. Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria. Proc Natl Acad Sci U S A 2016; 113: 4039-44.
82. Di Rita A, Peschiaroli A, D Acunzo P, Strobbe D, Hu Z, Gruber J, Nygaard M, Lambrughi M, Melino G, Papaleo E, Dengjel J, El Alaoui S, Campanella M, Dötsch V, Rogov VV, Strappazzon F, Cecconi F. HUWE1 E3 ligase promotes PINK1/PARKIN-independent mitophagy by regulating AMBRA1 activation via IKKα. Nat Commun 2018; 9: 3755.
83. Bernardini JP, Brouwer JM, Tan IK, Sandow JJ, Huang S, Stafford CA, Bankovacki A, Riffkin CD, Wardak AZ, Czabotar PE, Lazarou M, Dewson G. Parkin inhibits BAK and BAX apoptotic function by distinct mechanisms during mitophagy. EMBO J 2019; 38: e99916.

84. Di Rita A, Peschiaroli A, D Acunzo P, Strobbe D, Hu Z, Gruber J, Nygaard M, Lambrughi M, Melino G, Papaleo E, Dengjel J, El Alaoui S, Campanella M, Dötsch V, Rogov VV, Strappazzon F, Cecconi F. HUWE1 E3 ligase promotes PINK1/PARKIN-independent mitophagy by regulating AMBRA1 activation via IKKα. Nat Commun 2018; 9: 3755.
85. Yu J, Nagasu H, Murakami T, Hoang H, Broderick L, Hoffman HM, Horng T. Inflammasome activation leads to caspase-1-dependent mitochondrial damage and block of mitophagy. Proc Natl Acad Sci U S A 2014; 111: 15514-9.
86. Cadete VJ, Deschênes S, Cuillerier A, Brisebois F, Sugiura A, Vincent A, Turnbull D, Picard M, McBride HM, Burelle Y. Formation of mitochondrial-derived vesicles is an active and physiologically relevant mitochondrial quality control process in the cardiac system. J Physiol 2016; 594: 5343-62.
87. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, Englert JA, Rabinovitch M, Cernadas M, Kim HP, Fitzgerald KA, Ryter SW, Choi AM. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011; 12: 222-30.
88. Wang Y, Ning X, Gao P, Wu S, Sha M, Lv M, Zhou X, Gao J, Fang R, Meng G, Su X, Jiang Z. Inflammasome activation triggers caspase-1-mediated cleavage of cGAS to regulate responses to DNA virus infection. Immunity 2017; 46: 393-404.
89. Corrales L, Woo SR, Williams JB, McWhirter SM, Dubensky TW Jr, Gajewski TF. Antagonism of the STING pathway via activation of the AIM2 inflammasome by intracellular DNA. J Immunol 2016; 196: 3191-8.
90. Caielli S, Athale S, Domic B, Murat E, Chandra M, Banchereau R, Baisch J, Phelps K, Clayton S, Gong M, Wright T, Punaro M, Palucka K, Guiducci C, Banchereau J, Pascual V. Oxidized mitochondrial nucleoids released by neutrophils drive type I interferon production in human lupus. J Exp Med 2016; 213: 697-713.
91. Cadwell K, Liu JY, Brown SL, Miyoshi H, Loh J, Lennerz JK, Kishi C, Kc W, Carrero JA, Hunt S, Stone CD, Brunt EM, Xavier RJ, Sleckman BP, Li E, Mizushima N, Stappenbeck TS, Virgin HW 4th. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature 2008; 456: 259-63.
92. Adolph TE, Tomczak MF, Niederreiter L, Ko HJ, Böck J, Martinez-Naves E, Glickman JN, Tschurtschenthaler M, Hartwig J, Hosomi S, Flak MB, Cusick JL, Kohno K, Iwawaki T, Billmann-Born S, Raine T, Bharti R, Lucius R, Kweon MN, Marciniak SJ, Choi A, Hagen SJ, Schreiber S, Rosenstiel P, Kaser A, Blumberg RS. Paneth cells as a site of origin for intestinal inflammation. Nature 2013; 503: 272-6.
93. Khaloian S, Rath E, Hammoudi N, Gleisinger E, Blutke A, Giesbertz P, Berger E, Metwaly A, Waldschmitt N, Allez M, Haller D. Mitochondrial impairment drives intestinal stem cell transition into dysfunctional Paneth cells predicting Crohn's disease recurrence. Gut 2020; 69: 1939-51.
94. Jackson DN, Panopoulos M, Neumann WL, Turner K, Cantarel BL, Thompson-Snipes L, Dassopoulos T, Feagins LA, Souza RF, Mills JC, Blumberg RS, Venuprasad K, Thompson WE, Theiss AL. Mitochondrial dysfunction during loss of prohibitin 1 triggers Paneth cell defects and ileitis. Gut 2020; 69: 1928-38.
95. Benmerzoug S, Rose S, Bounab B, Gosset D, Duneau L, Chenuet P, Mollet L, Le Bert M, Lambers C, Geleff S, Roth M, Fauconnier L, Sedda D, Carvalho C, Perche O, Laurenceau D, Ryffel B, Apetoh L, Kiziltunc A, Uslu H, Albez FS, Akgun M, Togbe D, Quesniaux VFJ. STING-dependent sensing of self-DNA drives silica-induced lung inflammation. Nat Commun 2018; 9: 5226.
96. Giordano L, Gregory AD, Pérez Verdaguer M, Ware SA, Harvey H, DeVallance E, Brzoska T, Sundd P, Zhang Y, Sciurba FC, Shapiro SD, Kaufman BA. Extracellular release of mitochondrial DNA: triggered by cigarette smoke and detected in COPD. Cells 2022; 11: 369.
97. Chung KW, Dhillon P, Huang S, Sheng X, Shrestha R, Qiu C, Kaufman BA, Park J, Pei L, Baur J, Palmer M, Susztak K. Mitochondrial damage and activation of the STING pathway lead to renal inflammation and fibrosis. Cell Metab 2019; 30: 784-99.e5.
98. Chen K, Feng L, Hu W, Chen J, Wang X, Wang L, He Y. Optineurin inhibits NLRP3 inflammasome activation by enhancing mitophagy of renal tubular cells in diabetic nephropathy. FASEB J 2019; 33: 4571-85.
99. Tang C, Han H, Yan M, Zhu S, Liu J, Liu Z, He L, Tan J, Liu Y, Liu H, Sun L, Duan S, Peng Y, Liu F, Yin XM, Zhang Z, Dong Z. PINK1-PRKN/PARK2 pathway of mitophagy is activated to protect against renal ischemia-reperfusion injury. Autophagy 2018; 14: 880-97.
100. Wilkins HM, Carl SM, Weber SG, Ramanujan SA, Festoff BW, Linseman DA, Swerdlow RH. Mitochondrial lysates induce inflammation and Alzheimer's disease-relevant changes in microglial and neuronal cells. J Alzheimers Dis 2015; 45: 305-18.
101. Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, Lautrup S, Hasan-Olive MM, Caponio D, Dan X, Rocktäschel P, Croteau DL, Akbari M, Greig NH, Fladby T, Nilsen H, Cader MZ, Mattson MP, Tavernarakis N, Bohr VA. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat Neurosci 2019; 22: 401-12.
102. Dhir A, Dhir S, Borowski LS, Jimenez L, Teitell M, Rötig A, Crow YJ, Rice GI, Duffy D, Tamby C, Nojima T, Munnich A, Schiff M, de Almeida CR, Rehwinkel J, Dziembowski A, Szczesny RJ, Proudfoot NJ. Mitochondrial double-stranded RNA triggers antiviral signalling in humans. Nature 2018; 560: 238-42.
103. Lepelley A, Della Mina E, Van Nieuwenhove E. Enhanced cGAS-STING-dependent interferon signaling associated with mutations in ATAD3A. J Exp Med 2021; 218: 10.
104. Al Khatib I, Deng J, Lei Y, Torres-Odio S, Rojas GR, Newman LE, Chung BK, Symes A, Zhang H, Huang SN, Pommier Y, Khan A, Shadel GS, West AP, Gibson WT, Shutt TE. Activation of the cGAS-STING innate immune response in cells with deficient mitochondrial topoisomerase TOP1MT. Hum Mol Genet 2023; 32: 2422-40.
105. Christensen MH, Jensen SB, Miettinen JJ, Luecke S, Prabakaran T, Reinert LS, Mettenleiter T, Chen ZJ, Knipe DM, Sandri-Goldin RM, Enquist LW, Hartmann R, Mogensen TH, Rice SA, Nyman TA, Matikainen S, Paludan SR. HSV-1 ICP27 targets the TBK1-activated STING signalsome to inhibit virus-induced type I IFN expression. EMBO J 2016; 35: 1385-99.
106. Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cadwell K, Cecconi F, Choi AMK, Choi ME, Chu CT, Codogno P, Colombo MI, Cuervo AM, Deretic V, Dikic I, Elazar Z, Eskelinen EL, Fimia GM, Gewirtz DA, Green DR, Hansen M, Jäättelä M, Johansen T, Juhász G, Karantza V, Kraft C, Kroemer G, Ktistakis NT, Kumar S, Lopez-Otin C, Macleod KF, Madeo F, Martinez J, Meléndez A, Mizushima N, Münz C, Penninger JM, Perera RM, Piacentini M, Reggiori F, Rubinsztein DC, Ryan KM, Sadoshima J, Santambrogio L, Scorrano L, Simon HU, Simon AK, Simonsen A, Stolz A, Tavernarakis N, Tooze SA, Yoshimori T, Yuan J, Yue Z, Zhong Q, Galluzzi L, Pietrocola F. Autophagy in major human diseases. EMBO J 2021; 40: e108863.
107. Yum S, Li M, Fang Y, Chen ZJ. TBK1 recruitment to STING activates both IRF3 and NF-κB that mediate immune defense against tumors and viral infections. Proc Natl Acad Sci U S A 2021; 118: e2100225118.

108. Thomsen MK, Nandakumar R, Stadler D, Malo A, Valls RM, Wang F, Reinert LS, Dagnaes-Hansen F, Hollensen AK, Mikkelsen JG, Protzer U, Paludan SR.Lack of immunological DNA sensing in hepatocytes facilitates hepatitis B virus infection. Hepatology 2016; 64: 746-59.
109. Galluzzi L, Pietrocola F, Bravo-San Pedro JM, Amaravadi RK, Baehrecke EH, Cecconi F, Codogno P, Debnath J, Gewirtz DA, Karantza V, Kimmelman A, Kumar S, Levine B, Maiuri MC, Martin SJ, Penninger J, Piacentini M, Rubinsztein DC, Simon HU, Simonsen A, Thorburn AM, Velasco G, Ryan KM, Kroemer G. Autophagy in malignant transformation and cancer progression. EMBO J 2015; 34: 856-80.
110. Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, Shen S, Kepp O, Scoazec M, Mignot G, Rello-Varona S, Tailler M, Menger L, Vacchelli E, Galluzzi L, Ghiringhelli F, di Virgilio F, Zitvogel L, Kroemer G. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science 2011; 334: 1573-7.
111. Riley JS, Tait SW. Mitochondrial DNA in inflammation and immunity. EMBO Rep 2020; 21: e49799.
112. Spitz AZ, Zacharioudakis E, Reyna DE, Garner TP, Gavathiotis E. Eltrombopag directly inhibits BAX and prevents cell death. Nat Commun 2021; 12: 1134.
113. Amgalan D, Garner TP, Pekson R, Jia XF, Yanamandala M, Paulino V, Liang FG, Corbalan JJ, Lee J, Chen Y, Karagiannis GS, Sanchez LR, Liang H, Narayanagari SR, Mitchell K, Lopez A, Margulets V, Scarlata M, Santulli G, Asnani A, Peterson RT, Hazan RB, Condeelis JS, Oktay MH, Steidl U, Kirshenbaum LA, Gavathiotis E, Kitsis RN. A small-molecule allosteric inhibitor of BAX protects against doxorubicin-induced cardiomyopathy. Nat Cancer 2020; 1: 315-28.
114. Yamazaki T, Galluzzi L. BAX and BAK dynamics control mitochondrial DNA release during apoptosis. Cell Death Differ 2022; 29: 1296-98.
115. Swanson SK, Born T, Zydowsky LD, Cho H, Chang HY, Walsh CT, Rusnak F. Cyclosporin-mediated inhibition of bovine calcineurin by cyclophilins A and B. Proc Natl Acad Sci U S A 1992; 89: 3741-5.