

Review

Control of host mitochondria by
bacterial pathogensSaverio Marchi,^{1,*} Gianluca Morrone,² Paolo Pinton,³ and Lorenzo Galluzzi^{4,5,6,7,8,*}

Mitochondria control various processes that are integral to cellular and organismal homeostasis, including Ca²⁺ fluxes, bioenergetic metabolism, and cell death. Perhaps not surprisingly, multiple pathogenic bacteria have evolved strategies to subvert mitochondrial functions in support of their survival and dissemination. Here, we discuss nonimmunological pathogenic mechanisms that converge on the ability of bacteria to control the mitochondrial compartment of host cells.

Introduction

Despite originating in the context of an endosymbiotic relationship >1.45 billion years ago, modern mitochondria remain at the very center of eukaryotic life as they control a variety of cellular processes that are fundamental for the preservation of both cellular and organismal homeostasis [1,2]. Mitochondria are structurally delimited by two membranes which delineate an inner mitochondrial matrix and an intermembrane space (IMS). The mitochondrial matrix houses 2–10 copies of a small (approximately 16 568 base pairs in humans) circular genome generally referred to as mitochondrial DNA (mtDNA) as well as (i) a functional machinery for protein synthesis, and (ii) numerous enzymes involved in multiple cellular functions (see below). The inner mitochondrial membrane (IMM) forms pronounced invaginations called cristae, resulting in a considerable increase in IMM surface area that is instrumental for the mitochondria to synthesize large amounts of ATP via oxidative phosphorylation (OXPHOS). Moreover, mitochondria are intimately involved in the regulation of intracellular Ca²⁺ fluxes and contain a refined molecular machinery that precipitates regulated cell death (RCD) via apoptosis or **mitochondrial permeability transition (MPT, see Glossary)**-dependent regulated necrosis [3]. Finally, mitochondria have acquired the ability to emit and decode molecular signals elicited by infection and other stress conditions, constituting one of the first lines of cellular defense against both viral and bacterial pathogens [4]. Thus, various pathogenic organisms that colonize the intracellular microenvironment have evolved strategies to govern the mitochondrial functions of host cells in support of their own survival, replication, and dissemination (Table 1).

While the mechanisms through which bacterial pathogens inhibit innate immune signaling by host cells in support of immunoevasion have been recently discussed in detail [5] (Box 1), a unified and updated overview of the nonimmune mitochondrial processes that bacteria subvert to their own benefit is missing. Here, we critically summarize the ability of pathogenic bacteria to sabotage bioenergetic metabolism, Ca²⁺ fluxes, as well as **mitophagy** and apoptotic cell death by targeting the mitochondria of host cells.

Bioenergetic metabolism

In normoxic conditions, most eukaryotic cells harness glycolysis to convert glucose into pyruvate, which enters the mitochondria to generate acetyl-CoA and reducing equivalents via the **tricarboxylic acid (TCA) cycle**. Such reducing equivalents are then oxidized to produce 30–36 ATP molecules (per glucose molecule) via OXPHOS. Conversely, in hypoxic environments,

Highlights

Mitochondria, the evolutionary successors of an ancient endosymbiotic prokaryote, occupy a central position in the biology of modern eukaryotic cells.

Numerous pathogenic bacteria have evolved strategies to subvert the mitochondrial functions of host cells in support of proliferation and dissemination.

The control of metabolism, Ca²⁺ fluxes, autophagy, and regulated cell death at mitochondrial level provides invading pathogens with a considerable evolutionary advantage.

¹Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy

²Department of Biomedical Sciences & Public Health, Marche Polytechnic University, Ancona, Italy

³Department of Medical Sciences, Section of Experimental Medicine, Laboratory for Technologies of Advanced Therapies (LTTA), University of Ferrara, Ferrara, Italy

⁴Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA

⁵Sandra and Edward Meyer Cancer Center, New York, NY, USA

⁶Caryl and Israel Englander Institute for Precision Medicine, New York, NY, USA

⁷Department of Dermatology, Yale School of Medicine, New Haven, CT, USA

⁸Université de Paris, Paris, France

*Correspondence: s.marchi@univpm.it (S. Marchi) and deadoc80@gmail.com (L. Galluzzi).

eukaryotic cells resort to the glycolytic conversion of glucose into lactate (which provides only 2 ATP molecules per glucose molecule but does not require molecular oxygen as OXPHOS does). In many cases, bacterial infection is accompanied by a global metabolic rewiring from OXPHOS to glycolysis that may be detrimental to invading pathogens [6]. As an example, phagocytic cells exposed to lipopolysaccharides (LPS) experience a robust inhibition of the TCA cycle coupled with the accumulation of some of its intermediates, such as succinate and itaconate, in support of glycolytic metabolism and lactate production [7]. Besides regulating the emission of proinflammatory signals by infected macrophages [8], itaconate strongly inhibits bacterial isocitrate lyase, hence limiting the growth of multiple pathogens such as *Mycobacterium tuberculosis* and *Salmonella enterica* [9]. Of note, efficient OXPHOS is generally associated with mitochondrial elongation [10], suggesting that LPS-dependent inhibition of the TCA cycle may also benefit invading pathogens indirectly as a consequence of altered mitochondrial dynamics [11] (see below).

Irrespective of this possibility, other pathogens such as *Pseudomonas aeruginosa* can proliferate by harnessing succinate, which accumulates in the airway as a result of impaired mitochondrial activity driven by cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations [12]. Similarly, *Brucella abortus* disrupts mitochondrial metabolism and OXPHOS in host cells to favor glycolysis as it can utilize lactate for proliferating [13]. While a similar trophic pathway has been proposed for *M. tuberculosis* [14], accurate metabolic assessments suggest that *M. tuberculosis* does not shift host cell metabolism towards glycolysis but instead establishes an ATP-depleted quiescent state (i.e., suppressed OXPHOS coupled with low glycolytic rates) and harnesses fatty acid intake for survival [15]. This bioenergetic rewiring appears to be sustained by the production of ketone bodies coupled to the accumulation of lipid droplets in infected cells [16], leading to the acquisition of the pathognomonic 'foamy phenotype' associated classically with *M. tuberculosis* infection.

Intracellular bacteria such as *Chlamydia trachomatis* actively boost OXPHOS, not only as they favor mitochondrial fusion [17] but also as they ensure elevated glucose intake from the extracellular microenvironment [18], ultimately supporting bacterial proliferation as a consequence of abundant ATP production. Interestingly, such an effect may originate from Toll-like receptor 2 (TLR2) activation by bacterial lipopeptides, which appear to sustain OXPHOS in the context of upregulated glycolysis. A concomitant increase in OXPHOS and glycolysis has also been observed upon *Staphylococcus aureus* infection [19] in the absence of major changes in mitochondrial dynamics (at least in the early phases of infection) [20]. However, such a response not only favors the survival of invading pathogens as a result of high ATP levels but also supports innate immune signaling in both immune cells (i.e., monocytes) [19] and non-immune cells (i.e., keratinocytes) [21].

Taken together, these observations exemplify the coevolution of bacterial versus host (immune) metabolic responses, indicating that invading pathogens rapidly adapt to bioenergetic alterations for their own survival (Figure 1).

Ca²⁺ fluxes

Alterations in Ca²⁺ signaling frequently contribute to bacterial pathogenicity, as demonstrated by the fact that numerous bacterial toxins evoke intracellular Ca²⁺ oscillations [22]. While increased cytosolic Ca²⁺ levels are normally a consequence of influx from the extracellular milieu, or opening of reticular stores, Ca²⁺ ions cross the outer mitochondrial membrane (OMM) through the voltage-dependent anion channels (VDACs) and accumulate in large amounts inside the mitochondrial matrix due to (i) the physical proximity of the mitochondria to the endoplasmic reticulum (ER); (ii) the negative electrochemical potential established across the IMM, which acts as a driving

Glossary

Autophagy: an evolutionary conserved process ensuring the removal of dispensable or cytotoxic cytosolic material through lysosomal degradation.

Autophagy receptors: components of the autophagy machinery involved in the recognition of specific substrates destined to lysosomal degradation.

Fission: a multistep process through which mitochondria split in support of replication or mitophagy.

Fusion: a multistep process through which mitochondria fuse in support of improved bioenergetic metabolism or mtDNA redistribution.

LC3-associated phagocytosis

(LAP): an LC3-dependent process that enables the uptake and lysosomal degradation of extracellular pathogens and dead cell corpses.

Mitochondria-associated ER

membranes (MAMs): specialized regions of the endoplasmic reticulum membrane that are physically and functionally connected to mitochondria.

Mitochondrial permeability

transition (MPT): rapid alteration in the permeability of the inner mitochondrial membrane that causes a specific variant of regulated necrosis.

Mitophagy: a variant of autophagy that selectively targets permeabilized or otherwise dysfunctional mitochondria.

Permeability transition pore

complex (PTPC): the multicomponent pore of the inner mitochondrial membrane responsible for mitochondrial permeability transition (MPT).

Tricarboxylic acid (TCA) cycle:

a series of chemical reactions that converts acetyl-CoA into NADH and FADH₂ in support of oxidative phosphorylation and ATP production by mitochondria.

Table 1. Control of mitochondrial functions by pathogens^a

Pathogen	Bacterial factor(s)	Mitochondrial target(s)	Cellular response	Outcome	Refs
<i>Acinetobacter baumannii</i>	OmpA	DRP1	Mitochondrial fragmentation ROS production	Host cell death induction	[20]
<i>Brucella abortus</i>	–	–	Metabolic rewiring	Improved pathogen survival	[13]
<i>Chlamydia trachomatis</i>	pORF5	BAX BCL2	Limited CYCS release Apoptosis inhibition	Improved pathogen survival	[98]
	–	–	Metabolic rewiring	Improved pathogen survival	[18]
<i>Helicobacter pylori</i>	VacA	DRP1	Mitochondrial fission BAX activation	Host cell death induction	[50]
	VacA	–	Reduced BCL2 expression	Host cell death induction	[109]
<i>Legionella pneumophila</i>	Lpg1137	STX17	Autophagy inhibition	Improved pathogen survival	[82]
	SidF	BNIP3	BNIP3 inhibition	Improved pathogen survival	[93]
	MitF	DRP1	Mitochondrial fission Metabolic rewiring	Improved pathogen survival	[58]
	LncP	–	ATP transport	Improved pathogen survival	[83]
	VipD	–	$\Delta\psi$ loss CYCS release	Host cell death induction	[97]
<i>Listeria monocytogenes</i>	LLO	NLRX1	Inhibition of ROS production Mitophagy inhibition	Improved pathogen survival	[66]
	LLO	MICOS10	Mitochondrial fission	Improved pathogen survival	[42,54]
<i>Mycobacterium tuberculosis</i>	ESX-1 Rv01654	BIM	Caspase activation	Host cell death induction	[99,110]
	Rv0674	mtDNA	ROS production Inhibition of ATP production	Improved pathogen survival	[100]
	Rv0694 ESAT-6	–	Metabolic rewiring	Improved pathogen survival	[14,16]
	–	–	–	–	–
<i>Neisseria gonorrhoeae</i>	PorB	–	Ultrastructural defects	Host cell death induction	[51]
	PorB	–	$\Delta\psi$ loss CYCS release	Host cell death induction	[52]
	OMV	–	MOMP	Host cell death induction	[53]
<i>Pseudomonas aeruginosa</i>	T3SS	NLRC4 inflammasome	mtDNA release ROS production	Improved pathogen survival	[90]
	ExoS	–	Autophagy inhibition	Improved pathogen survival	[91]
	OMV	–	MOMP	Host cell death induction	[53]
<i>Shigella flexneri</i>	IpaD	–	Caspase activation	Host cell death induction	[104]
	–	BCL2	ROS production $\Delta\psi$ loss	Host cell death induction	[31]
<i>Staphylococcus aureus</i>	PVL	–	MPT Caspase activation	Host cell death induction	[103]
	Alpha-toxin	NRLP3 inflammasome	Separation of mitochondria from intracellular bacteria	Improved pathogen survival	[64]
	–	–	Metabolic rewiring	Improved pathogen survival	[21]
<i>Stenotrophomonas maltophilia</i>	OmpA	BAX	ROS production Intracellular Ca^{2+} increase	Host cell death induction	[106]

^aAbbreviations: $\Delta\psi$, mitochondrial transmembrane potential; MOMP, mitochondrial outer-membrane permeabilization; MPT, mitochondrial permeability transition; mtDNA, mitochondrial DNA; OMVs, outer-membrane vesicles; ROS, reactive oxygen species; T3SS, type 3 secretion system.

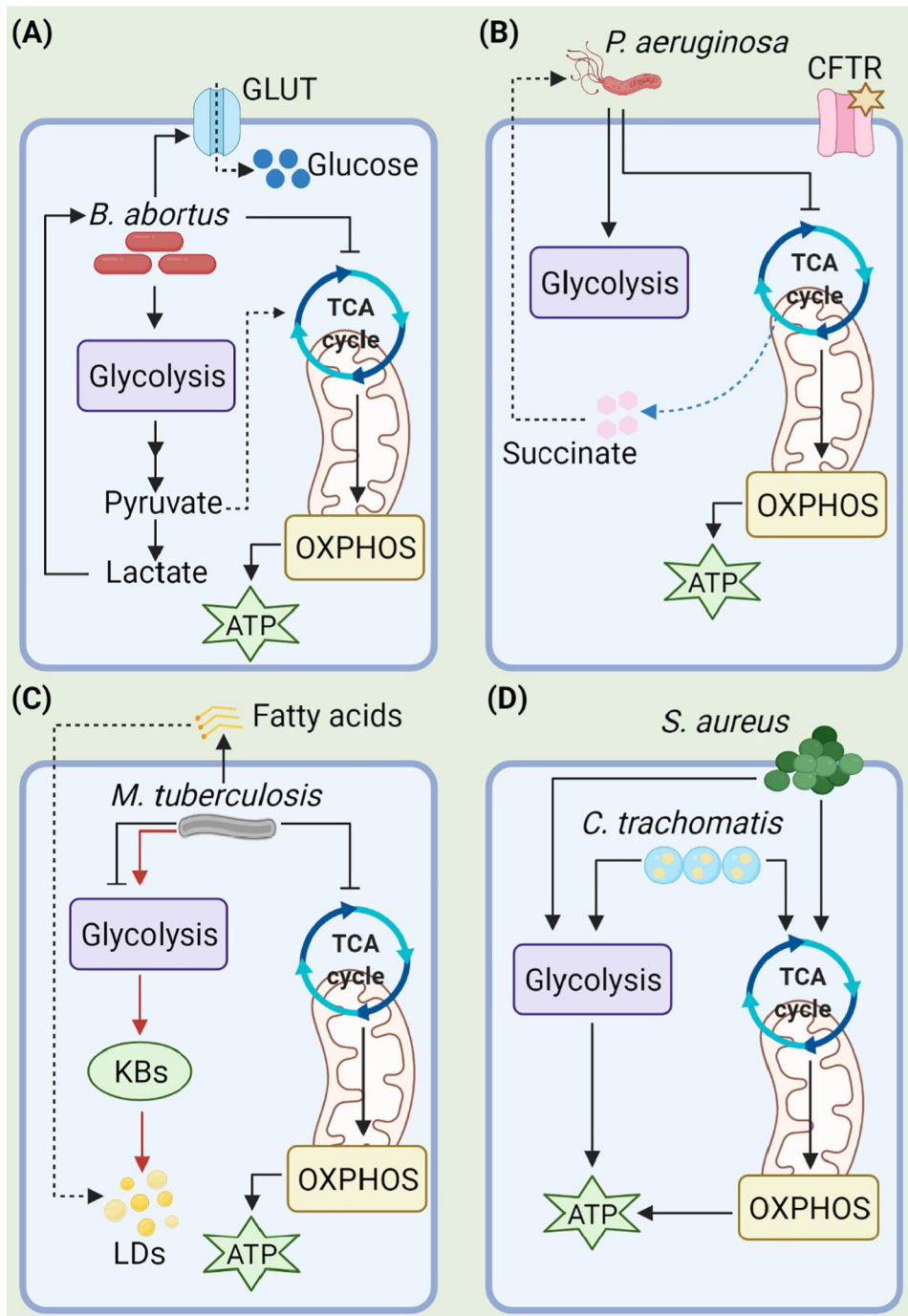
Box 1. Innate immune signaling by mitochondria

The ability of cells to engage the immune system in response to stressful conditions, including (but not limited to) pathogenic challenges, is intimately associated with mitochondrial functions, thereby constituting a key link between intracellular and organismal homeostasis. For instance, mitochondrial derangements caused by infection can lead to the buildup of reactive oxygen species (ROS) and mitochondrial DNA (mtDNA) molecules in the cytoplasm, culminating with the activation of the NLR family pyrin domain containing 3 (NLRP3), NLR family CARD domain containing 4 (NLRC4), or absent in melanoma 2 (AIM2) inflammasome and consequent secretion of mature interleukin 1 beta (IL1B, best known as IL-1 β) and IL-18. Alternatively, oxidized mtDNA accumulating in the cytosol of infected cells can promote cyclic GMP-AMP synthase (CGAS) and stimulator of interferon response cGAMP interactor 1 (STING1) signaling, resulting in the initiation of NF- κ B- and interferon regulatory factor 3 (IRF3)-dependent proinflammatory transcriptional programs. Moreover, the mitochondrial antiviral signaling protein (MAVS), a key signal transducer in various pathways that detect cytosolic double-stranded RNA to initiate antiviral responses based on type I interferon (IFN), is localized to the outer mitochondrial membrane (OMM). Finally, several mitochondrial components, including mtDNA, transcription factor A, mitochondrial (TFAM) and the inner mitochondrial membrane (IMM)-restricted lipid cardiolipin, mediate robust immunostimulatory signals once released in the extracellular environment, de facto operating as damage-associated molecular patterns (DAMPs) even in the absence of infectious challenges [4,108].

force for Ca²⁺ entry; and (iii) the presence of a regulated Ca²⁺-permeable channel, the mitochondrial calcium uniporter (MCU) complex [23,24].

Bacteria-driven cytosolic Ca²⁺ elevations have been associated with RCD via MPT-driven necrosis downstream of mitochondrial Ca²⁺ overload and consequent opening of the **permeability transition pore complex (PTPC)** (see below) [25]. Both *S. aureus* and the atypical fish pathogen *Mycobacterium fortuitum* appear to proficiently initiate this cascade of events, but while the latter has been suggested to drive mitochondrial Ca²⁺ overload by favoring the assembly of **mitochondria-associated ER membranes (MAMs)**, the implication of MAMs in mitochondrial Ca²⁺ accumulation elicited by *S. aureus* remains to be established [26,27]. *Streptococcus pneumoniae* also causes massive mitochondrial Ca²⁺ entry and collapse of the electrochemical gradient, potentially leading to PTPC activation [28]. However, rather than promoting RCD, mitochondrial Ca²⁺ overload in cells infected by *S. pneumoniae* appears to drive innate immune signaling via the release of mtDNA into the cytosol [28–30], pointing to the involvement of hitherto unidentified RCD-delaying factors for optimal *S. pneumoniae* pathogenicity (see below). Indeed, while an excessively rapid activation of RCD in host cells (prior to pathogen replication) is detrimental to invading bacteria, late RCD (upon pathogen replication) may be advantageous as it favors dissemination. In line with this notion, early signs of mitochondrial dysfunction have been documented upon *Shigella flexneri* infection, partially linked to mitochondrial Ca²⁺ elevations and PTPC opening [31]. However, *S. flexneri* actively prevents premature RCD through the type 3 secretion system (T3SS) effector IpgD, which inhibits Ca²⁺ release from the ER by targeting inositol 1,4,5 trisphosphate receptor (IP₃R) channels [32,33].

Altered mitochondrial Ca²⁺ homeostasis also supports the pathogenicity of various bacteria irrespective of active RCD control [34]. Indeed, moderate increases in mitochondrial Ca²⁺ levels promote bioenergetic metabolism, including ATP production [23,24], which may reasonably sustain bacterial growth during prolonged infection. In line with this notion, shortly after infection, *Listeria monocytogenes* drives listeriolysin O (LLO)-dependent cytosolic Ca²⁺ elevations from both extracellular and intracellular sources [35], rapidly evolving in transient mitochondrial Ca²⁺ accumulation via MCU [36] and acetyl-CoA production via the Ca²⁺-sensitive pyruvate dehydrogenase (PDH) complex [37]. In turn, accumulating acetyl-CoA favors the acetylation of rubicon **autophagy** regulator (RUBCN), a key regulator of a non-canonical form of autophagy with anti-bacterial effects termed **LC3-associated phagocytosis (LAP)** [38,39]. Importantly, abolition of mitochondrial Ca²⁺ uptake in myeloid cells via MCU deletion improves LAP and bacterial neutralization, demonstrating that *L. monocytogenes* safeguards its intracellular growth in a Ca²⁺-dependent manner [36].



Trends in Microbiology

Figure 1. Bacterial control of mitochondrial metabolism in host cells. *Brucella abortus* favors glucose uptake via plasma membrane glucose transporters (GLUTs) as it inhibits oxidative phosphorylation (OXPHOS), culminating with lactate accumulation in support of pathogen viability (A). *Pseudomonas aeruginosa* harnesses the succinate accumulating as a result of impaired OXPHOS in cells with cystic fibrosis transmembrane conductance regulator (CFTR) mutations in support of colonization (B). *Mycobacterium tuberculosis* has been

(Figure legend continued at the bottom of the next page.)

Taken together, these observations highlight various mechanisms of pathogenicity involving the ability of invading bacteria to control mitochondrial Ca^{2+} fluxes in host cells. This can be achieved by altering the composition of the MCU complex, which comprises both channel-forming and regulatory subunits [40], or by targeting mitochondrial Ca^{2+} -efflux systems [41]. In the case of *L. monocytogenes*, increased levels of the MCU regulator mitochondrial calcium uptake 1 (MICU1) [42] appear to enable efficient mitochondrial Ca^{2+} entry upon release from reticular stores, achieving not only a boost in mitochondrial metabolism but also protection from excessive cytosolic Ca^{2+} levels that reflects the ability of MICU1 to regulate the Ca^{2+} threshold for MCU opening [43]. Mitochondrial Ca^{2+} elevations could also be obtained by altering the activity of solute carrier family 8 member B1 (SLC8B1, best known as NCLX) [42], which is regulated at the post-transcriptional level [44]. However, to the best of our knowledge, no invading pathogen has been formally demonstrated to control mitochondrial Ca^{2+} homeostasis in host cells via NCLX. Finally, mitochondrial Ca^{2+} fluxes can be elicited by altering the IP_3R -dependent coupling of the ER and mitochondria at MAMs. This mechanism, which is also expected to prevent autophagy-dependent pathogen clearance [45], has been documented in cells infected by *C. trachomatis*, which can activate IP_3Rs via the inclusion membrane protein MrcA [46].

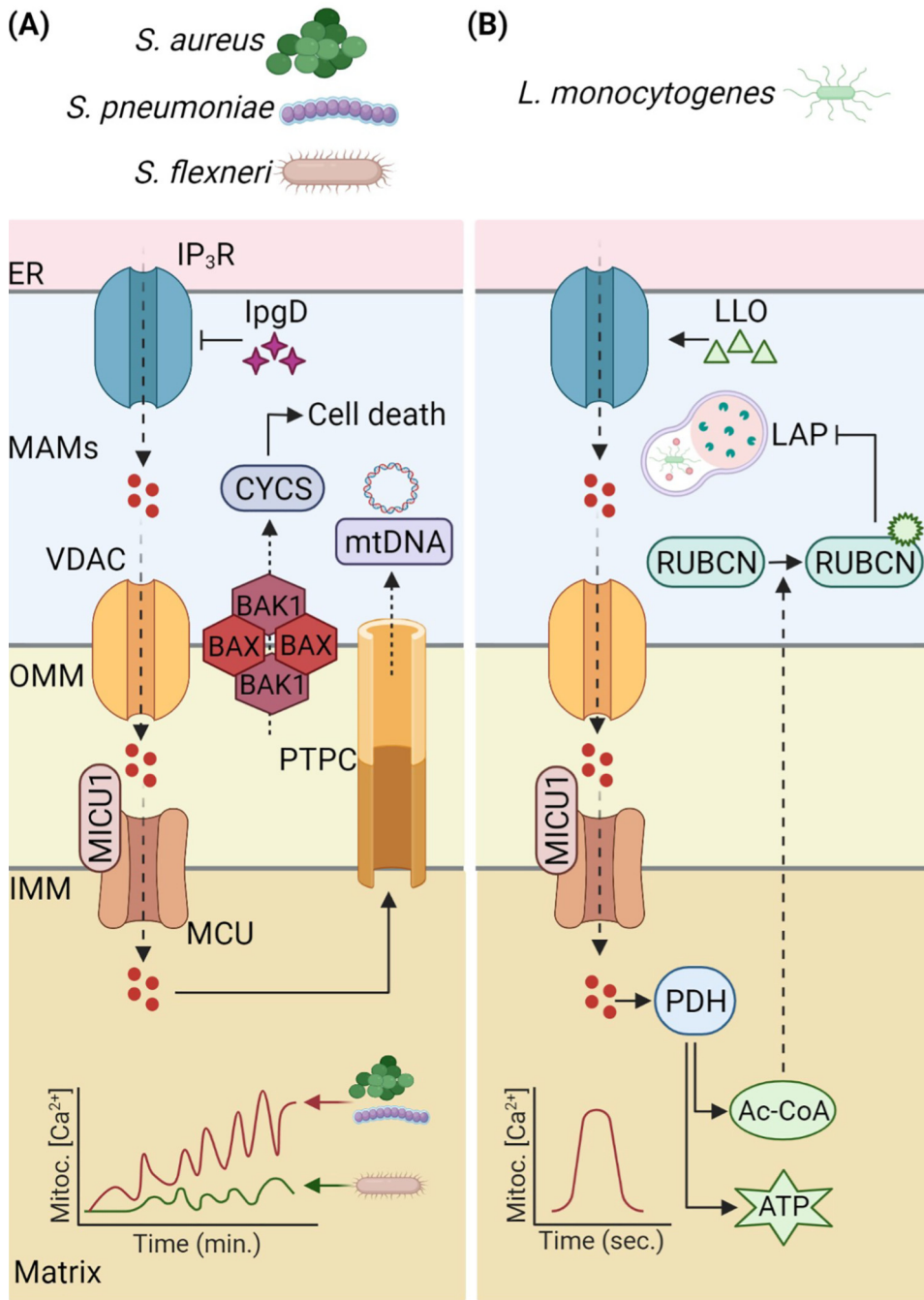
In summary, the key role of mitochondrial Ca^{2+} at the interface between bioenergetic metabolism and RCD regulation [47] stands out as an ideal target for manipulation by bacterial pathogens at different stages of infection (Figure 2). In turn, counteracting the strategies that bacteria have evolved to control the amplitude and kinetics of mitochondrial Ca^{2+} fluxes may represent a promising strategy for the development of novel antimicrobials.

Mitochondrial dynamics

Mitochondria undergo continuous **fusion** and **fission** events, which are tightly regulated at the molecular level. While mitochondrial elongation is mainly promoted by mitofusins (MFNs) at the OMM and OPA1 mitochondrial dynamin-like GTPase (OPA1) at the IMM, fission is generally initiated by the translocation of the cytosolic factor, dynamin 1-like (DNM1L, best known as DRP1) to the OMM, where it marks the site of mitochondrial division. Multiple bacterial species remodel the mitochondrial network, generally as they promote fission in support of RCD during the late infection phases [5]. Indeed, the proapoptotic factor BCL2 associated X, apoptosis regulator (BAX), and BCL2 antagonist/killer 1 (BAK1) [48] also recruit DRP1 to the OMM to promote fragmentation [49]. Specifically, these molecular events underlie host cell death induced by the vacuolating cytotoxin A (VacA) of *Helicobacter pylori* [50] as well as the secreted porin B (PorB) of *Neisseria gonorrhoeae* [51–53]. Along similar lines, LLO from *L. monocytogenes* is responsible for mitochondrial fragmentation and the concomitant bioenergetics crisis that characterize the early phase of infection [54]. However, this occurs through a noncanonical DRP1-independent mechanism [55] that involves (at least in part) mitochondrial contact site and cristae organizing system subunit 10 (MICOS10) [42].

However, mitochondrial fission does not systematically correlate with apoptosis initiation but rather participates in different pathophysiological processes, including metabolic adaptation [56] and the control of redox homeostasis [57]. For instance, a type 4 secretion system (T4SS) effector protein from *Legionella pneumophila* targets mitochondria and promotes rapid DRP1-dependent fission, but not overt RCD, initiating a series of mitochondrial alterations that ensure

proposed to inhibit both glycolysis and OXPHOS and to rely on the uptake of exogenous fatty acids for survival (black) as well as to divert glycolysis towards the production of ketone bodies (KBs) in support of fatty acid accumulation (red) (C). *Staphylococcus aureus* and *Chlamydia trachomatis* boost both glycolysis and OXPHOS to increase intracellular ATP availability (D).



Trends in Microbiology

Figure 2. Alterations of mitochondrial Ca^{2+} homeostasis imposed by invading pathogens. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Shigella flexneri* can all mobilize Ca^{2+} ions from the endoplasmic reticulum (ER) via inositol 1,4,5 trisphosphate receptor (IP₃R) channel, resulting in the accumulation of Ca^{2+} in the mitochondrial matrix via voltage-dependent anion channels (VDACs) at the outer mitochondrial membrane (OMM) and the mitochondrial calcium uniporter (MCU) complex at the inner mitochondrial membrane (IMM). However, while *S. aureus* and *S. pneumoniae* do so in an accentuated manner, rapidly resulting in innate immune signaling via cytosolic mitochondrial DNA (mtDNA) regulated cell

(Figure legend continued at the bottom of the next page.)

bacterial replication [58]. These might include reduced reactive oxygen species (ROS) generation [59] and chronic 5' AMP-activated protein kinase (AMPK) activation [60], which is also involved in the fragmentation-coupled mitophagy [61,62]. Moreover, deletion of mitofusin 2 (*MFN2*), which participates in mitochondrial fusion, from macrophages results in extensive mitochondrial fragmentation, altered respiration and reduced ROS levels, but no overt RCD, ultimately allowing for the survival and dissemination of both *L. monocytogenes* and *M. tuberculosis* [63]. A similar pathway of ROS inhibition has been documented in methicillin-resistant *S. aureus* (MRSA) [64]. In this latter case, however, the physical dissociation between ROS-producing mitochondria and cytosolic pathogens appears to be involved in pathogenicity [64].

These observations delineate a mechanism whereby mitochondrial fission and subcellular relocalization limit ROS generation, either by facilitating the degradation of ROS-producing mitochondria by mitophagy [65], as observed for *Listeria* spp. [66], or by cooperating with other alterations, including metabolic reprogramming (see above), ultimately setting up ideal conditions for bacterial growth. At least apparently at odds with this notion, *C. trachomatis* indirectly promotes mitochondrial elongation upon inhibiting fission via specific microRNAs (miRNAs) [67], ultimately boosting ATP production to sustain proliferation in epithelial cells [17]. Such a metabolic alteration is accompanied by an increase in ROS levels [68], but *C. trachomatis* exploits them for activating caspase 1 (CASP1) in further support of growth [69].

Specific cell types, including macrophages, promptly react to bacterial invasion by MFN1/MFN2-dependent fusion, a process that is required for optimal activation of defense mechanisms, including autophagy and the secretion of antimicrobial cytokines [63,70,71]. Consistent with this notion, loss of DRP1 potentiates innate immune defenses driven by mitochondrial species such as ROS and mtDNA [72] (Box 1). Similar observations have also been made in adipocytes infected by the eukaryotic pathogen *Toxoplasma gondii*, although in this case the protective effects of mitochondrial fusion originate from the ability of elongated mitochondria to efficiently use fatty acids and hence restrict their availability for the pathogen [73]. Taken together, these observations suggest that most (but not all) bacteria harness mitochondrial fission as a strategy to control host mitochondria in support of proliferation and dissemination.

MAMs represent key hubs where mitochondrial dynamics are regulated [74], at least in part reflecting their versatility and multifunctional nature [75]. Suggesting that MAMs may also be targeted by invading pathogens, Omp85 from *Neisseria* spp. controls lipid homeostasis in support of pathogenicity [76,77], and the human Omp85 human homolog SAMM50 sorting and assembly machinery component (SAMM50) actively participates in the regulation of MAM dynamics from the OMM [78,79]. Moreover, LegS2 (a T4SS effector from *L. pneumophila*) has been detected at both ER and mitochondrial membranes [80], indicating a putative MAM localization from which it might interfere with sphingolipid homeostasis and autophagy [81]. Yet another *L. pneumophila* effector (i.e., Lpg1137) accumulates at MAMs to promote the degradation of the scaffold protein syntaxin 17 (STX17) and disrupt ER–mitochondria communication, ultimately inhibiting autophagy in support of pathogen survival [82]. Of note, *L. pneumophila* also secretes a factor commonly known as *Legionella* nucleotide carrier protein (LncP) that integrates at the IMM to regulate ATP transport [83]. This event appears to contribute to pathogenicity at least in

death (RCD), the type 3 secretion system (T3SS) effector IpgD from *S. flexneri* actively prevents RCD in the early phases of infection upon binding to IP₃R channels (A). During *Listeria monocytogenes* infection, mitochondrial Ca²⁺ waves promote the activation of the pyruvate dehydrogenase (PDH) complex, ultimately resulting in accumulation of acetyl-CoA (Ac-CoA), acetylation of rubicon (RUBCN), and inhibition of LC3-associated phagocytosis (LAP) (B). Abbreviations: BAK1, BCL2 antagonist/killer 1; BAX, BCL2 associated X, apoptosis regulator; CYCS, cytochrome c, somatic; MAMs, mitochondria-associated ER membranes; MICU1, mitochondrial calcium uptake 1; LLO, listeriolysin O.

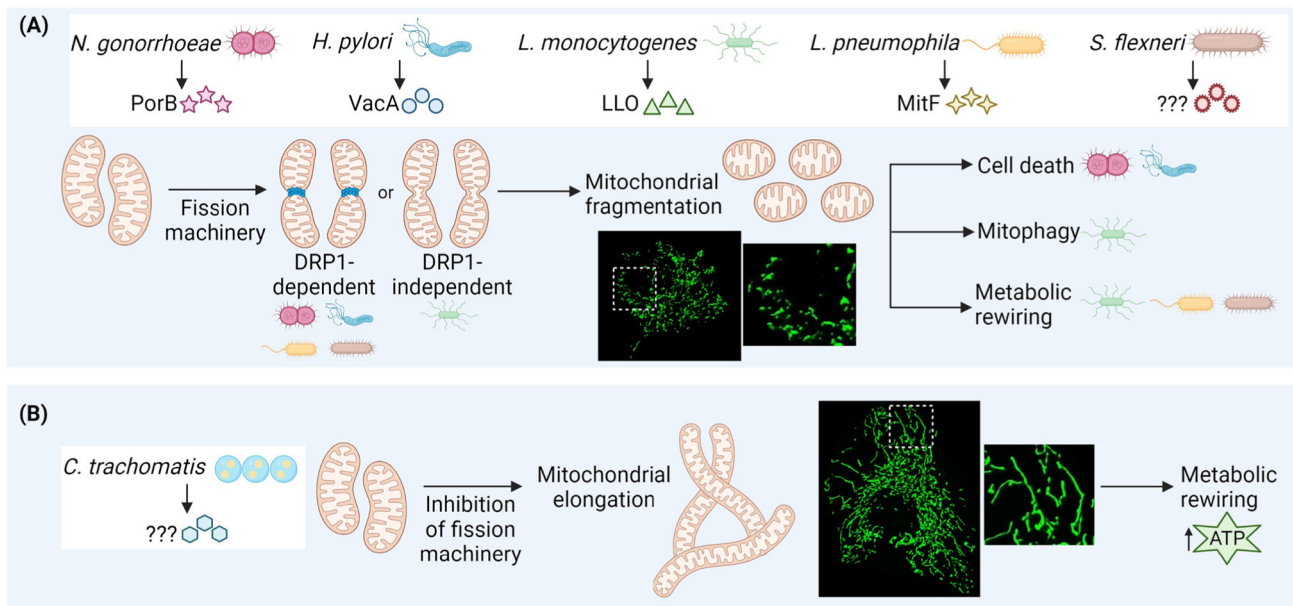
part by repressing autophagy [83]. In addition, *P. aeruginosa* actively inhibits autophagy in the context of cystic fibrosis, although in this case such an effect originates from the stabilization (rather than the destabilization) of ER–mitochondria contacts [84]. Whether this process involves quorum sensing (QS) molecules, which normally account for *Pseudomonas*-related mitochondrial dysfunctions [85,86], remains to be established.

Irrespective of these and other unsolved issues, mitochondrial dynamics and MAMs stand out as preferential targets for invading pathogens to survive and proliferate in host cells (Figure 3), at least in part reflecting the central involvement of MAMs in autophagy regulation [87] and innate immune signaling (Box 1).

Mitophagy and cell death

Autophagy and RCD are critical for the preservation of intracellular and organismal homeostasis [3], respectively, hence representing major targets for host cell control by pathogenic bacteria. Active RCD induction by invading pathogens normally stems from massive intracellular replication, implying that it occurs in the context of failed pathogen control by autophagic responses [88]. As mitochondria are crucial players in specific variants of autophagy (mitophagy) and RCD (mitochondrial apoptosis and MPT-driven regulated necrosis), bacteria have evolved several strategies to control these processes at the mitochondrial level.

Bacterial invasion generally drives a pronounced autophagic response that targets not only the pathogen itself (so-called xenophagy) but also mitochondria damaged by infection (mitophagy) [25]. These responses rely on a common molecular machinery but involve specific **autophagy receptors** [89]. For instance, the T3SS of *P. aeruginosa* promotes mitochondrial damage coupled to the release of ROS and mtDNA that is actively contained by mitophagy [90]. Pointing to an



Trends in Microbiology

Figure 3. Shifts in mitochondrial dynamics upon bacterial infection. Numerous pathogenic bacteria encode factors that promote mitochondrial fission, via mechanisms that may or may not involve dynamin 1 like (DNM1L, best known as DRP1). This can support metabolic rewiring in host cells, favor mitophagy, or precipitate cell death (A). Conversely, *Chlamydia trachomatis* promotes mitochondrial elongation (by inhibiting fission) in support of increased ATP production via a hitherto unidentified factor (B). Abbreviations: LLO, listeriolysin O; PorB, porin B; VacA, vacuolating cytotoxin A.

antimicrobial activity for these responses, *P. aeruginosa* developed multiple mechanisms to inhibit autophagy in host cells [91]. Conversely, *L. monocytogenes* actively drives mitophagy via LLO to quench ROS production in infected macrophages, which not only favors cytosolic pathogen persistence [66] but also inhibits phagocytosis [92]. Of note, LLO-driven mitophagy results from the direct interaction between LLO and the receptor NLR family member X1 (NLRX1) independently of the canonical pathway mediated by phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1), and hence preferentially occurs in cells with high NLRX1 levels such as macrophages [66].

For several bacteria, optimal pathogenicity involves the temporal control of RCD in host cells to enable pathogen replication in the context of inhibited cell death, but ultimately facilitates cellular breakdown in support of pathogen dissemination. Different effectors from the T4SS of *L. pneumophila* initially prevent apoptotic RCD by neutralizing BAX and BAK1 [93–95] or inducing the ATP synthase to operate in reverse mode [96] to preserve mitochondrial transmembrane potential and avoid mitochondrial collapse. Conversely, at later stages of infection, *L. pneumophila* actively drives BAK1-independent cell death to facilitate bacterial dissemination [97]. pORF5 from *C. trachomatis* also inhibits RCD by attenuating mitochondrial dysfunction, as evidenced by reduced BAX levels, quenched release of cytochrome *c*, somatic (CYCS) into the cytosol, and enhanced activation of the cytoprotective protein BCL2 apoptosis regulator (BCL2) [98]. Interestingly, this effect appears to originate from the upregulation of high mobility group box 1 (HGMB1), a conserved protein involved in autophagy and apoptosis regulation [98].

M. tuberculosis is well known for its capacity to promote the death of host cells in support of dissemination. One of the major mechanisms underlying such ability converges on Bcl-2 family proteins, especially the proapoptotic factor BCL2-like 11 (BCL2L11, best known as BIM), which can be activated by the pathogen ESX-1 secretion system and ESAT-6 protein [99]. Moreover, several mycobacterial proteins localize to the mitochondrial matrix and drive apoptosis in host macrophages by promoting ROS generation [100]. In the latter case, RCD may occur via MPT-driven necrosis rather than apoptosis, as the PTPC is particularly sensitive to ROS elevations [101]. Moreover, instances of mixed RCD scenarios involving both apoptotic and necrotic components have been documented in the context of *S. aureus* infection [102,103]. Other bacteria have been shown to employ a range of mechanisms to promote mitochondrial RCD. These include *S. flexneri*, which drives RCD in host cells via invasion plasmid antigen D (IpaD) [104], as well as the extracellular bacteria *Acinetobacter baumannii* and the nosocomial pathogen *Stenotrophomonas maltophilia*, whose cytotoxicity involves the outer membrane protein A (OmpA) [20,105,106]. Similarly, outer membrane vesicles (OMVs) from *N. gonorrhoeae*, uropathogenic *Escherichia coli*, and *P. aeruginosa* have all been shown to drive mitochondrial RCD in macrophages upon depletion of MCL1 apoptosis regulator, BCL2 family member (MCL1) [53].

Taken together, these observations exemplify various strategies through which bacterial pathogens control mitophagy and RCD at the level of mitochondria (Figure 4).

Concluding remarks

Most, if not all, pathogenic bacteria have evolved a panel of strategies to control mitochondrial functions in host cells, largely reflecting the key position that mitochondria occupy in virtually all facets of the biology of modern eukaryotes [24]. It is tempting to speculate that the predisposition of bacteria to converge prevalently on mitochondria rather than other organelles, such as the ER or lysosomes, reflects the evolutionary origin of mitochondria. Indeed, mitochondria emerged from an endosymbiotic interaction between ancestral alpha proteobacteria (the evolutionary ancestors of modern Gram-negative bacteria) [107]. This implies that (at least some degree of)

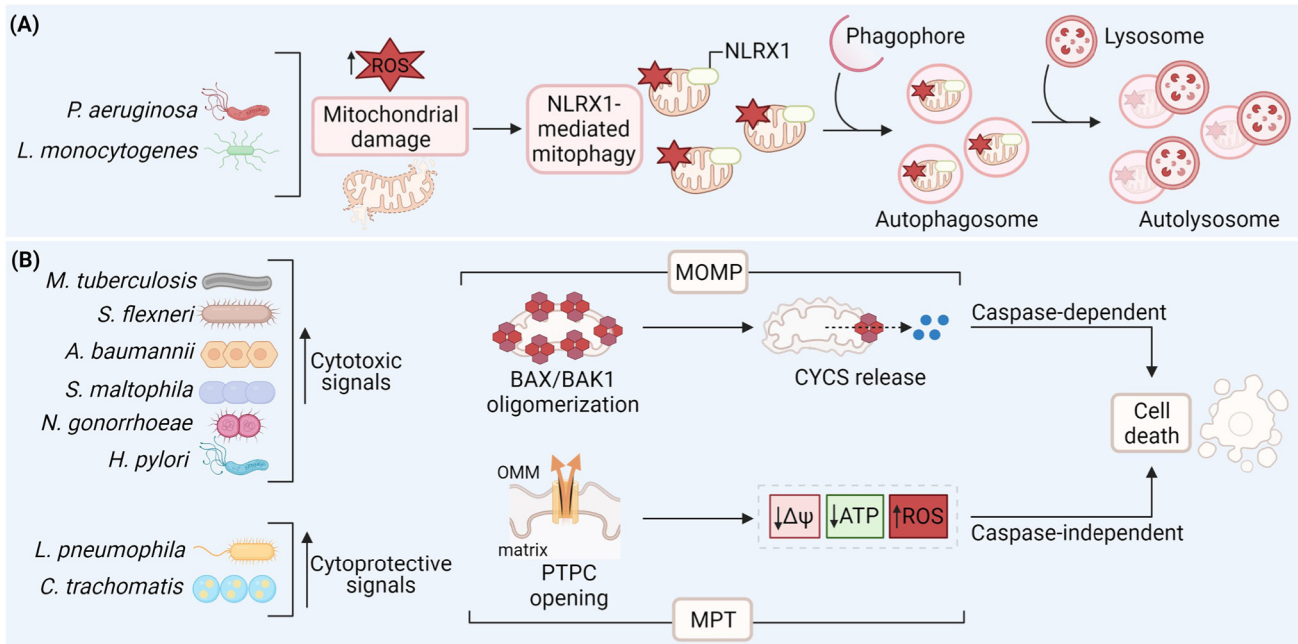
Outstanding questions

Do all pathogenic bacteria control, at least to some degree, mitochondrial activity in host cells?

What is the relative contribution of nonimmunological vs. immunological pathways to the evolutionary pressure existing on the control of mitochondrial functions by pathogens?

Is the preferential interaction between invading bacteria and host mitochondria a reflection of the endosymbiotic origin of the latter?

Will strategies aimed at disrupting the capacity of bacterial pathogens to control mitochondrial functions in the host translate into novel antimicrobials?



Trends in Microbiology

Figure 4. Control of mitophagy and regulated cell death (RCD) by invading pathogens. Mitochondrial damage caused by *Pseudomonas aeruginosa* and *Listeria monocytogenes* is associated with an increase in reactive oxygen species (ROS) that drives NLR family member X1 (NLRX1)-dependent mitophagy (A). A variety of bacterial species encode cytotoxic and cytoprotective factors that interact with the molecular machinery causing mitochondrial outer membrane permeabilization (MOMP) or mitochondrial permeability transition (MPT) to control caspase-dependent and caspase-independent forms of regulated cell death (B). Abbreviations: $\Delta\psi_m$, mitochondrial transmembrane potential; BAK1, BCL2 antagonist/killer 1; BAX, BCL2 associated X, apoptosis regulator; CYCS, cytochrome c, somatic; PTPC, permeability transition pore complex.

structural or functional homology between modern mitochondria and contemporary bacteria persisting throughout evolution may explain (at least some of the) interactions between mitochondrial component and pathogen factors. However, such a possibility does not directly account for the multipronged interactions between modern Gram-positive bacteria and eukaryotic pathogens with mitochondria. Thus, modern pathogens may simply have evolved strategies to control host mitochondria as a direct consequence of the robust evolutionary pressure existing on key processes that impinge on mitochondrial activity, including (but perhaps not limited to) RCD and innate immune signaling. Although other issues still remain open (see [Outstanding questions](#)), the functional interactions between invading bacteria and host mitochondria stand out as key aspects of pathogenicity. Additional studies are needed to elucidate the therapeutic potential of drugs specifically conceived to disrupt such bacteria–mitochondria intersections.

Acknowledgments

The figures have been created with [BioRender.com](#). S.M. is supported by the Italian Ministry of Health (GR-2016-02364602), Nanoblend, and local funds from Marche Polytechnic University (Ancona, Italy). P.P. is supported by the Italian Association for Cancer Research (AIRC, IG-23670), Telethon (GGP11139B), the Ministry of Education, University and Research – Progetti di Rilevante Interesse Nazionale (PRIN, 2017 E5L5P3), and local funds from the University of Ferrara. The L.G. laboratory is supported by a Breakthrough Level 2 grant from the US DoD BRCP (#BC180476P1), by the 2019 Laura Ziskin Prize in Translational Research (#ZP-6177, PI: Formenti) from the Stand Up to Cancer (SU2C), by a Mantle Cell Lymphoma Research Initiative (MCL-RI, PI: Chen-Kiang) grant from the Leukemia and Lymphoma Society (LLS), by a startup grant from the Department of Radiation Oncology at Weill Cornell Medicine (New York, USA), by a Rapid Response Grant from the Functional Genomics Initiative (New York, USA), by industrial collaborations with Lytix Biopharma (Oslo, Norway) and Phosplatin (New York, USA), and by donations from Phosplatin (New York, USA), the Luke Heller TECPR2 Foundation (Boston, USA), Sotio a.s. (Prague, Czech Republic), and Onxeo (Paris, France).

Declaration of interests

L.G. has received research funding from Lytx Biopharma and Phosplatin, as well as consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, OmniSEQ, Onxeo, The Longevity Laboratories, Inzen, and the Luke Heller TECPR2 Foundation. All other authors have no conflicts to disclose.

References

- Gray, M.W. *et al.* (1999) Mitochondrial evolution. *Science* 283, 1476–1481
- Fan, L. *et al.* (2020) Phylogenetic analyses with systematic taxon sampling show that mitochondria branch within Alphaproteobacteria. *Nat. Ecol. Evol.* 4, 1213–1219
- Galluzzi, L. *et al.* (2018) Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ.* 25, 486–541
- Galluzzi, L. *et al.* (2012) Mitochondria: master regulators of danger signalling. *Nat. Rev. Mol. Cell Biol.* 13, 780–788
- Tiku, V. *et al.* (2020) Mitochondrial functions in infection and immunity. *Trends Cell Biol.* 30, 263–275
- Gleeson, L.E. *et al.* (2016) Cutting edge: mycobacterium tuberculosis induces aerobic glycolysis in human alveolar macrophages that is required for control of intracellular bacillary replication. *J. Immunol.* 196, 2444–2449
- Russell, D.G. *et al.* (2019) Immunometabolism at the interface between macrophages and pathogens. *Nat. Rev. Immunol.* 19, 291–304
- Murphy, M.P. and O'Neill, L.A.J. (2018) Krebs cycle reimaged: the emerging roles of succinate and itaconate as signal transducers. *Cell* 174, 780–784
- Michelucci, A. *et al.* (2013) Immune-responsive gene 1 protein links metabolism to immunity by catalyzing itaconic acid production. *Proc. Natl. Acad. Sci. U. S. A.* 110, 7820–7825
- Yao, C.H. *et al.* (2019) Mitochondrial fusion supports increased oxidative phosphorylation during cell proliferation. *eLife* 8, e41351
- Kapetanovic, R. *et al.* (2020) Lipopolysaccharide promotes Drp1-dependent mitochondrial fission and associated inflammatory responses in macrophages. *Immunol. Cell Biol.* 98, 528–539
- Riquelme, S.A. *et al.* (2019) CFTR-PTEN-dependent mitochondrial metabolic dysfunction promotes *Pseudomonas aeruginosa* airway infection. *Sci. Transl. Med.* 11, eaav4634
- Czyz, D.M. *et al.* (2017) *Brucella abortus* induces a Warburg shift in host metabolism that is linked to enhanced intracellular survival of the pathogen. *J. Bacteriol.* 199, e00227–17
- Billig, S. *et al.* (2017) Lactate oxidation facilitates growth of *Mycobacterium tuberculosis* in human macrophages. *Sci. Rep.* 7, 6484
- Cumming, B.M. *et al.* (2018) *Mycobacterium tuberculosis* induces decelerated bioenergetic metabolism in human macrophages. *eLife* 7, e39169
- Singh, V. *et al.* (2012) *Mycobacterium tuberculosis*-driven targeted recalibration of macrophage lipid homeostasis promotes the foamy phenotype. *Cell Host Microbe* 12, 669–681
- Kurihara, Y. *et al.* (2019) *Chlamydia trachomatis* targets mitochondrial dynamics to promote intracellular survival and proliferation. *Cell. Microbiol.* 21, e12962
- Siegl, C. *et al.* (2014) Tumor suppressor p53 alters host cell metabolism to limit *Chlamydia trachomatis* infection. *Cell Rep.* 9, 918–929
- Lachmandas, E. *et al.* (2016) Microbial stimulation of different Toll-like receptor signalling pathways induces diverse metabolic programmes in human monocytes. *Nat. Microbiol.* 2, 16246
- Tiku, V. *et al.* (2021) Outer membrane vesicles containing OmpA induce mitochondrial fragmentation to promote pathogenesis of *Acinetobacter baumannii*. *Sci. Rep.* 11, 618
- Wickersham, M. *et al.* (2017) Metabolic stress drives keratinocyte defenses against *Staphylococcus aureus* infection. *Cell Rep.* 18, 2742–2751
- Tran Van Nhieu, G. *et al.* (2018) Ca²⁺ signals triggered by bacterial pathogens and microdomains. *Biochim. Biophys. Acta* 1865, 1838–1845
- Murphy, E. and Steenbergen, C. (2021) Regulation of mitochondrial Ca²⁺ uptake. *Annu. Rev. Physiol.* 83, 107–126
- Giorgi, C. *et al.* (2018) The machineries, regulation and cellular functions of mitochondrial calcium. *Nat. Rev. Mol. Cell Biol.* 19, 713–730
- Galluzzi, L. *et al.* (2017) Molecular definitions of autophagy and related processes. *EMBO J.* 36, 1811–1836
- Stelzner, K. *et al.* (2020) Intracellular *Staphylococcus aureus* perturbs the host cell Ca²⁺ homeostasis to promote cell death. *mBio* 11, e02250–20
- Datta, D. *et al.* (2018) *Mycobacterium fortuitum*-induced ER-mitochondrial calcium dynamics promotes calpain/caspase-12/caspase-9 mediated apoptosis in fish macrophages. *Cell Death Dis.* 4, 30
- Nerlich, A. *et al.* (2018) Pneumolysin induced mitochondrial dysfunction leads to release of mitochondrial DNA. *Sci. Rep.* 8, 182
- Yamazaki, T. *et al.* (2020) Mitochondrial DNA drives abscopal responses to radiation that are inhibited by autophagy. *Nat. Immunol.* 21, 1160–1171
- Matz, K.M. *et al.* (2019) The role of nucleic acid sensing in controlling microbial and autoimmune disorders. *Int. Rev. Cell Mol. Biol.* 345, 35–136
- Carneiro, L.A. *et al.* (2009) *Shigella* induces mitochondrial dysfunction and cell death in nonmyleoid cells. *Cell Host Microbe* 5, 123–136
- Sun, C.H. *et al.* (2017) The *Shigella* type III effector IpgD recodes Ca²⁺ signals during invasion of epithelial cells. *EMBO J.* 36, 2567–2580
- Rosa, N. *et al.* (2020) Type 3 IP₃ receptors: The chameleon in cancer. *Int. Rev. Cell Mol. Biol.* 351, 101–148
- Imre, G. (2020) The involvement of regulated cell death forms in modulating the bacterial and viral pathogenesis. *Int. Rev. Cell Mol. Biol.* 353, 211–253
- Drams, S. and Cossart, P. (2003) Listeriolysin O-mediated calcium influx potentiates entry of *Listeria monocytogenes* into the human Hep-2 epithelial cell line. *Infect. Immun.* 71, 3614–3618
- Li, T. *et al.* (2021) *Listeria monocytogenes* upregulates mitochondrial calcium signaling to inhibit LC3-associated phagocytosis as a survival strategy. *Nat. Microbiol.* 6, 366–379
- Denton, R.M. (2009) Regulation of mitochondrial dehydrogenases by calcium ions. *Biochim. Biophys. Acta* 1787, 1309–1316
- Wong, S.W. *et al.* (2018) Rubicon: LC3-associated phagocytosis and beyond. *FEBS J.* 285, 1379–1388
- Datan, E. and Salman, S. (2020) Autophagic cell death in viral infection: Do TAM receptors play a role? *Int. Rev. Cell Mol. Biol.* 357, 123–168
- Kamer, K.J. and Mootha, V.K. (2015) The molecular era of the mitochondrial calcium uniporter. *Nat. Rev. Mol. Cell Biol.* 16, 545–553
- Palty, R. *et al.* (2010) NCLX is an essential component of mitochondrial Na⁺/Ca²⁺ exchange. *Proc. Natl. Acad. Sci. U. S. A.* 107, 436–441
- Carvalho, F. *et al.* (2020) *Listeria monocytogenes* exploits mitochondrial contact site and cristae organizing system complex subunit Mic10 to promote mitochondrial fragmentation and cellular infection. *mBio* 11, e03171–19
- Payne, R. *et al.* (2017) MICU2 restricts spatial crosstalk between InsP₃R and MCU channels by regulating threshold and gain of MICU1-mediated inhibition and activation of MCU. *Cell Rep.* 21, 3141–3154
- Kostic, M. *et al.* (2015) PKA phosphorylation of NCLX reverses mitochondrial calcium overload and depolarization, promoting survival of PINK1-deficient dopaminergic neurons. *Cell Rep.* 13, 376–386

45. Cardenas, C. *et al.* (2010) Essential regulation of cell bioenergetics by constitutive InsP3 receptor Ca²⁺ transfer to mitochondria. *Cell* 142, 270–283
46. Nguyen, P.H. *et al.* (2018) *Chlamydia trachomatis* inclusion membrane protein MrcA interacts with the inositol 1,4,5-trisphosphate receptor type 3 (ITPR3) to regulate extrusion formation. *PLoS Pathog.* 14, e1006911
47. Marchi, S. *et al.* (2020) Ca²⁺ Fluxes and cancer. *Mol. Cell* 78, 1055–1069
48. Glab, J.A. *et al.* (2020) Bcl-2 family proteins, beyond the veil. *Int. Rev. Cell Mol. Biol.* 351, 1–22
49. Maes, M.E. *et al.* (2019) Completion of BAX recruitment correlates with mitochondrial fission during apoptosis. *Sci. Rep.* 9, 16565
50. Jain, P. *et al.* (2011) *Helicobacter pylori* vacuolating cytotoxin A (VacA) engages the mitochondrial fission machinery to induce host cell death. *Proc. Natl. Acad. Sci. U. S. A.* 108, 16032–16037
51. Kozjak-Pavlovic, V. *et al.* (2009) Bacterial porin disrupts mitochondrial membrane potential and sensitizes host cells to apoptosis. *PLoS Pathog.* 5, e1000629
52. Deo, P. *et al.* (2018) Outer membrane vesicles from *Neisseria gonorrhoeae* target PorB to mitochondria and induce apoptosis. *PLoS Pathog.* 14, e1006945
53. Deo, P. *et al.* (2020) Mitochondrial dysfunction caused by outer membrane vesicles from Gram-negative bacteria activates intrinsic apoptosis and inflammation. *Nat. Microbiol.* 5, 1418–1427
54. Stavru, F. *et al.* (2011) *Listeria monocytogenes* transiently alters mitochondrial dynamics during infection. *Proc. Natl. Acad. Sci. U. S. A.* 108, 3612–3617
55. Stavru, F. *et al.* (2013) Atypical mitochondrial fission upon bacterial infection. *Proc. Natl. Acad. Sci. U. S. A.* 110, 16003–16008
56. Kraus, F. *et al.* (2021) Function and regulation of the divisome for mitochondrial fission. *Nature* 590, 57–66
57. Willems, P.H. *et al.* (2015) Redox homeostasis and mitochondrial dynamics. *Cell Metab.* 22, 207–218
58. Escoll, P. *et al.* (2017) *Legionella pneumophila* modulates mitochondrial dynamics to trigger metabolic repurposing of infected macrophages. *Cell Host Microbe* 22, 302–316
59. Harada, T. *et al.* (2007) Evasion of *Legionella pneumophila* from the bactericidal system by reactive oxygen species (ROS) in macrophages. *Microbiol. Immunol.* 51, 1161–1170
60. Francione, L. *et al.* (2009) *Legionella pneumophila* multiplication is enhanced by chronic AMPK signalling in mitochondrially diseased *Dictyostelium* cells. *Dis. Models Mechan.* 2, 479–489
61. Toyama, E.Q. *et al.* (2016) Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. *Science* 351, 275–281
62. Pervaiz, S. *et al.* (2020) Redox signaling in the pathogenesis of human disease and the regulatory role of autophagy. *Int. Rev. Cell Mol. Biol.* 352, 189–214
63. Tur, J. *et al.* (2020) Mitofusin 2 in macrophages links mitochondrial ROS production, cytokine release, phagocytosis, autophagy, and bactericidal activity. *Cell Rep.* 32, 108079
64. Cohen, T.S. *et al.* (2018) *S. aureus* evades macrophage killing through NLRP3-dependent effects on mitochondrial trafficking. *Cell Rep.* 22, 2431–2441
65. Burman, J.L. *et al.* (2017) Mitochondrial fission facilitates the selective mitophagy of protein aggregates. *J. Cell Biol.* 216, 3231–3247
66. Zhang, Y. *et al.* (2019) *Listeria* hijacks host mitophagy through a novel mitophagy receptor to evade killing. *Nat. Immunol.* 20, 433–446
67. Chowdhury, S.R. *et al.* (2017) *Chlamydia* preserves the mitochondrial network necessary for replication via microRNA-dependent inhibition of fission. *J. Cell Biol.* 216, 1071–1089
68. Boncompain, G. *et al.* (2010) Production of reactive oxygen species is turned on and rapidly shut down in epithelial cells infected with *Chlamydia trachomatis*. *Infect. Immun.* 78, 80–87
69. Abdul-Sater, A.A. *et al.* (2010) Enhancement of reactive oxygen species production and chlamydial infection by the mitochondrial Nod-like family member NLRX1. *J. Biol. Chem.* 285, 41637–41645
70. Silwal, P. *et al.* (2021) Mitofusin-2 boosts innate immunity through the maintenance of aerobic glycolysis and activation of xenophagy in mice. *Commun. Biol.* 4, 548. <https://doi.org/10.1038/s42003-021-02073-6>
71. Ning, Y. *et al.* (2021) Mitochondrial fusion mediated by mitofusin 1 regulates macrophage mycobactericidal activity by enhancing autophagy. *Infect. Immun.* IA10030621
72. Park, S. *et al.* (2015) Defective mitochondrial fission augments NLRP3 inflammasome activation. *Sci. Rep.* 5, 15489
73. Pernas, L. *et al.* (2018) Mitochondria restrict growth of the intracellular parasite *Toxoplasma gondii* by limiting its uptake of fatty acids. *Cell Metab.* 27, 886–897
74. Perrone, M. *et al.* (2020) The role of mitochondria-associated membranes in cellular homeostasis and diseases. *Int. Rev. Cell Mol. Biol.* 350, 119–196
75. Rowland, A.A. and Voeltz, G.K. (2012) Endoplasmic reticulum-mitochondria contacts: function of the junction. *Nat. Rev. Mol. Cell Biol.* 13, 607–625
76. Genevrois, S. *et al.* (2003) The Omp85 protein of *Neisseria meningitidis* is required for lipid export to the outer membrane. *EMBO J.* 22, 1780–1789
77. Kozjak-Pavlovic, V. *et al.* (2011) Neisserial Omp85 protein is selectively recognized and assembled into functional complexes in the outer membrane of human mitochondria. *J. Biol. Chem.* 286, 27019–27026
78. Modi, S. *et al.* (2019) Miro clusters regulate ER-mitochondria contact sites and link cristae organization to the mitochondrial transport machinery. *Nat. Commun.* 10, 4399
79. Rochin, L. *et al.* (2020) ORP5 Transfers phosphatidylserine to mitochondria and regulates mitochondrial calcium uptake at endoplasmic reticulum – mitochondria contact sites. *bioRxiv* 695577. <https://doi.org/10.1101/695577>
80. Escoll, P. *et al.* (2017) MAMs are attractive targets for bacterial repurposing of the host cell: MAM-functions might be key for undermining an infected cell. *BioEssays* 39, 1600171
81. Rolando, M. *et al.* (2016) *Legionella pneumophila* S1P-lyase targets host sphingolipid metabolism and restrains autophagy. *Proc. Natl. Acad. Sci. U. S. A.* 113, 1901–1906
82. Arasaki, K. *et al.* (2017) *Legionella* effector Lpg1137 shuts down ER-mitochondria communication through cleavage of syntaxin 17. *Nat. Commun.* 8, 15406
83. Dolezal, P. *et al.* (2012) *Legionella pneumophila* secretes a mitochondrial carrier protein during infection. *PLoS Pathog.* 8, e1002459
84. Rimessi, A. *et al.* (2020) Pharmacological modulation of mitochondrial calcium uniporter controls lung inflammation in cystic fibrosis. *Sci. Adv.* 6, eaax9093
85. Maurice, N.M. *et al.* (2019) *Pseudomonas aeruginosa* induced host epithelial cell mitochondrial dysfunction. *Sci. Rep.* 9, 11929
86. Smith, R.P. *et al.* (2020) The mechanisms and cell signaling pathways of programmed cell death in the bacterial world. *Int. Rev. Cell Mol. Biol.* 352, 1–53
87. Hamasaki, M. *et al.* (2013) Autophagosomes form at ER-mitochondria contact sites. *Nature* 495, 389–393
88. Kimmey, J.M. and Stallings, C.L. (2016) Bacterial pathogens versus autophagy: implications for therapeutic interventions. *Trends Mol. Med.* 22, 1060–1076
89. Farré, J.C. and Subramani, S. (2016) Mechanistic insights into selective autophagy pathways: lessons from yeast. *Nat. Rev. Mol. Cell Biol.* 17, 537–552
90. Jabir, M.S. *et al.* (2015) Mitochondrial damage contributes to *Pseudomonas aeruginosa* activation of the inflammasome and is downregulated by autophagy. *Autophagy* 11, 166–182
91. Rao, L. *et al.* (2021) *Pseudomonas aeruginosa* survives in epithelia by ExoS-mediated inhibition of autophagy and mTOR. *EMBO Rep.* 22, e50613
92. Bonilla, D.L. *et al.* (2013) Autophagy regulates phagocytosis by modulating the expression of scavenger receptors. *Immunity* 39, 537–547
93. Banga, S. *et al.* (2007) *Legionella pneumophila* inhibits macrophage apoptosis by targeting pro-death members of the Bcl2 protein family. *Proc. Natl. Acad. Sci. U. S. A.* 104, 5121–5126
94. Laguna, R.K. *et al.* (2006) A *Legionella pneumophila*-translocated substrate that is required for growth within

- macrophages and protection from host cell death. *Proc. Natl. Acad. Sci. U. S. A.* 103, 18745–18750
95. Speir, M. *et al.* (2017) *Legionella pneumophila* strain 130b evades macrophage cell death independent of the effector SidF in the absence of flagellin. *Front. Cell. Infect. Microbiol.* 7, 35
 96. Escoll, P. *et al.* (2021) Reverting the mode of action of the mitochondrial FOF1-ATPase by *Legionella pneumophila* preserves its replication niche. *bioRxiv* 2021.2005.2012.443790
 97. Zhu, W. *et al.* (2013) Induction of caspase 3 activation by multiple *Legionella pneumophila* Dot/Icm substrates. *Cell. Microbiol.* 15, 1783–1795
 98. Lei, W. *et al.* (2017) *Chlamydia trachomatis* plasmid-encoded protein pORF5 protects mitochondrial function by inducing mitophagy and increasing HMGB1 expression. *Pathog. Dis.* 75. <https://doi.org/10.1093/femspd/ftx111>
 99. Aguiló, N. *et al.* (2014) Bim is a crucial regulator of apoptosis induced by *Mycobacterium tuberculosis*. *Cell Death Dis.* 5, e1343
 100. Dubey, R.K. *et al.* (2021) Mycobacterial origin protein Rv0674 localizes into mitochondria, interacts with D-loop and regulates OXPHOS for intracellular persistence of *Mycobacterium tuberculosis*. *Mitochondrion* 57, 241–256
 101. Bonora, M. *et al.* (2015) Molecular mechanisms of cell death: central implication of ATP synthase in mitochondrial permeability transition. *Oncogene* 34, 1475–1486
 102. Essmann, F. *et al.* (2003) *Staphylococcus aureus* alpha-toxin-induced cell death: predominant necrosis despite apoptotic caspase activation. *Cell Death Differ.* 10, 1260–1272
 103. Genestier, A.L. *et al.* (2005) *Staphylococcus aureus* Panton-Valentine leukocidin directly targets mitochondria and induces Bax-independent apoptosis of human neutrophils. *J. Clin. Invest.* 115, 3117–3127
 104. Arizmendi, O. *et al.* (2016) Macrophage apoptosis triggered by IpaD from *Shigella flexneri*. *Infect. Immun.* 84, 1857–1865
 105. Morris, F.C. *et al.* (2019) The mechanisms of disease caused by *Acinetobacter baumannii*. *Front. Microbiol.* 10, 1601
 106. Wang, X. *et al.* (2020) *Stenotrophomonas maltophilia* outer membrane protein A induces epithelial cell apoptosis via mitochondrial pathways. *J. Microbiol.* 58, 868–877
 107. Roger, A.J. *et al.* (2017) The origin and diversification of mitochondria. *Curr. Biol.* 27, R1177–R1192
 108. Galluzzi, L. *et al.* (2018) Linking cellular stress responses to systemic homeostasis. *Nat. Rev. Mol. Cell Biol.* 19, 731–745
 109. Matsumoto, A. *et al.* (2011) *Helicobacter pylori* VacA reduces the cellular expression of STAT3 and pro-survival Bcl-2 family proteins, Bcl-2 and Bcl-XL, leading to apoptosis in gastric epithelial cells. *Digest. Dis. Sci.* 56, 999–1006
 110. Lee, K.I. *et al.* (2021) Recombinant Rv1654 protein of *Mycobacterium tuberculosis* induces mitochondria-mediated apoptosis in macrophage. *Microbiol. Immunol.* 65, 178–188