Lipopolysaccharide, Inflammation and Mitochondria-Targeted Antioxidants

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Lipopolysaccharide (LPS), the major component of the outer membrane of Gram-negative bacteria, is the most abundant proinflammatory agent. Considerable evidence indicates that LPS challenge inescapably causes oxidative stress and mitochondrial dysfunction, leading to cell and tissue damage. Increased mitochondrial reactive oxygen species (mtROS) generation triggered by LPS is known to play a key role in the progression of the inflammatory response. mtROS at excessive levels impair electron transport chain functioning, reduce the mitochondrial membrane potential, and initiate lipid peroxidation and oxidative damage of mitochondrial proteins and mtDNA. Over the past 20 years, a large number of mitochondria-targeted antioxidants (mito-AOX) of different structures that can accumulate inside mitochondria and scavenge free radicals have been synthesized. Their protective role based on the prevention of oxidative stress and the restoration of mitochondrial function has been demonstrated in a variety of common diseases and pathological states.

mitochondria-targeted antioxidants inflammation LPS

1. Mechanisms of LPS-Triggered Inflammation

Inflammatory reactions play a critical role in LPS-induced tissue injury, which is caused by the adhesion and migration of leucocytes through the epithelium, the production of a variety of proinflammatory mediators by monocytes/macrophages, and oxidative stress driven by excess generation of reactive oxygen and nitrogen species. As the most abundant proinflammatory agent, LPS activates the systemic and cellular inflammatory response largely due to signaling through Toll-like receptor 4 (TLR4), which is expressed not only in immune cells but also in almost all cell types [1][2][3]. In mammalian cells, LPS-induced activation of TLR4 occurs through a series of interactions with several adapter proteins to facilitate its recognition by the TLR4/MD-2 receptor complex, which causes TLR4 oligomerization and recruitment of its numerous downstream adaptors. LPS/TLR4 signaling can be divided into MyD88-dependent and MyD88-independent (TRIF-dependent) pathways, leading to nuclear transcription factors NF-κB-, AP-1-, and IRF3-mediated induction of a wide range of pro- and anti-inflammatory mediators, such as cytokines, chemokines, eicosanoids, and others [4][5]. Stimulation of immune, epithelial, endothelial, and other cells by pro-inflammatory mediators results in excessive ROS/RNS generation, which is potentially damaging to all cellular compartments.

Recently, TLR4-independent LPS sensing pathways have been described [6]. First, transient receptor potential (TRP) channels have been identified as non-TLR membrane-bound sensors of LPS, and second, caspase-4/5 (and caspase-11 in mice) have been established as cytoplasmic sensors for LPS [6].

LPS has been shown to activate inflammasomes—cytosolic multiprotein complexes that mediate the propagation of the inflammatory response within the innate and the adaptive immune system as well as in epithelial cells [7][8][9][10]. Inflammasome activation is evoked by extra- and intracellular pathogens, such as Gram-negative bacteria, and/or by danger signals to activate caspase-1, resulting in a caspase-1-dependent, highly inflammatory form of cell death—pyroptosis [9][10]. It is thought that in Gram-negative infections, pyroptosis plays a key role in the destruction of intracellular bacterial replication niches. Inflammasomes are responsible for the maturation of proinflammatory cytokines, including IL-1β and IL-18, and for their secretion through the formation of pores in the plasma membrane [9][11][12]. The most studied inflammasome, NLRP3, is implicated in many different pathologies such as cancer and metabolic, neurodegenerative, and inflammatory diseases. Activation of the NLRP3 inflammasome occurs in two steps via different activating signals. Through TLR4 activation, LPS participates in the priming of inflammasome activation to initiate the transcription of NLRP3, inactive pro-IL-1β, and pro-IL-18 via NF-κB [11]. The second signals, which are notably diverse, include mtROS, derived mainly from ETC electron leakage [11], and initiate assembly of the inflammasome complex and, among other things, maturation of pro-IL-1β and pro-IL-18.

2. Generation of mtROS and Their Role in Normal and Pathological Conditions

ROS is a general term encompassing oxygen-free radicals, including superoxide ion (O_2^{-}) and hydroxyl radical ($^{\cdot}OH$), and nonradical oxygen substrates, e.g., hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$). ROS are produced during a wide range of biochemical reactions within the cell and within different cell compartments (mitochondria, peroxisomes, and endoplasmic reticulum). There are many cell proteins, bearing thiols, catecholamines, hydroquinones, and flavins, that may participate in intracellular ROS production. Although ROS can be produced in the cytosol by NADPH oxidases and xanthine oxidase, the major sources of ROS are mitochondria [13][14]. Simultaneously, mitochondria are a major target for damages by their own ROS.

Mitochondria can contain more than a dozen enzymatic sources of mtROS [15][16]. However, there is a consensus now that the mitochondrial respiratory chain is a primary source of mtROS, which are generated by the leakage of electrons from the ETC, resulting in a partial reduction in molecular oxygen. Mitochondrial complexes I (NADH-ubiquinone oxidoreductase) and III (cytochrome C oxidoreductase) are assumed to be a predominant source of superoxide generation under pathological conditions [13][17][18][19]. In particular, superoxide is generated by the reaction of O_2 with electrons originating either from direct transport from NADH under conditions of a slow respiration rate (due to low ATP demand or mitochondrial damage) or from the reverse electron transport (RET) from complex II (succinate dehydrogenase) to complex I under conditions of a high protonmotive force or when there is a high NADH/NAD^+ ratio in the matrix [13][17][18][19].

In healthy tissues under physiological conditions, mtROS generation and their removal by endogenous scavenging compounds and enzymes are tightly controlled by a complex antioxidant defense network including superoxide dismutase (SOD), catalase, ascorbic acid, tocopherol, reduced glutathione (GSH), etc. SOD catalyzes the conversion of superoxide to hydrogen peroxide, which, in turn, is converted to water by glutathione peroxidase

(GPx). Under oxidative stress, the expression of antioxidant genes is activated by translocation of nuclear factor E2-related factor 2 (Nrf2) from the cytoplasm to the nucleus [20][21].

mtROS are necessary for the cell due to their essential role in various intracellular signaling pathways, including mitochondrial quality control by autophagy [22][23]. Disturbance of the fine-tuning of the equilibrium between mtROS generation and scavenging leads to excessive ROS production, resulting in severe damage of single cells and whole organs, loss of function, and then organism failure [24][25]. Numerous pathological conditions and diseases such as sepsis, cancer, metabolic diseases, neurodegenerative diseases, and others are triggered or accompanied by an increased level of mtROS [26][27][28]. At the cellular level, the most harmful effects of mtROS are associated with oxidation-triggered sustained damage of mitochondrial nucleic acids, proteins, and lipids, resulting in the impairment of ETC functioning and ATP production [28][29][30][31][32][33]. For example, mtROS-induced oxidation of cardiolipin polyunsaturated fatty acids damages cristae curvatures, reduces ETC complex activity, initiates cardiolipin translocation from the inner to the outer mitochondrial membrane, and triggers cytochrome C release into the cytosol, which is critical for the mitochondrial cell death pathway [34]. Furthermore, mtROS can oxidize proteins of the mitochondrial permeability transition pore, enhancing cytochrome C and mitochondrial DNA (mtDNA) release. mtDNA is especially sensitive to damage by ROS due to a lack of protective histones and its proximity to the ETC [35][36]. mtROS-initiated release of mtDNA is an important trigger of systemic inflammation, which is recognized by cells as a virulent pathogen motive [32]. Inflammatory conditions are commonly accompanied by excessive NO production, which, in turn, can interact with superoxide to generate the highly toxic peroxynitrite ($ONOO^-$) [37][38].

3. LPS Triggers mtROS Generation

Enhancement of ROS generated in both the cytosol and the mitochondria is an important step in LPS signaling that links the activation of TLR4 with the NF-kB-driven expression of proinflammatory mediators. Numerous animal models of sepsis (LPS or CLP) have demonstrated common abnormalities: increased level of ROS, decreased antioxidant capacity, and mitochondrial oxidative damage [37][39][40]. LPS-triggered generation of mitochondrial superoxide measured usually with the fluorogenic dye MitoSOX was demonstrated in different cell types, such as microglia [41][42], muscle myoblasts [43], gingival fibroblasts [44], human pulmonary bronchial epithelial cells [45], macrophages [46], and others. In addition, the decline in antioxidative enzymes and glutathione content caused by LPS contributes to the impairment of endogenous antioxidant defense and the subsequent increase in mtROS generation [47][48][49][50][51].

In a wide range of cell types, LPS application disturbs cellular energetics, which manifests itself in a decline in respiratory complex activity, decline in the mitochondrial membrane potential, reduction in mitochondrial respiration, and suppression of ATP production in a tissue-, time-, and dose-dependent manner [52][53][54][55][56][57][58][59][60]. A critical step in these disturbances is associated with excessive ROS generation [61][54][62][13][14]. In innate immune cells, LPS has been shown to switch the metabolic reprogramming from oxidative phosphorylation to aerobic glycolysis as a survival response maintaining the cellular ATP level [41][46][63][64], which results in the

slowing or reversing of electron transport through respiratory complex I and a subsequent increase in ROS production.

The intrinsic mechanisms linking TLR4 signaling and mtROS have been studied mainly in phagocytic cells such as macrophages in which both cytosolic and mitochondrial ROS generation is also related to their bactericidal activity [65][66]. Thus, it has been shown that LPS-triggered induction of mtROS is mediated by a complex I-associated protein evolutionarily conserved signaling intermediate in Toll pathways (ECSIT), which plays a key role in complex I assembly and stability [66][67]. Upon LPS stimulation, the TLR signaling adapter tumor necrosis factor receptor-associated factor 6 (TRAF6) is translocated to the mitochondria and ubiquitinates ECSIT, resulting in its enrichment at the mitochondrial periphery, thus leading to the augmentation of mitochondrial and cellular ROS generation [66]. TRAF6 also mediates the ubiquitination of the small GTPase Rac, maintaining it in an active GTP-loaded state, which is necessary for the full activation of the ROS-producing machinery [68]. In addition, it was demonstrated in macrophages that LPS activates mitochondrial mitofusin2 (Mfn2) expression, which has been shown to be a required step for mtROS generation. *Mfn2*$^{-/-}$ macrophages are not be able to produce mtROS and proinflammatory mediators in response to LPS [69]. Whether the above mechanisms exist in other cell types remains unknown.

4. Mitochondria-Targeted Antioxidants and Their Application against LPS-Triggered Inflammation

Generally, antioxidants are substances that can accept or donate electron(s) to eliminate the unpaired condition of free radicals, thus neutralizing them. Antioxidant drugs can either scavenge free radicals or turn into new free radicals, which in some cases are less active and dangerous than initial ones [70]. Antioxidants can also break chain reactions [71] as well as affect ROS-regulated enzymes through controlling the cellular level of free radicals [72][73][74][75]. The natural defense mechanisms are supplied by enzymatic and non-enzymatic antioxidants, which are distributed within the cell cytoplasm and organelles (such as SOD, GPx and reductase, catalase, vitamins, minerals, polyphenols, albumin, transferrin, ferritin, and a variety of others), whereas foods and supplements provide a wide variety of exogenous natural ones (e.g., vitamins B, C, and E; ions Zn, Cu, and Se; flavonoids; omega-3 fatty acids; *L*-carnitine; and Q-enzyme Q10).

4.1. Conjugates with Lipophilic Cations

An era of investigations applying mito-AOX conjugates began half a century ago when V. Skulachev and colleagues demonstrated the ability of lipophilic cations, such as triphenylphosphonium (TPP^+), to accumulate within mitochondria due to the large MMP (negative inside) [76]. In numerous chimeric mito-AOX compounds synthesized later, lipophilic cations, which provide drug accumulation several hundred-fold in the mitochondrial matrix, were grafted to antioxidant moieties, which quenched electrons from the respiratory chain, thus diminishing ROS elevation [77]. Conjugates designed in such a way are widely used as a tool for research, as well as for diagnostic and therapeutic purposes, including drug delivery (for review, see [78][79].

Triphenylphosphonium derivatives have been mainly used as a mitochondrial targeting moiety. They are conjugated with quinone derivatives (ubiquinone in MitoQs [80] or plastoquinone in SkQs [14][81]); with superoxide dismutase and catalase mimetics in MitoTEMPO and MitoTEMPOL, respectively [82]; and with vitamin E in MitoVitE [83], etc. Inside mitochondria, these chimeric mito-AOX undergo red/ox cycling: they not only quench radicals but also can be reduced afterward by the ETC.

Most of the in vivo studies and clinical trials were performed with MitoQ and SkQ1. As both compounds are found to be localized at the matrix-facing side of the inner mitochondrial membrane with their antioxidant portion and alkyl chain, their main protective activity is to prevent lipid peroxidation [84][85]. TPP-based mito-AOX accumulate preferentially in healthy and hyperpolarized mitochondria but not within injured mitochondria, which carry a lower membrane potential and therefore are capable of taking up lower doses of therapeutic antioxidants than normal ones [86][87].

TPP-based antioxidants have been widely used in both in vitro experiments on various types of cells exposed to LPS (Table 1) and in vivo experiments on typical animal models of inflammation or sepsis (administration of LPS or cecal ligation and puncture; Table 2). Each cellular model mimics a specific pathological state or disorder associated with mtROS-induced inflammation. Among examples in Table 1 is LPS- or bacteria-induced mitochondrial dysfunction in oligodendrocytes (model of multiple sclerosis) [85], renal tubular cells (pyelonephritis and acute kidney injury) [88][89], microglia (neurodegeneration) [42], hepatocytes (liver failure) [90], endothelial cells (vascular abnormalities) [60][91], muscle myoblasts (diaphragm weakness) [43], gingival fibroblasts (periodontitis) [44], intestinal epithelial cells (impaired gut barrier function) [20], and others.

Table 1. In vitro effects of mitochondria-targeted antioxidants.

Inflammatory Model	Cells	Mito-AOX	Major Findings	Reference
LPS *E. coli*	Macrophages	MitoQ 50-100 nM	↓ Cellular ROS; ↓ IL-1β mRNA and protein expression	[65]
LPS *E. coli*	BV-2 murine microglial cells	MitoTEMPO 200 μM	↓ Mitochondrial and cellular ROS; ↓ iNOS and COX-2 expression; ↓ TNF-α, IL-1β, IL-6 content; ↓ NF-κB activation	[42]
LPS *E. coli*	Primary cultured frog urinary bladder epithelial cells	MitoQ 25 nM	↓ Cellular ROS; prevention of fatty acid oxidation decline and lipid droplet accumulation	[56]
LPS *E. coli*	Intestinal epithelial cell line-6 (IEC-6)	MitoQ 1 μM	Stimulation of nuclear translocation of Nrf2	[20]

Inflammatory Model	Cells	Mito-AOX	Major Findings	Reference
LPS *E. coli*	NRK-52E (rat renal proximal tubular cell line)	MitoQ 1 μM	↓ Cellular ROS; ↓NLRP3 inflammasome activation; ↓ IL-1β, IL-18, and caspase-1	[89]
Mixture of cytokines + LPS *E. coli*	C2C12 muscle myoblasts	MitoTEMPOL 10 mg/L	↓ Mitochondrial superoxide generation; prevention of reduction in cell width	[43]
LPS *E. coli* + PepG *S. aureus*	HUVEC-C	MitoQ 1 μM	↓ Cellular ROS; restoration of MMP; ↓ IL-1β, IL-6, and IL-8	[91]
LPS *E. coli* + PepG *S. aureus*	HUVEC-C	Melatonin, 0.1, 1.0, 10, 100, and 500 μM; MitoVitE, 5 μM	↓ IL-6 and IL-8; ↓ NF-kB activation; ↓ loss of MMP; ↑ GSH level; ↓ decline in metabolic activity	[48][92]
LPS *P. gingivalis*	Human gingival fibroblasts	MitoTEMPO 50 μM	↓ Mitochondrial ROS; ↓ IL-6, IL-1β, and TNF-α production; ↓ activation of NF-B	[44]
Inflammatory mediators generated by incubation of white blood cells with LPS *E. coli*	Buffalo rat liver cell line-3A (BRL-3A)	MitoTEMPO, 500 nM	↓ Mitochondrial and cellular ROS; ↓iNOS mRNA; ↓ IL-6	[90]
LPS *E. coli* + IFN-γ + TNFα	HUVEC	Mitoquinone (MQ) 1 μM	↓ Cellular ROS; ↓ tyrosine nitration and iNOS protein expression; recovery of O_2 consumption and complex I activity	[60]
LPS *E. coli* + succinate	Bone marrow-derived macrophages	Dimethyl malonate, 10 mM; MitoQ, 500 nM; MitoTEMPO, 0.5–1 mM	↓ Cellular ROS, IL-1β, and HIF-1α; ↑ IL-1RA and IL-10	[46]
E. coli lysate + activated leucocytes	Primary culture rat kidney cells	SKQR1 10 nM	↓ Cellular ROS; ↓ cell dearth	[88]
LPS *E. coli*	Primary oligodendrocytes	SkQ1 5-10 nM	Restoration of myelin synthesis	[85]
LPS *E. coli*	Cardiomyocytes	Melatonin 100 μM	↓ Cellular ROS; ↓ loss of MMP; ↑ content of GSH,	[47]

Inflammatory Model	Cells	Mito-AOX	Major Findings	Reference
			SOD; ↓ decline in BAP31 expression; ↑ cell viability	
LPS *E. coli*	Primary neonatal rat cardiomyocytes	Melatonin 100 μM	↓ IL-6, TNF-α, mRNA levels; ↓Bax and ↑ Bcl-2 expression; ↑ autophagy;	[93]
LPS *E. coli*	Human alveolar epithelial cells	Melatonin, 800 μM	↓ cellular ROS; ↓ MDA; ↑ SOD and GPx levels; prevention of LPS-induced epithelial–mesenchymal transition through Nrf2 activation	[49]
LPS *E. coli*	Macrophages RAW 264.7	Mn-porphyrin-oligopeptide conjugate, 10 μM	↓ LPS-induced cell dearth	[94]
LPS *E. coli*	Cardiomyocytes (H9C2 cell line)	SS-31, 10 μM	↓ ROS; ↓ MDA; ↓ mRNA level of IL-6, IL-1β, and TNF-α; normalized activity of GPx and SOD; ↓ MMP decline; ↑ ATP	[50]
	Murine microglial		↓ ROS; effect is mediated by Fis1;	

Model of Infection	Species	Organ Investigated	Mito-AOX	Mode of Antioxidant Application	Major Findings	Reference
LPS *E. coli*	Rat, mouse	Heart	MitoQ 500 μM	Given water orally for 2 days	↓ Oxidative stress; ↓ mitochondrial dysfunction; ↓ cardiac TNF-α level; ↓ reductions in cardiac pressure generation; ↓ caspase 3 and 9 activity	[98]
LPS *E. coli*	Mouse	Gut, serum	MitoQ 4 mg/kg	i.v. injection 15 min before LPS	↓ Gut barrier dysfunction, restoration of the level of tight junction proteins (ZO-1 and occludin); ↓ intestinal inflammatory response; ↑ SOD	[20]

Model of Infection	Species	Organ Investigated	Mito-AOX	Mode of Antioxidant Application	Major Findings	Reference
					and GSH level; ↓TNF-*α*, IL-1, IL-6, and NO in intestines and plasma	
LPS *E. coli*	Rat	Liver, serum	MitoTEMPO 50 nmol/kg; SKQ1 5 nmol/kg	i.p., 24 and 1 h before LPS	↓ iNOS expression; ↓ plasma NO; ↓liver damage	[90]
LPS *E. coli*	Rat (7-day-old pups)	Kidney	SkQR1 100 nmol/kg	i.p., 3 h before LPS	↓Acute kidney injury; preservation of cell proliferative activity	[99]
E. coli lysate	Rat	Kidney	SkQR1 500 nmol/kg in total	i.p., 1, 12, 24, 36, and 48 h after intraurethral bacteria injection	↓ Renal cell dearth and animal mortality, restoration of Bcl-2 level in kidney; ↓TNF-α in kidney	[88]
LPS *E. coli* + PepG *S. aureus*	Rat	Liver, kidney, lungs, heart, gut	7.5 µmol/kg MitoQ, then 5 µmol/kg/h MitoQ	As a bolus i.v. infusion for 6 h after LPS+PepG	↓ Acute liver and renal dysfunction; ↑ MMP in most organs	[91]
LPS *E. coli* + PepG *S. aureus*	Rat	Liver, kidney	1.5 µmol/kg MitoQ or MitoVitE or melatonin, then 1 µmol/kg/h MitoQ, MitoVitE, or melatonin	As a bolus i.v. infusion for 5 h after LPS+PepG	↓ Mitochondrial damage; ↓ organ dysfunction; ↓ inflammatory response	[100]
CLP	Mouse	Kidney	MitoTEMPO 10 mg/kg	i.p., 6 h after operation	↓ Mitochondrial ROS, protection of complex I and II/III respiration; ↑ SOD; ↓ renal dysfunction (improved renal microcirculation and GFR); ↑	[53]

Model of Infection	Species	Organ Investigated	Mito-AOX	Mode of Antioxidant Application	Major Findings	Reference
					survival of animals	
CLP	Mouse	Diaphragm	MitoTEMPOL 10 mg/kg/d	i.p., immediately after operation and 24 h later or only 6 h after operation	↓ Diaphragm weakness; ↓ mitochondrial superoxide generation; prevention of mitochondrial dysfunction; ↓ proteolytic enzyme activities; ↓ depletion of myosin heavy-chain protein content	[43]
LPS *E. coli*	Mouse	Heart	Melatonin 20 mg/kg/d	i.p., 48 h before LPS	↓ Cardiomyopathy; ↓ caspase 3 activation and cardiomyocyte apoptosis	[47]
LPS *E. coli*	Mouse	Heart	Melatonin 20 mg/kg/d	i.p., for 7 days before LPS	↓ Myocardial dysfunction and inflammation; ↓ cardiomyocyte apoptosis; ↑ AMPK activity and autophagy	[93]
LPS *E. coli*	Mouse (pregnant)	Placenta	Melatonin 5.0 mg/kg	i.p., 30 min before and 150 min after LPS	↓ Placental oxidative stress, hypoxic stress, and ER stress	[101]
CLP	Mouse	Diaphragm	Melatonin 30 mg/kg	i.p., four doses: 30 min before operation, just after operation, and 4 and 8 h after operation	↓ Respiratory chain failure; restoration of the redox status	[102]

Model of Infection	Species	Organ Investigated	Mito-AOX	Mode of Antioxidant Application	Major Findings	Reference
CLP	Rat	Liver, kidney, lung, heart, diaphragm	Melatonin 10 mg/kg	i.p. 30 min before and 6 h after operation	↑ Level of GSH; ↓ MDA; ↓ tissue oxidative damage	[51]
LPS *E. coli*	Mouse	Heart	SS-31 5 mg/kg	i.p., 30 min after LPS	↓ ROS; restoration of myocardial damage; ↑ ATP; ↓ mRNA level of IL-6, IL-1β, and TNF-α; ↓ apoptosis;↑ SOD and GPx	[50]
LPS *E. coli*	Mouse	Liver, serum	XJB-5-131 2 μmol/kg	i.v. 1 h before LPS	↓ Hepatic iNOS expression, ↓ blood nitrite level	[96]
LPS *E. coli*	Mouse	Hippocampus	SS-31 5 mg/kg	LPS microinjection in the hippocampi SS-31 i.p. 30 min before LPS and then once daily for 3 days thereafter	↓ ROS, MDA, IL-6, and TNF-α; ↑ SOD; ↓ hippocampal cell apoptosis; ↑ BDNF expression and synaptic protein levels, maintenance of hippocampal neuron morphology; ↓ memory impairment	[103]
CLP	Mouse	Lung, kidney, liver	SS-31 5 mg/kg	i.p, immediately and 5 h after operation	↓ ROS, MDA, TNF-α, MPO activity, iNOS, and NF-κB p65; ↑ ATP; ↓ apoptosis, ↓ the histological damage; ↓ organ dysfunction, no result on mouse survival rate	[104]
CLP	Mouse	Hippocampus	SS-31 5 mg/kg	i.p, immediately after operation and	↓ ROS; ↓ NLRP3 and IL-1β; ↑ ATP; ↓ mitochondrial dysfunction; ↓	[97] [89] [105]

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organs, such as the heart, kidney, liver, lung, and others, after oral, i.v., or i.p. administration [77][107].

Model of Infection	Species	Organ Investigated	Mito-AOX	Mode of Antioxidant Application	Major Findings	Reference
		[98]		once daily for 6 days thereafter	apoptosis; ↓ behavior and cognitive deficits; ↓ mortality rate	[108]
Live *E. coli* bacteria	Rat	Serum [53]	M40401 (SOD mimetic) 0.25, 2.5, 25 μmol/kg/h	i.v. infusion 0.5 and 3 h after bacterial challenge	Maintenance of a normal mean arterial pressure; ↓ TNF-α and IL-1β, ↓ mortality	[91] [106] [99]

differences, mito-AOX were nephroprotective (Table 2). SKQR1 was also highly protective against acute pyelonephritis induced by intraurethral infection [88]. In the frog urinary bladder epithelium, which possesses the characteristics of the mammalian kidney collecting duct, MitoQ effectively inhibited LPS-induced ROS generation, the decline in fatty acid oxidation, and subsequent accumulation of lipid droplets, demonstrating a key role of mtROS in the shift of intracellular lipid metabolism under the influence of bacterial stimuli [56].

The impairment of gut permeability is a serious consequence of dysbiosis. MitoQ has been shown to improve intestinal permeability and inhibit LPS-induced bacterial translocation via a decrease in oxidative stress and restoration of the level of tight junction proteins (occludin and ZO-1) in the gut epithelium [20]. The authors showed that MitoQ alleviates LPS-induced oxidative stress in intestinal epithelial cells, triggering the nuclear translocation of the nuclear factor Nrf2, which, in turn, stimulates the expression of its downstream antioxidant genes [20].

Data presented in Table 2 indicate that the protective effect of mito-AOX can be observed independently on the differences in the administration protocol (application of mito-AOX before, immediately after LPS administration /CLP or some time later). Even a six-hour delay in therapy with a single dose of MitoTEMPO significantly increased mitochondrial respiration and improved renal function and survival of animals [53]. Both immediate and delayed administration of the dismutase mimetic MitoTEMPOL was found to prevent sepsis-induced diaphragm weakness in a similar mode [40]. These observations are very important due to their clinical relevance.

However, some studies have reported that TPP-conjugated compounds fail to inhibit mtROS-mediated injuries [109] or even have a detrimental effect on mitochondrial function. For example, in cultured mesangial cells, MitoQ, MitoTEMPOL, and MitoVitE at a dose of 1 μM inhibited oxidative phosphorylation [110]. Application of MitoQ (500 nM) to proximal tubule cells led to mitochondrial swelling and depolarization [111]. Both MitoQ (500 nM) and MitoTEMPOL (10 μM) had a marked negative effect on the respiration of myoblasts compared to controls [112]. The studies mentioned above revealed that the negative effect of TPP-conjugated compounds on mitochondrial function is related to the toxicity of the carbon alkyl chain of the cation moiety itself [110][111][112]. Another reason for TPP-conjugated mito-AOX toxicity is their ability to be pro-oxidants that generate superoxide via redox cycling [84] [113]. A high concentration of antioxidants as well as other factors (the redox potential of matrix environments, the presence of Cu, Fe, and Zn ions) could reverse their behavior from anti- to pro-oxidant, subsequently causing toxic effects [87][114]. The pro-oxidant effect of MitoQ and other related compounds applied at high concentrations (more than 1 μM) has been shown to kill tumor cells, considering mito-AOX as potential chemotherapeutic drugs [87][115]

[116]. However, no pro-oxidant effect of MitoQ and other targeted quinones was demonstrated in mice who were fed antioxidants [117].

Since the probability of an adverse side effect of cation-conjugated mito-AOX provided by either a cation moiety or pro-oxidative behavior depends critically on their concentration; when dealing with this type of mito-AOX, it is particularly important to choose the relevant concentration, which, in turn, depends on a given cell type. For example, our experiments revealed that frog urinary bladder epithelial cells, demonstrating high tolerance to LPS, are very sensitive to the toxic effect of MitoQ (IC_{50} = 400 nM) [56]. At doses higher than 25 nM, it reduced the oxygen consumption rate and cell viability, whereas the antioxidant potency of MitoQ and the ability to restore the LPS-induced decline in fatty acids oxidation were observed at a dose of 25 nM [56], which is much less than that in most other in vitro works [65][118][119][120]. Of note, the concentrations of mito-AOX used in in vitro experiments were much higher than those that can be achieved pharmacologically and were associated with protective effects in vivo [121].

4.2. Other Mitochondria-Targeted Conjugates

There was an attempt to design mito-AOX using the mitochondrial protein import machinery, which delivers nuclear-encoded mitochondrial proteins inside the mitochondria via translocase through the outer and inner membranes (TOM and TIM complexes, respectively). A mitochondria-targeted macrocyclic SOD mimetic was synthesized by attaching the mitochondria-targeting sequence peptide to the porphyrin ring of the manganese porphyrin complex MnMPy4P. The resulting construct MnMPy3P–MTS reportedly demonstrated a decrease in LPS-induced cell death in activated macrophages [94].

Another example of the successful application of mito-AOX against LPS is the hemigramicidin–TEMPO conjugate XJB-5-131, which consists of a stable nitroxide radical and a portion of the membrane-active cyclopeptide antibiotic gramicidin S. The gramicidin segment was used to target the nitroxide payload to mitochondria because antibiotics of this type have a high affinity for bacterial membranes [96]. XJB-5-131 limited the LPS-induced inflammatory response both in vitro in macrophages and in vivo in a mice septic model [96].

4.3. Melatonin

Melatonin is a natural antioxidant produced mainly by the pineal gland as well as by most of the organs and tissues. Frequent use of melatonin for treatment of insomnia is based on its traditionally accepted role as a hormonal regulator of the circadian rhythm. Besides this, melatonin possesses antiapoptotic, anti-inflammatory, and antitumor activity, as well as powerful antioxidant properties. These facts alongside its profoundly safe side-effect profile make it possible to propose melatonin as a promising adjunctive drug for different pathological states, including inflammation and sepsis (for review, see [122][123][124][125][126]).

Melatonin was first reported as a potent, broad-spectrum antioxidant and free-radical scavenger in the early 1990s [127]. The electron-rich melatonin molecule provides its antioxidant power via a cascade of scavenging reactions. Unlike classical antioxidants that have the potential to act as anti- and pro-oxidants via redox cycling [128],

melatonin forms several stable end products excreted in the urine, which is believed to exclude its pro-oxidant effect [129]. Although the high lipid solubility of melatonin favors its entering all cells and subcellular compartments, melatonin is specifically targeted to mitochondria, where it enters via the oligopeptide transporters PEPT1 and PEPT2 [130]. In addition, melatonin is produced within mitochondria, and its generation can be inducible [131][132]. For these reasons, mitochondria have the highest level of melatonin.

Melatonin is one of the most important endogenous factors in limiting oxidative stress. It provides antioxidant defense via a plethora of mechanisms. Melatonin by itself and also its endogenous metabolites directly scavenge free radicals, bind heavy metals associated with radical production, reduce the membrane potential, and stimulate ETC complex activity and ATP synthesis [133][134][135]. Moreover, melatonin potentiates the activity of a wide variety of antioxidant enzymes. It inhibits the ubiquitination of Nrf2, allowing its binding with the antioxidant response element, which, in turn, activates the transcription of antioxidant genes [136][137]. Melatonin augments the SIRT3 signaling pathway, which protects mitochondria from oxidative damage, upregulates the synthesis of GSH, and acts synergistically with vitamin C, vitamin E, and GSH to scavenge free radicals [128][138].

Numerous experimental studies have revealed the antioxidant and anti-inflammatory properties of melatonin, both in vitro and in vivo. Typical examples are presented in Table 1 and Table 2. On different cells challenged with LPS (HUVECs, cardiomyocytes, alveolar epithelial cells), it was shown that melatonin decreases ROS generation [47][49] and production of proinflammatory cytokines [48][49][93] and increases cellular antioxidant content (SOD, GSH) [47][48][92] through upregulation of Nrf2 expression [49]. Interestingly, not only melatonin but also its structurally related indolamine compounds (6-hydroxymelatonin, tryptamine or indole-3-carboxylic acid) possess antioxidant properties [48].

The beneficial application of melatonin was demonstrated in two animal models of sepsis—administration of LPS and CLP. Melatonin, being commonly injected i.p. before or after sepsis initiation, significantly improved sepsis-induced organ dysfunction (heart, kidney, liver, lung, placenta) by decreasing oxidative tissue damage and the inflammatory response, preserving mitochondrial function [47][51][93][100][101][139]. In the latest works on the septic cardiomyopathy model, it was shown that LPS suppresses the expression of B cell receptor-associated protein 31 (BAP31), a key regulator of endoplasmic reticulum stress, and melatonin could restore BAP31 expression. The knockdown of BAP31 attenuated the beneficial effects of melatonin on mitochondrial function and endoplasmic reticulum homeostasis under LPS [47], suggesting that, at least in part, melatonin contributes to the preservation of cardiac function in septic cardiomyopathy via regulation of BAP31 expression and stability. Another work demonstrated that autophagy plays a critical role in melatonin-induced myocardial protection. Thus, melatonin protects against LPS-induced septic myocardial injury by activating the AMPK-mediated autophagy pathway and further inhibiting mitochondrial injury and myocardial apoptosis [93].

4.4. Cell-Permeable Peptide Antioxidants

In the middle of the 2000s, a family of cell-permeable small synthetic tetrapeptides (Szeto–Schiller peptides (SS peptides)) was introduced as mitochondria-targeted antioxidants. The electron-scavenging abilities of SS peptides

were provided by aromatic–cationic motifs in their molecules [140][141][142]. SS peptides readily penetrate the cell via diffusion, selectively accumulate within mitochondria, and concentrate in the IMM without reaching the mitochondrial matrix. In contrast to the MMP-driven entry of triphenylphosphonium-based conjugates into the mitochondria, the accumulation of SS peptides is independent of the MMP and does not depolarize the mitochondrial membrane. For this reason, SS peptides can penetrate not only normal mitochondria but also damaged ones with a low MMP [140].

The most studied peptide of this family is SS-31 (elamipretide, Bendavia™, MTP-131, d-Arg-Dmt-Lys-Phe-NH_2), which, in addition to its mtROS-scavenging ability, links selectively to cardiolipin by electrostatic and hydrophobic interactions [143][144]. Thus, SS-31 is now positioned more as a cardiolipin stabilizer/protector than as a mtROS scavenger.

Cardiolipin is readily oxidized by mtROS, which leads to multiple injuries. Oxidized cardiolipin disrupts the structure of respiratory supercomplexes to inhibit electron transfer and oxidative phosphorylation [34]. Translocation of oxidized cardiolipin from the IMM into the OMM provides a docking station for NLRP3 inflammasome assembly, and it can trigger mitochondrial fission and initiate mitophagy [145]. Binding of SS-31 to cardiolipin inhibits cardiolipin peroxidation, stabilizes cristae curvatures [143][144][146][147], and restores the stability and activity of respiratory complexes [148].

The linking of SS-31 to cardiolipin also inhibits the peroxidase activity of cytochrome C to result in decreasing mtROS production and improving the coupling between oxygen consumption and ATP synthesis [144]. SS-31 enhances ATP levels even under conditions of low substrate and oxygen supply, such as ischemia [143][146], or in increased energy demand states, such as sepsis and others pathologies [50][149][150]. The restoration of mitochondrial functioning by SS-31 can prevent a wide range of downstream cellular events, e.g., inflammasome activation and cytokine expression, autophagy, apoptosis, and necrosis. The beneficial effects of SS-31 were reported in different disease models (for review, see [151]), demonstrating the existence of a common mechanism mediating its action in different pathological conditions.

The protective effect of SS-31 against LPS was demonstrated in several in vitro and in vivo models (see Table 1 and Table 2). In LPS-treated cells and CPL/LPS-challenged mice, SS-31 decreased apoptosis, improved sepsis-induced organ dysfunction, restored morphological damage, and reversed mitochondrial dysfunction [50][103][104][105]. It also attenuated ROS and MDA levels [50][103][104][105], maintained ATP production [50][104][105], and suppressed pro-inflammatory cytokine expression [50][103][104][105].

Several successive clinical trials in phases 1-3 were conducted in patients with cardiac, renal, skeletal muscle, and ophthalmic problems, as well as in mitochondrial myopathy patients (for review, see [151]). No adverse side effects of SS-31 were found until now. The safety of using SS-31, a drug with multiple beneficial pharmacological properties, for organs most affected by sepsis is particularly important. Very promising preclinical and clinical trial findings encourage to develop SS-31-based therapeutic approaches for the treatment of sepsis and other pathologies.

4.5. Suppressors of Site IQ and IIIQ Electron Leakage

Recently, small molecules from different chemical families that specifically suppress mitochondrial superoxide/H_2O_2 production (S1QELs for site I_Q [152] and S3QELs for site III_{Qo} [153]) were identified by chemical screening. They bind directly to complex I or III and selectively suppress electron leakage without inhibiting oxidative phosphorylation [152][153], as well as inhibit the reverse electron flow through complex I [154]. They do not cause cytotoxicity at their effective concentrations [153] and do not participate in redox recycling [155].

The cytoprotective effect of S1QELs against oxidative damage has been demonstrated in animal (rat, mouse), human, and different cellular models [153][156][157]. S1QELs protected against ischemia-reperfusion injury in a perfused mouse heart [158]. In a murine model of asystolic cardiac arrest, S1QELs diminished myocardial ROS, as well as improved myocardial function after cardiopulmonary resuscitation, neurologic outcomes, and survival [159]. In recent papers, S1QELs and S3QELs have been offered as promising investigation tools for elucidating the functioning of I_Q and III_{Qo} sites in normal and pathological conditions, opening up new possibilities for better therapy [155][160]. Given the fact that LPS-driven mtROS are generated predominantly by mitochondrial complex I, S1QELs can potentially be specific suppressors of LPS-induced mtROS production, gently withstanding LPS-induced oxidative stress. However, the efficiency of S1QELs and S3QELs in a sepsis animal model or LPS-induced injury remains poorly investigated and warrants further research.

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