Redox Biology 13 (2017) 170–181

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Mitochondria-meditated pathways of organ failure upon inflammation

Andrey V. Kozlov[a,*], Jack R. Lancaster Jr.[b], Andras T. Meszaros[c], Adelheid Weidinger[a]

[a] Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, AUVA Research Center, Donaueschingen Str. 13, 1200 Vienna, Austria
[b] University of Pittsburgh, Departments of Pharmacology & Chemical Biology, Surgery, and Medicine, 1341A Thomas E. Starzl Biomedical Science Tower, PA 15261, United States
[c] University of Szeged, Institute of Surgical Research, 6720 Szeged, Hungary

ARTICLE INFO

Keywords:
Liver failure
Mitochondria
Reactive oxygen species
Signaling
Inflammation

ABSTRACT

Liver failure induced by systemic inflammatory response (SIRS) is often associated with mitochondrial dysfunction but the mechanism linking SIRS and mitochondria-mediated liver failure is still a matter of discussion. Current hypotheses suggest that causative events could be a drop in ATP synthesis, opening of mitochondrial permeability transition pore, specific changes in mitochondrial morphology, impaired Ca^{2+} uptake, generation of mitochondrial reactive oxygen species (mtROS), turnover of mitochondria and imbalance in electron supply to the respiratory chain. The aim of this review is to critically analyze existing hypotheses, in order to highlight the most promising research lines helping to prevent liver failure induced by SIRS. Evaluation of the literature shows that there is no consistent support that impaired Ca^{++} metabolism, electron transport chain function and ultrastructure of mitochondria substantially contribute to liver failure. Moreover, our analysis suggests that the drop in ATP levels has protective rather than a deleterious character. Recent data suggest that the most critical mitochondrial event occurring upon SIRS is the release of mtROS in cytoplasm, which can activate two specific intracellular signaling cascades. The first is the mtROS-mediated activation of NADPH-oxidase in liver macrophages and endothelial cells; the second is the acceleration of the expression of inflammatory genes in hepatocytes. The signaling action of mtROS is strictly controlled in mitochondria at three points, (i) at the site of ROS generation at complex I, (ii) the site of mtROS release in cytoplasm via permeability transition pore, and (iii) interaction with specific kinases in cytoplasm. The systems controlling mtROS-signaling include pro- and anti-inflammatory mediators, nitric oxide, Ca^{2+} and NADPH-oxidase. Analysis of the literature suggests that further research should be focused on the impact of mtROS on organ failure induced by inflammation and simultaneously providing a new theoretical basis for a targeted therapy of overwhelmed inflammatory response.

1. Introduction

Mitochondrial dysfunction is often associated with multiple organ failure (MOF), also referred to as multiple organ dysfunction syndrome (MODS), induced by dysregulated systemic inflammatory response (SIR). This pathological process, known as systemic inflammatory response syndrome (SIRS) [1,2], is a common cascade accompanying sepsis, trauma, burns, acute pancreatitis, ischemia, anaphylaxis and a number of other diseases. Despite huge efforts in the preclinical and clinical research field, pathogenesis of MOF is still not clearly understood. Mitochondria are good candidates for playing a key role in this process (reviewed in [3–5]), because they are essential components of almost all eukaryotic cells, controlling several important cellular functions, such as adenosine triphosphate (ATP) synthesis [6], regulation of Ca^{++} homeostasis (reviewed in [7,8]), generation of reactive oxygen species (ROS) (reviewed in [9–14]), activation of apoptosis

Abbreviations: ADP, adenosine diphosphate; ANT, adenine nucleotide translocator; ATP, adenosine triphosphate; Bax, BCL2-associated X protein; Bcl-xL, B-cell lymphoma-extra large; CLP, cecal ligation and puncture; CyP, cyclophilin; DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; ERK, extracellular-signal regulated; GRIM19, retinoic-interferon-induced mortality; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; IL, interleukin; i.v., intravenous; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LD_{50}, median lethal dose; LPS, lipopolysaccharide; MAP, mitogen-activated protein; MKK4, MAP kinase kinase; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure; mPTP, mitochondrial permeability transition pore; mtROS, mitochondrial reactive oxygen species; NO, nitric oxide; $O_2^{\bullet -}$, superoxide radical; $ONOO^-$, peroxynitrite; PAMP, pathogen-associated molecular pattern; PCLS, precision cut liver slices; PiC, phosphate carrier; PK, protein kinase; $ONOO^-$, peroxynitrite; RIP, receptor-interacting protein; ROS, reactive oxygen species; SHP1, src homology 1 domain containing protein tyrosine phosphatase; SIR, systemic inflammatory response; SIRS, systemic inflammatory response syndrome; STAT3, signal transducer and activator of transcription 3; TLR, Toll-like receptor; TNF alpha, tumor necrosis factor alpha; TNFR1, TNF receptor type 1

* Corresponding author.
E-mail address: Andrey.Kozlov@trauma.lbg.ac.at (A.V. Kozlov).

http://dx.doi.org/10.1016/j.redox.2017.05.017
Received 5 April 2017; Received in revised form 24 May 2017; Accepted 24 May 2017
Available online 25 May 2017

(reviewed in [15]) and maintenance of intracellular redox potential.

The liver is one of the most susceptible organs to SIR [16], and manifestation of liver dysfunction nearly always accompanies SIRS [17]. Liver dysfunction, in turn, has dramatic consequences for the whole body, inducing encephalopathy and cerebral edema, coagulopathy, cardiovascular instability, respiratory and renal failure. Thus, liver failure itself may induce MOF contributing to the lethal fate of SIR. Consequently, prevention of liver dysfunction may ameliorate MOF/MODS and improve clinical outcome and survival of patients with SIRS.

Liver failure has already been associated with mitochondrial dysfunction [18,19] and inflammation (reviewed in [20]), both contributing to a wide range of liver diseases. It has been shown that liver inflammation, accompanied by the activation of immune cells in liver tissue, is highly associated with hepatocellular carcinoma (reviewed in [21]) and both alcoholic and non-alcoholic fatty liver diseases (reviewed in [22]). This suggests that mitochondrial dysfunction links inflammation and liver failure.

Single studies usually address only selected mitochondrial functions instead of providing a complete view in the context of inflammation. This may be a reason for controversial data in the literature on the pathologic impact of mitochondrial dysfunction, ranging from critical to unimportant contribution to MOF/MODS. Another body of literature suggests that an increase in mitochondrial turnover can be a sign of mitochondrial dysfunction. These reports address the changes in mitochondrial biogenesis [23–25] or/and autophagy [26]; (reviewed in [27,28]), assuming that these changes are due to an increased number of damaged/dysfunctional mitochondria, although the majority of mitochondria appeared normal [29].

The aim of this review was to summarize data which confirm or contradict contribution of specific mitochondrial functions to liver inflammation-induced organ failure. We analyzed the existing literature hypothesizing that there are two prerequisites for the critical role of mitochondrial dysfunction: (i) in all species which are susceptible to SIR, either mitochondrial structure or function(s) will be impaired in a similar manner, and (ii) if such impairment of mitochondrial function (s) occurs, then a similar damage should cause liver failure also in other pathological settings. Consequently, we consider that mechanisms of liver dysfunction have similar pathways in humans and in animal models.

1.1. Factors inducing acute SIR

The activation of the inflammatory response aims at combating pathogens. This reaction is induced by so-called damage-associated molecular pattern molecules (DAMPs) ([30], reviewed in [31]). A subgroup of DAMPs are microbial pathogen-associated molecular pattern molecules (PAMPs), such as structural components and nucleic acids of viruses (reviewed in [32]), lipopolysaccharide (LPS) of Gram-negative bacteria and peptidoglycan of Gram-positive bacteria (reviewed in [33]). Both DAMPs and PAMPs activate innate and adaptive immune responses predominantly via Toll-like receptors [34]. If the regulatory mechanisms of the inflammation fail, the response may become excessive, resulting in an overwhelming SIR. Although intended as a self-protection program, this undesirable side effect of the activation of the immune system can cause damage to host cells and induce MODS/MOF [35–37]. The mechanisms and pathways of MODS/MOF-inducing systemic inflammatory response are subject of many investigations and have already been extensively reviewed [38–44]. However, the exact mechanisms underlying this deleterious effect have still not clearly been uncovered. As a matter of fact, many mammals develop MOF in response to SIR, often leading to death. The mortality resulting from SIR in the clinics is still very high [45–47], even in modern intensive care units (reviewed in [4]).

The most common and reproducible way to induce SIR in experimental animal models is administration of the pathogen-associated molecular pattern molecule LPS, a Gram-negative bacterial toxin. To date, the majority of mechanistic data on SIR are based on LPS models. LPS induces MOF/MODS in different species in a similar way as can be characterized by elevated levels of circulating tissue damage markers [48,49]. However, the concentrations of LPS needed to induce similar damage as well as LD_{50} differ from species to species (Table 1). A prominent feature of LPS-induced SIR is a dose-dependent increase in TNF-α levels. Xenobiotics, like D-Galactosamine sensitize hepatocytes to apoptosis triggered by TNF-α, at least partly by a transcriptional block. In such models, a small amount of LPS, as little as a few micrograms/kg is able to induce severe hepatic damage [50]. Moreover, it was demonstrated that desensitization of the mitochondrial permeability transition pore leads to a protection against liver injury despite the maintained early TNF-α response [18]. Accordingly, on the one hand, the above mentioned evidences demonstrate crucial role of mitochondria in the process. On the other hand, inter-species differences in the sensitivity to LPS might be connected to regulatory characteristics of pore opening as well. If we consider mitochondrial dysfunction as the critical issue for organ failure upon SIR, we expect that different doses of LPS in different species should induce similar changes in mitochondria. This consideration assumes that intracellular signaling pathways mediating mitochondrial dysfunction, predominantly define the sensitivity to LPS and/or other DAMPs/PAMPs in various species. The question whether or not different species in fact manifest similar impairment of liver mitochondria upon SIR will be discussed in the following sections.

Table 1
Susceptibility of different species to LPS.

Species	Pig	Rabbit	Dog	Cat	Rat	Mouse
LD_{50} LPS (mg/kg, i.v.)	0.1**	0.5*	1.0*	2.2*	7.3*	7.7*

* Registry of toxic effects of chemical substances [51].
** Maximum dose reported.

1.2. Effect of SIR on mitochondrial structure

Ultra-structural alterations of liver mitochondria have been reported from various animal species and as well as from septic patients. Crouser et al. observed mild to moderate mitochondrial swelling, and occasionally high-amplitude swelling with concomitant loss of mitochondrial membrane integrity in experiments with LPS-treated feline [52]. They also reported that cyclosporine A pretreatment attenuated LPS-induced mitochondrial ultra-structural abnormalities, suggesting the involvement of permeability transition pore opening in mitochondrial swelling [53]. Hypertrophic mitochondria with reduced matrix electron density and irregular cristae were also found in post-mortem samples of critically ill patients [54]. In contrast, in another study, most mitochondria of liver samples taken from septic patients were normal in appearance, with intact organelle membrane [29]. These results were confirmed in a parallel study performed in mice. Livers of animals subjected to cecal ligation and puncture (CLP) did not manifest consistent abnormalities in mitochondria or nuclei [29]. Similarly, in another CLP mice study, the vast majority of liver mitochondria in the CLP group appeared normal, but increased number of intracellular vacuoles were observed in hepatocytes and identified as autophagosomes [55]. Furthermore, electron microscopic examination of isolated liver mitochondria and liver tissue taken from rats subjected to LPS did not evoke changes in the morphology of mitochondria neither in isolated mitochondria nor in liver tissue [56]. Also an increased number of intracellular vacuoles were observed in hepatocytes in close vicinity to mitochondria in liver samples from LPS-treated rats, which were identified as dilated endoplasmic reticulum (ER) [57].

Taken together, the majority of papers reported normal appearance of mitochondria. However, intracellular vesicles have often been found which were either interpreted as autophagosomes or dilated ER. Both of