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Mitochondrial damage pathways in ventilator induced lung injury (VILI): an update

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Abstract

Although reduced tidal volumes have improved patient survival during ventilation for acute lung injury, further improvements will require pharmacologic interventions of the cellular pathways for inflammation and injury. We previously reported that pretreatment with mitochondrial targeted mtDNA repair enzymes largely prevented lung injury and inflammation during a protocol for moderately severe ventilation induced lung injury. GSH/GSSG ratios indicated that free radical production had been reduced to baseline levels by treatment. The central role of the alveolar macrophages and cellular mechanisms of injury are discussed. This includes a rapid calcium entry and mitochondrial production of excessive reactive oxygen species. Excessive ROS can then result in activation of the NLRP3 inflammasome and secretion of IL-1 and IL-18 by caspase-1. A simultaneous activation of NFkB to transcribe pro forms of the cytokines is stimulated by damage associated molecular pattern (DAMP) recognition receptors. These are primarily TLR4 responding to various cellular damage products and TLR9 responding to mtDNA fragments that appear to be primarily involved. Intervention in these pathways could result in useful future clinical treatments.

Keywords

ventilator induced lung injury; Mitochondria; Macrophages; Calcium channels; Inflammasome; Cytokines

Previous experimental studies indicate a direct relationship of lung vascular permeability and edema formation to the time and gas pressures used for mechanical ventilation[1–3]. Ventilator induced lung injury (VILI) is a significant contributor to clinical mortality during mechanical ventilation, and reduction of tidal volumes has improved overall patient survival for acute lung injury (ALI) conditions requiring mechanical ventilation[4]. Since tidal volumes cannot be significantly reduced further, pharmacological interventions are needed which can treat the diverse range of pathologies requiring mechanical ventilation. Therefore, understanding the pathways involved in initiation and sustaining lung injury during mechanical ventilation is essential.

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Toward this end, Hashizume and Associates pretreated mice with fusion protein constructs consisting of a TAT sequence for cell entry, a mitochondrial targeting sequence from manganese superoxide dehydrogenase (mnSOD), a hemagglutinin tag for immunologic localization and a histidine tail[5]. Also included were either of two glycosylase mtDNA repair enzymes, Endonuclease III to remove oxidized pyrimidines[6], or 8-oxoguanine DNA glycosylase 1 (OGG1) to remove oxidized purines[7] from damaged mtDNA[8]. The presence of these constructs was demonstrated in the mitochondria of both studies. Three levels of lung vascular permeability and edema were produced by adjusting ventilation time and peak inflation pressure (PIP)[1;3]. Bronchoalveolar lavage (BAL) albumen increased by two-fold during minimal injury, 42-fold in moderate injury, and 86-fold in the severe injury group. Pretreatment with mtDNA repair enzymes significantly reduced BAL albumen and lung edema towards control levels in minimal and moderate injury but not in the severe injury group. However, all severely injured animals in the enzyme treated group survived the protocol whereas none of the untreated severe injury group survived to complete the protocol. The dramatic increases in IL-6 and MIP-2 after moderate injury were also prevented with repair enzyme pretreatment, and a higher percentage of intact mitochondrial DNA was maintained compared to the untreated group. However, enzyme pretreatment did not attenuate the very large increases in edema or cytokines with severe injury. The dramatic decreases in the total glutathione pool and GSH/GSSG ratio after moderate injury were also prevented by enzyme pretreatment. In contrast, enzyme pretreatment did not affect glutathione changes with a very severe injury. Thus, the marked increase in ROS production, lung injury and inflammation during high PIP ventilation was attenuated by pretreatment with the mtDNA repair enzymes in all but the fatal degree of lung injury. The survival benefit of mtDNA repair enzymes in the severe injury group undoubtedly related to protective effects on other organs besides the lung.

Calcium entry through stretch activated cation channels is a key component for initiating stretch induced lung injury. Calcium entry with increased reactive oxygen species (ROS) has been demonstrated during mechanical stretch in cultured cells systems of pulmonary epithelial cells[9;10], pulmonary endothelial cells[11], and precision cut lung slices[12]. Gadolinium, an inhibitor of TRPV4 channels was found to dramatically reduce vascular permeability and edema in isolated lungs during high PIP lung injury[13]. The increases in segmental pulmonary vascular filtration coefficients in arterial, microvascular, and vein segments were also largely prevented by gadolinium treatment[14]. In more specific studies, Hamanaka et al.[15] measured filtration coefficients in isolated lungs of wild type and TRPV4 knockout mice with graded increases in PIP and temperature. TRPV4 is gated by a diverse range of stimuli including mechanical stretch, heat, phorbol asters, epoxyeicosatrienoic acids and is expressed in a broad range of tissues[15]. Filtration coefficients progressively increased with time at 40°C temperature in lungs ventilated at the lowest PIP, and also increased proportional to PIP at lower temperatures. Temperature and PIP had an additive effect on pulmonary vascular permeability. No significant increases from control were observed in filtration coefficients of lungs from TRPV4 knockout mice subjected to the higher temperatures or airway pressures. Lung surface calcium intensity measurements progressively increased as PIP increased from 15 cmH2O to 35 cmH2O in lungs from wild

type mice but did not increase in lungs from TRPV4 knockout mice or wild type mice treated with ruthenium red, a TRPV4 inhibitor.

The rapid influx of intracellular calcium produces calcium loading of mitochondria and enhanced free radical production. Mitochondria normally leaked small amounts of superoxide anions during the process of oxidative phosphorylation at complexes 1, 2 and 3 in the electron transport chain[16]. These baseline levels of superoxide are normally converted to H2O2 by manganese superoxide dismutase (mnSOD) in the inner membrane, copper zinc SOD (CuZnSOD) in the outer membrane and cytoplasm along with reduced glutathione (GSH). Mitochondria normally must maintain low levels of oxidants because the mitochondria DNA (mtDNA) is 10 to 100 times more susceptible to oxidative damage than nuclear DNA[17]. These scavengers systems can be overwhelmed during calcium influx causing excess mitochondrial leak of free radicals which can overwhelm cellular scavengers systems. When significant damage occurs to mitochondrial DNA and electron transport enzymes, a positive feedback can develop to cause progressive increases in mtDNA damage and continuing further increases in ROS production.

Although stretch of both epithelium and endothelium increase Ca2+ entry and ROS production with leakage of fluid into alveoli and transport of inflammatory cells through pulmonary vascular and epithelial cell junctions[18–21], the key lung cell type responsible for initiating the injury has been shown to be the alveolar macrophage[22–25]. Alveolar macrophages make up approximately 80% of the innate immune cells recovered by lung lavage from uninjured lungs. High PIP ventilation causes rapid activation and adhesion of alveolar macrophages by stretch induced deformation such that only 6% of their baseline numbers were recovered by lung lavage after only 10 minutes of ventilation with 45 cmH2O PIP[26]. Prior depletion of alveolar macrophages dramatically reduced lung injury after high PIP ventilation[26;27]. The rapid calcium entry into macrophages upon initiation of high PIP ventilation appears to be essential for initiating these vascular permeability effects. In particular, the stretch activated nonselective cation channel, TRPV4, plays an essential role in calcium entry because deletion or blockade of this channel is protective against injury[28;29]. Restoration of TRPV4 competent macrophages to TRPV4 knockout mice restored susceptibility to mechanical lung injury[29]. Activation of TRPV4 channels in isolated lung alveolar macrophages using a phorbol ester increased calcium entry and markedly increased production of both superoxide and nitric oxide in alveolar macrophages from wild type mice but not from TRPV4 knockout mice[29].

Activation of alveolar macrophages is doubly destructive because in a quiescent state they secrete humoral signals that prevent activation of T and B lymphocytes and other macrophages species, whereas activation changes their cytokine secretion to activate these cells, increases the activation and chemotaxis of neutrophils, and cause release of a plethora of enzymes that degrade proteins and connective tissues such as the matrix metalloproteinases (MMP-2 and MMP-9)[30–34]. In addition, alveolar macrophages appear to closely adhere to epithelial junction areas, so they are well positioned to cause the observed endothelial and epithelial junction openings as well as the separation of epithelium from basement membrane observed during VILI[1;35].

The mtDNA repair enzymes have previously been shown to protect against oxidative damage in both pulmonary endothelial cells and isolated lungs[36–38]. Studies by Hashizume et al.[6;7] measured an increased ROS production using moderate levels of mechanical lung injury as indicated by a total glutathione pool reduced to 25% of control and a GSH/GSSH ratio 40% of control. These were restored to normal values by pretreatment with the mtDNA repair enzymes, suggesting that mitochondrial ROS production was returned to near control levels. In the severe injury group, the GSH measurements, as well as indices of lung injury, were not altered by pretreatment, even though survival was improved.

The mitochondrial burst of ROS sets in motion a complex process for release of IL-1b and IL-18 from macrophages[39–41], a major cause of the injury and inflammation in VILI and many other types of acute lung injury (ALI) (Figure 1). Entry of free ATP Also contributes to cell activation but likely on a slower timescale the ROS burst[42]. Free radicals cause activation of an inflammasome formed when nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 (NLRP3) translocates to the mitochondria endoplasmic reticulum membranes and recruits the adapter molecule, apoptosisassociated spec like protein containing a caspase activation and recruitment domain (ASC) as well as caspase-1[43;44]. Wu et al.[45] demonstrated that mitochondrial ROS rather than NADPH oxidase generated ROS were responsible for the NLRP3 activation during the stretch injury. However, the release of cytokines by macrophages is a two-stage process which also involves activation of toll-like receptor (TLR) dependent pathways. TLR4 and TLR9 are receptors involved in damage associated molecular pattern (DAMP) recognition[44–46]. Mice deficient in either TLR4 receptor protein or its adapter protein, myeloid differentiation factor 88 (My88), had significantly reduced production of IL-6 and the neutrophil chemotactic factor, MIP-2, as well as lung vascular permeability and edema after high PIP ventilation[47]. Tissue levels of IkB were also not significantly reduced in TLR4 or My88 knockout mice during VILI, indicating a reduced activation of nuclear factor-kB (NFkB). TLR activation of NFkB is essential to transcribe pro-IL-1 and pro-IL-18 which are then converted to their active forms, IL-1 and IL-18 by caspase-1. TLR4 is activated by a number of interstitium and nuclear breakdown products such as low molecular weight hyaluronic acid, uric acid, heparin sulfate, tenascin-C and HMGB1[44]. TLR9 also uses the adapter protein, My88 to activate NFkB, but is activated by mitochondrial or bacterial DNA fragments[39]. In addition, caspase-1 also cleaves gasdermin D (GSDMD) to produce a pore forming N-terminal fragment which allows the cytokines to pass through the cell membrane[43]. IL-1 and IL-18 are essential for progression of inflammation and lung injury during VILI[48]. IL-1 receptor blockade or genetic deletion of receptors decreased vascular protein permeability, lung edema and neutrophil influx in animals during injurious ventilation[49;50].

The ability of the mtDNA repair enzymes to interrupt the positive feedback cycle between mtDNA damage and increased oxidative ROS production can be attributed to repair of mtDNA damage, which then increases mtDNA transcripts for oxidative phosphorylation proteins and attenuates ROS production. If unchecked this positive feedback of ROS production and mitochondrial damage can lead to cell death and dysfunction[16]. However, the protective effect of these enzymes is very rapid compared to the time required for protein transcription. Increases in lung vascular permeability occur within 10 – 30 minutes during high PIP ventilation[1;3;38;51;52], and GSH oxidation was returned to control levels by

Endonuclease III treatment. The rapid action of quenching ROS production may relate to a chaperone function for aconitase such as described for OGG1[53;54], or stabilization of mtDNA to prevent fragments (DAMPs) from entering endosomes and stimulating TLR9 receptors within the same cell or neighboring cells[39]. Future studies for interrupting stretch activated ion channels[55], DAMP production and their activation of cell receptors may be fruitful for clinical treatment of mechanical lung injury[39;44]. For example Lee et al.[56] significantly reduced trauma induced injury using a polyethylenimine mesh to trap DNA fragments.

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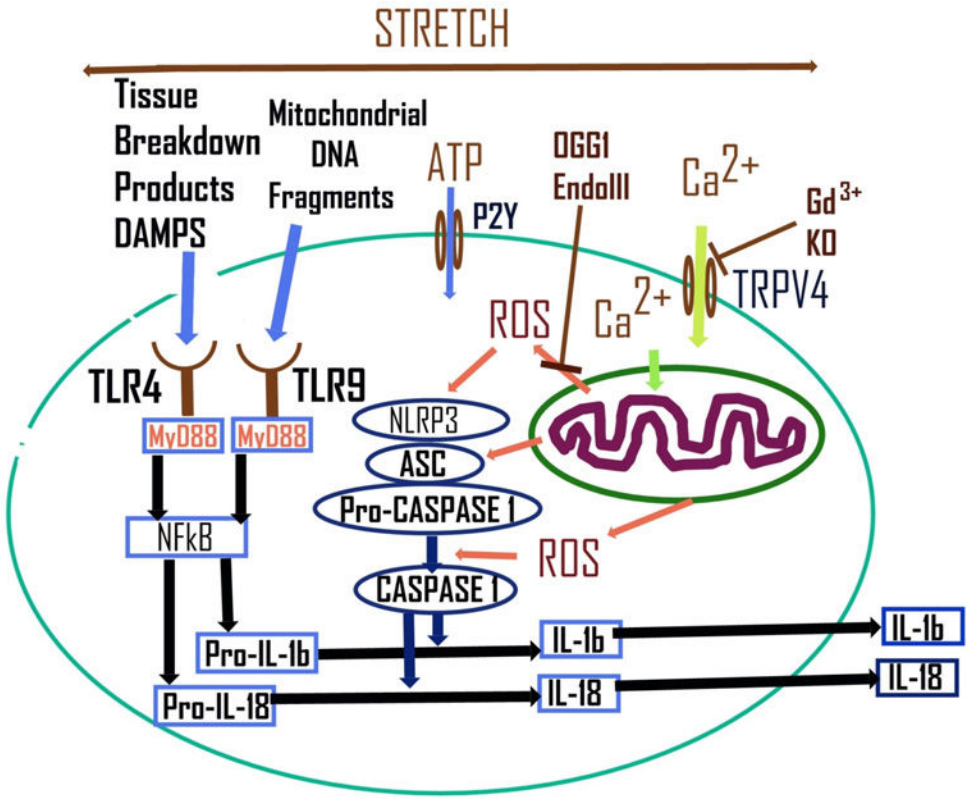

Figure 1.