Autophagy facilitates ventilator-induced lung injury partly through activation of NF-κB pathway

Min Gao*  Donglei Liu*  Yuming Du  Rongqing Sun  Luosha Zhao

* Min Gao and Donglei Liu contributed equally to this work

Corresponding Author: Luosha Zhao, e-mail: zls319@zzu.edu.cn

Source of support: Self financing

Mechanical ventilation is an important supportive therapy in the intensive care unit (ICU) to assist the critically ill patients with respiratory failure. But longer ventilation time has been proven to contribute to the lung injury which has been recognized as ventilator-induced lung injury (VILI). Recently studies have suggested that NF-κB signaling pathways may play a critical role in the process of inflammation and autophagy, and autophagy can reduce the damage of VILI partly by activating the NF-κB pathways. Thus, we propose that autophagy may facilitate ventilator-induced lung injury partly through activation of NF-κB pathway, which might be a new potential therapeutic target for ventilator-induced lung injury. Although the exact mechanism of autophagy and its exact role in the VILI need to be further explored, at least it provides us a potential target in the future prevention of VILI.

Key words: autophagy • ventilator-induced lung injury • NF-κB pathway

Full-text PDF: http://www.medscimonit.com/download/index/idArt/889746
Background

Mechanical ventilation is an important supportive therapy in the intensive care (ICU) to assist the critically ill patients with respiratory failure [1]. However, longer ventilation time has been proven to contribute to the lung injury as a pro-inflammatory response and so-called ventilator-induced lung injury (VILI) [1,2]. Prolonged mechanical ventilation (PMV) can affect many other organs such as the heart [3], which may develop a congestive heart failure after the PMV, and the diaphragm [4], which can experience atrophy after PMV. Because these complications may have potential relationships in patients subjected to mechanical ventilation, it is very important to investigate a new treatment strategy for VILI in the ICU.

Autophagy, also called macroautophagy, is an evolutionarily conserved process that recycles the intracellular components [5]. Basal autophagy plays a critical role in cellular homeostasis by eliminating excessive proteins and organelles [6]. However, the exact role of autophagy in the cellular death or survival is still complex, which means that in several situations, autophagy can be viewed as a survival mechanism during nutrient deprivation or metabolic stress, whereas in other situations, excessive autophagy represents another cellular death pathway (termed as autophagic cell death) [7]. Despite much progress has been made in understanding the physiologic and pathologic roles of autophagy, there is still no consensus that autophagy may act as a pro-survival or pro-death role. We propose the hypothesis that autophagy may facilitate ventilator-induced lung injury partly through activation of NF-κB pathway. Our hypothesis indicates that autophagy may be a new potential therapeutic target for the VILI in the intensive care unit.

Hypothesis

Recently increasing evidence has shown that autophagy can be up-regulated during many different situations, such as energy starvation, inflammation, cancer and other diseases [8]. Moreover, it is reported that autophagy can clear the cellular components, such as inflammasomes and cytokines, thus providing an important means of regulating inflammation [9]. Recently it is reported that VILI may be attributed to inflammation partly by NF-κB-IL-6 signaling pathways [10], which is one of the major regulation pathways of autophagy [11], thus there is no doubt that autophagy is activated after the ventilator-induced lung injury.

In fact, many reports have suggested that NF-κB signaling pathways play a critical role in the process of inflammation [12] and autophagy [13]. In the C57BL/6 mice model, Ben-Neriah Y and Karin M found that NF-κB-IL-6 signaling pathways could induce inflammation, contributing to VILI, and IκB kinase in the myeloid cells mediated ventilator-induced IL-6 production, inflammation, and lung injury [10]. Moreover, NF-κB plays an important role in both lung ischemia-reperfusion injury and VILI, which means anti-NF-κB antibody pretreatment to be beneficial for VILI, I/R and lung transplantation [14]. Furthermore, several studies have proven that autophagy regulated by NF-κB can significantly decrease the inflammatory reaction in many different situations [15]. In the cardiac ischemia-reperfusion injury, NF-κB can contribute to cardiac injury by promoting Beclin 1-associated autophagy [16]. In other experiments, impairment of autophagy results in an ameliorated inflammatory response to mechanical ventilation and decreases lung injury in the mice lacking autophagin-1/ATG4B by blockade of the NF-κB pathway [17]. Thus, many experiments suggest that autophagy activated during the inflammatory reaction is essential for the protection against VILI regulated by NF-κB pathway.

These studies have suggested that autophagy can act as a survival pathway in the process of inflammation against VILI. Previous studies have shown that autophagy can reduce the damage of VILI through NF-κB pathways in experimental research [17]. Thus, we propose that autophagy may play a role as a survival pathway during the VILI through the regulation of inflammatory response.

Conclusions

In recent years, increasing attention has been focused on the role of autophagy during VILI in the ICU. Although the mechanism of autophagy and its exact role in the VILI should be further explored, at least it provides us a potential target in the future prevention of VILI in the ICU.

Conflict of interest statement

The authors declare that they have no conflict of interest in any matter related to this work.

References:

1. Tremblay LN, Slutsky AS: Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med, 2006; 32(1): 24–33

2. Kuipers MT, van der Poll T, Schultz MJ et al: Bench-to-bedside review: Damage-associated molecular patterns in the onset of ventilator-induced lung injury. Crit Care, 2011; 15(6): 235
3. White AC: Long-term mechanical ventilation: management strategies. Respir Care, 2012; 57(6): 889–97
4. Powers SK, Wiggs MP, Solanek KJ et al: Ventilator-induced diaphragm dysfunction: cause and effect. Am J Physiol Regul Integr Comp Physiol, 2013; 305(5): R464–77
5. Yang ZJ, Chee CE, Huang S et al: The role of autophagy in cancer: therapeutic implications. Mol Cancer Ther, 2011; 10(9): 1533–41
6. Eskelinen EL: The dual role of autophagy in cancer. Curr Opin Pharmacol, 2011; 11: 294–300
7. Baehrecke EH: Autophagy: dual roles in life and death? Nat Rev Mol Cell Biol, 2005; 6(6): 505–10
8. Mizushima N, Levine B, Cuervo AM et al: Autophagy fights disease through cellular self-digestion. Nature, 2008; 451(7182): 1069–75
9. Jones SA, Mills KH, Harris J: Autophagy and inflammatory diseases. Immunol Cell Biol, 2013; 91(3): 250–58
10. Ko YA, Yang MC, Huang HT et al: NF-κB activation in myeloid cells mediates ventilator-induced lung injury. Respir Res, 2013; 14: 69
11. Salminen A, Hyttinen JM, Kauppinen A et al: Context-Dependent Regulation of Autophagy by IKK-NF-κB Signaling: Impact on the Aging Process. Int J Cell Biol, 2012; 2012: 849541
12. Ben-Neriah Y, Karin M: Inflammation meets cancer, with NF-κB as the matchmaker. Nat Immunol, 2011; 12(8): 715–23
13. Salminen A, Kaarniranta K, Kauppinen A: Beclin 1 interactome controls the crosstalk between apoptosis, autophagy and inflammasome activation: impact on the aging process. Aging Res Rev, 2013; 12(2): 520–34
14. Chiang CH, Pai HI, Liu SL: Ventilator-induced lung injury (VILI) promotes ischemia/reperfusion lung injury (IRI) and NF-κB antibody attenuates both injuries. Resuscitation, 2008; 79(1): 147–54
15. Hoesel B, Schmid JA: The complexity of NF-κB signaling in inflammation and cancer. Mol Cancer, 2013; 12: 86
16. Zeng M, Wei X, Wu Z et al: NF-κB-mediated induction of autophagy in cardiac ischemia/reperfusion injury. Biochem Biophys Res Commun, 2013; 436(2): 180–85
17. López-Alonso I, Aguirre A, González-López A et al: Impairment of autophagy decreases ventilator-induced lung injury by blockade of the NF-κB pathway. Am J Physiol Lung Cell Mol Physiol, 2013; 304(12): L844–52