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Review

The role of necroptosis in pulmonary diseases

Kenji Mizumura, MD, PhD[a,*], *Shuichiro Maruoka, MD, PhD*[a], *Yasuhiro Gon, MD, PhD*[a], *Augustine MK. Choi, MD*[b], *Shu Hashimoto, MD, PhD*[a]

[a]*Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan*
[b]*Joan and Sanford I. Weill Department of Medicine, New York-Presbyterian Hospital, Weill Cornell Medical College, New York, NY, USA*

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ABSTRACT

By regulating the cell number and eliminating harmful cells, programmed cell death plays a critical role in development, homeostasis, and disease. While apoptosis is a recognized form of programmed cell death, necrosis was considered a type of uncontrolled cell death induced by extreme physical or chemical stress. However, recent studies have revealed the existence of a genetically programmed and regulated form of necrosis, termed necroptosis. Necroptosis is defined as necrotic cell death that is dependent on receptor-interacting protein kinase 3 (RIPK3). RIPK3, receptor-interacting protein kinase 1 (RIPK1), and a mixed-lineage kinase domain-like protein (MLKL) form a multiprotein complex called a necrosome. Although necroptosis generally provides a cell-autonomous host defense, on the other hand, cell rupture caused by necroptosis induces inflammation through the release of damage-associated molecular patterns, such as mitochondrial DNA, HMGB1, and IL-1. Previously, necroptosis was considered an alternative to apoptosis, but it is becoming increasingly clear that necroptosis itself is relevant to clinical disease, independent of apoptosis. According to some recent studies, autophagy, a cellular process for organelle and protein turnover, regulates necroptosis. This review outlines the principal components of necroptosis and provides an overview of the emerging importance of necroptosis in the pathogenesis of pulmonary disease, including chronic obstructive pulmonary disease, lung cancer, infection, and sepsis. We also discuss the molecular relationship between necroptosis and autophagy. Strategies targeting necroptosis may yield novel therapies for pulmonary diseases.

Contents

*Corresponding author. Tel.: +81 3 3972 8111x2402; fax: +81 3 3972 2893.
E-mail addresses: mizumura.kenji@nihon-u.ac.jp (K. Mizumura), maruoka.shuichiro@nihon-u.ac.jp (S. Maruoka), gon.yasuhiro@nihon-u.ac.jp (Y. Gon), amc2056@med.cornell.edu (A.M.K. Choi), hashimoto.shu@nihon-u.ac.jp (S. Hashimoto).

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1. Introduction

Traditionally, necrosis was considered the result of overwhelming cytotoxic insults that require no specific molecular events [1] and apoptosis had been researched as the sole form of programmed cell death. However, emerging studies have reported the existence of a genetically programmed and regulated form of necrosis, known as necroptosis [2]. Necroptosis was first recognized as a caspase-independent cell death mechanism, induced by treatment with tumor necrosis factor (TNF) only in the presence of a pan-caspase inhibitor, such as zVAD-FMK [3]. Subsequent studies have revealed that assembly of the receptor-interacting protein kinase 1 (RIPK1)-receptor-interacting protein kinase 3 (RIPK3)-mixed-lineage kinase domain-like protein (MLKL) complex regulates necroptosis [4,5]. Currently, necroptosis is defined as a RIPK3-dependent necrotic cell death, and recent studies implicate it in clinical diseases [6]. Necroptosis plays a pathophysiological role in myocardial infarction [7], atherosclerosis [8], ischemia–reperfusion injury [9], and inflammatory bowel diseases. It has also been recently reported that necroptosis plays a role in the pathogenesis of pulmonary diseases, including chronic obstructive pulmonary disease (COPD), lung cancer, infection, and sepsis (Table 1). Researchers have drawn their attention towards necroptosis due to its potential importance in targeted therapy for pulmonary diseases [2,10,11]. Given that the pathogenesis of pulmonary disease is complex, necroptosis may exert both protective and injurious effects in various pulmonary diseases.

It is becoming increasingly clear that the molecular mechanism of necroptosis intersects between apoptosis and autophagy [1]. It was thought that necroptosis is an alternative to apoptosis for programmed cell death. However, accumulating evidence suggests that necroptosis is relevant to clinical disease, independent of apoptosis [6]. Apoptosis and necroptosis share several upstream signaling elements, and sensitivity to each death pathway is regulated by an overlapping cluster of regulatory molecules [6]. In addition, while autophagy is known as a lysosomal degradation system that engulfs the cytoplasm and organelles for cellular renovation and homeostasis, autophagy may regulate necroptosis [10]. Specifically, it has been shown that mitophagy, the autophagy-dependent elimination of mitochondria, regulates necroptosis, which contributes to the pathogenesis of COPD [10]. As both mitophagy and necroptosis target the mitochondria, it is clear that these two pathways overlap [12,13].

In this review, we examine the growing evidence favoring the contribution of necroptosis towards the pathogenesis of complex lung diseases, summarize the complex molecular relationship between necroptosis and autophagy, and discuss the dual nature of necroptosis in the lung. A better understanding of the protective and injurious effects of necroptosis in disease pathogenesis will help design personalized therapies for the treatment of lung diseases.

2. Molecular mechanisms of necroptosis

Necroptosis was first reported as a caspase-independent form of cell death in the presence of a pan-caspase inhibitor [3]. Necroptosis is defined as necrotic cell death dependent on RIPK3. RIPK3, RIPK1, and MLKL form a multiprotein complex called a necrosome (Fig. 1) [2]. Oligomerization and intramolecular auto-phosphorylation of RIPK3 leads to the recruitment and phosphorylation of MLKL, which exposes a 4-helical bundle domain after a conformational change in the pseudokinase domain [14,15]. Two mechanisms of MLKL have been proposed: one is a platform at the plasma membrane for the recruitment of Ca^{2+}or Na^{+} ion channels [16,17] and the other is a direct pore-forming complex recruited by the binding of the amino-terminus of the 4-helical bundle domain of MLKL to negatively charged phosphatidylinositolphosphates [18–20].

Various stimuli can lead to the activation of necroptosis [6] and examining the comprehensive list of stimuli inducing necroptosis from the current literature is beyond the scope of this review. Therefore, we summarize the death receptors (DRs) in the TNF superfamily and Toll-like receptors (TLRs) regulating necroptosis. The particular DR linked to necroptosis is TNF

Table 1 – Pathological roles of necroptosis in pulmonary diseases.

Diseases	Role of necroptosis	References
COPD	Mitophagy-regulated necroptosis contributes to air space enlargement.	Mizumura et al., 2014 [10]
Lung cancer	Novel selenosemicarbazone metal complexes contributes to anti-proliferative activity through induction of necroptosis in human lung adenocarcinoma epithelial cells.	Zec et al., 2014 [40]
	Protein disulfide isomerase PDIA6 mediates resistance to cisplatin-induced non-canonical cell death pathway sharing some necroptosis features.	Tufo et al., 2014 [41]
	Shikonin induced-necroptosis greatly reduces the lung metastasis of osteosarcoma.	Fu et al., 2013 [43]
Infection	Necroptosis processes viruses acquiring caspase 8 suppressors.	Upton et al., 2010 [45]
Sepsis	Necrosis causes sever inflammation through massive damage-associated molecular patterns (DAMPs) release.	Duprez et al., 2011 [48] Sharma et al., 2014 [49]

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