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Innate immunity to inhaled particles: A new paradigm of collective recognition

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Abstract

Major progress has been achieved in recent years to elucidate mechanisms driving the early response of pulmonary innate immune cells to inhaled micrometric and nanometric particles. Mononuclear phagocytes promptly categorize particles, alert immune network and engage crescendo responses for particle clearance and homeostasis restoration. Negatively charged particles directly interact with scavenger receptors A and B (SR-A and SR-B) and consequently activate specific signaling pathways, resulting in the production of TNF and IL-1 family members, which coordinate effective innate immune responses. Cytokine secretion also arises after a simple contact between particle-associated radicals and cell membranes. Reactive particles engage the passive release of constitutive alarmins, ensuing particle- or TNF-α-induced cell death and membranolysis. Finally, the inflammasome machinery represents the decisive intracellular platform that finely tune immune pathways engaged after SR activation, alarmin release, TNF-α production and cell homeostasis perturbations. Disturbance of these collective recognition processes prolongs particle persistence and innate immune responses that generate long-lasting adaptive immunity and cause chronic lung diseases.

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Sensing, Particles, Nanoparticles, Silica, Innate immunity, PRR, DAMP, HAMP, Cytokines, Alarmins and inflammasome.

Abbreviation

PRRs, Pattern Recognition Receptors; DAMPs, Damage-Associated Molecular Patterns; HAMPs, Homeostasis-Altering Molecular Processes; LMP, Lysosomal Membrane Permeabilization; CDE, Clathrin-Dependent Endocytosis; NLRP, NOD-like Receptor Rroteins.

1. Introduction

Interest in clarifying the immuno-pathophysiology of lung disorders induced by inorganic particles was initiated almost 30 years ago with the first description of a marked accumulation of neutrophils and activated macrophages (or mononuclear phagocytes) in the lungs of dust-exposed individuals with respiratory impairments [1]. Although additional immune cells and pathways have been identified that refine our understanding of the immune mechanisms leading to particle-induced chronic diseases [2], it remains to elucidate how innate immunity senses particles (inert or reactive) and elicits early tissue responses that have an essential role in eliminating particles or driving diseases such as fibrosis and cancer.

The innate immune system integrates a distinct set of receptors on phagocytes designated pattern recognition receptors (PRRs) and serving as sensors for monitoring the extracellular and intracellular compartments for signs of infection or tissue injury [3]. These sentinel receptors rely on sensing common structural and functional features associated with different classes of microorganisms termed pathogen-associated molecular patterns (PAMPs). The PRR system also detects debris from dying cells, known as danger-associated molecular patterns (DAMPs that comprise alarmins) and perturbations in cytoplasmic homeostasis, recently defined as homeostasis-altering molecular processes (HAMPs) [4]. The engagement of PRRs by PAMPs, DAMPs or HAMPs results in the production of master cytokines such as IL-1 and TNF family members that orchestrate effective immune responses [5].

A similar PRR-mediated sensing system for inhaled particles did initially not appear plausible because particles are different from biological structures such as microorganism cell-wall components or viral nucleic acids, which are avidly and specifically recognized by PRRs. The discovery that scavenger receptors (SR), a subfamily of PRRs, are dedicated to sense endogen low-density lipoprotein (LDL) particles and asbestos [6] changed the opinion of researchers in particle toxicology and suggested that innate immunity can specifically recognize particles and initiate responses against particles. In 1998, three distinct reports [7–9] concurrently revealed a new PRR-related intracellular sensing axis comprising nod-like receptors (NLRP), termed

inflammasome, that is pivotal in particle recognition and immune system activation (reviewed in Ref. [10]). Altogether, these unforeseen aspects of particle-sensing processes by PRRs have shaken up our knowledge of early host defense responses against particles.

Available evidence supports the view that the innate immune system senses particles such as silica, asbestos or titanium dioxide to promote their clearance and to prevent tissue injury. However, the inability of phagocytes to eliminate particles can result in inappropriate and prolonged activation of innate immunity responses [11]. The progressive development of fibrosis, cancer or autoimmune diseases after particle exposure appears when particles are refractory to clearance process, constantly activate PRR-mediated particle recognition, induce cytokine release and promote long-lasting adaptive immune responses and drive chronic diseases [12]. Thus, the fine regulation of innate immunity after its activation by particles is essential to restore homeostasis (Fig. 1).

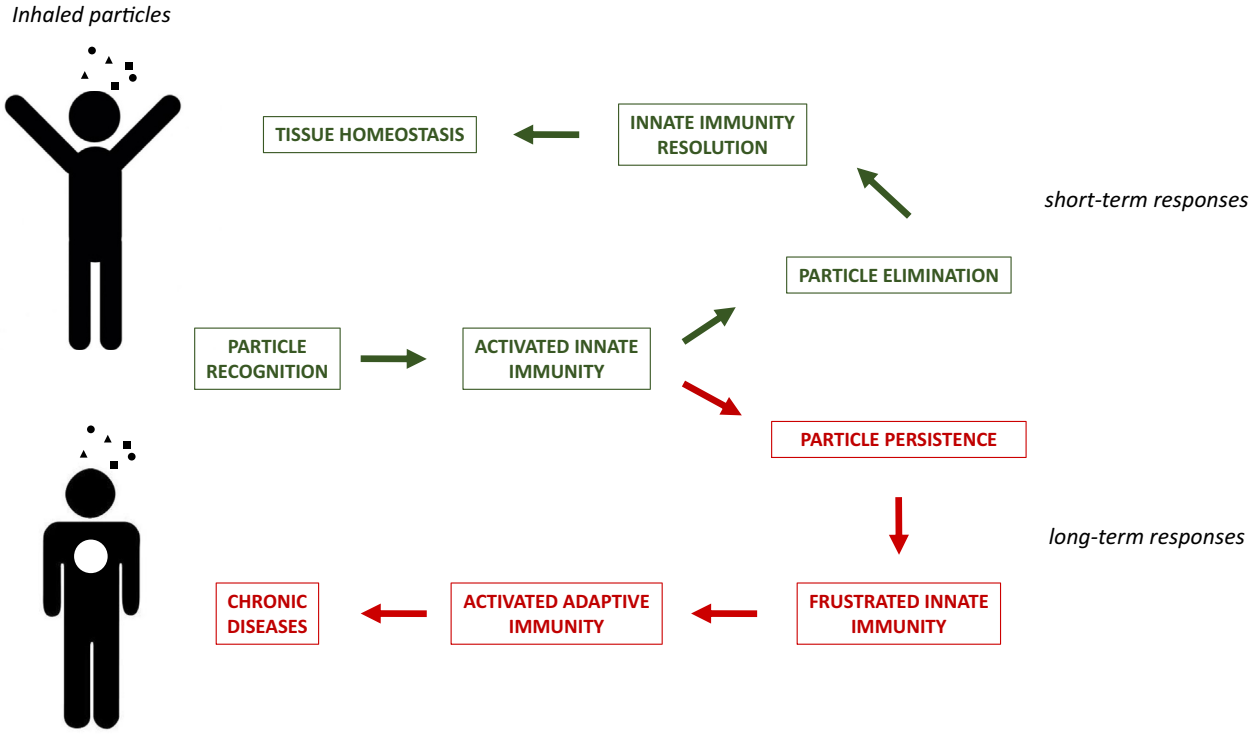
Here, we discuss some of the recent developments in particle sensing and describe the emerging concepts of micro- and nanoparticle-recognition systems that include different classes of PRRs (scavenger receptors and inflammasome machinery), DAMPs (alarmins) and HAMPs (membrane destabilization). These recognition systems survey the extracellular or cytosolic spaces for detecting particles themselves or particle-related cell signatures and operate in a complementary manner to promote effective responses to particles. Exploring the collective actions of the PRR pathways sensing particles represents a new frontier in particle toxicity, and is the focus of this review.

2. Initial pattern recognition receptor activation by particles

Scavenger receptor (SR) are integral membrane proteins that contribute to the recognition and elimination of foreign or altered-self targets. The SR subfamily abundantly present on mononuclear phagocytes comprises a diverse array of functional innate receptors sharing the ability to recognize polyionic ligands such as oxidized LDL particles [13]. SR-mediated sensing also represents the main PRR-related system to detect inhaled particles and initiate early tissue responses [14].

Among SR members, compelling studies support SR-A6 (MARCO) as critical in particle recognition. Expression

Fig. 1



Inappropriate activation of sensing processes leads to persistent particle accumulation, uncontrolled innate immune responses and chronic disease development. Phagocytes possess a sensing arsenal of pattern recognition receptors (PRRs) capable of recognizing and taking up inhaled particles. Engagement of this recognition system results in the deployment of innate immune responses accountable to clear particles from tissue to avoid tissue injury. After particle elimination, innate immune responses are controlled and tissue homeostasis is restored. The inability of the innate immune system to degrade and clear particles results into frustrated innate immune responses that lead to the establishment of long-lasting adaptive immunity and cause chronic diseases for which no specific therapy is available.