Most microorganisms that enter the lower respiratory tract, as well as presumably commensal bacteria that colonize the upper respiratory tract, fail to establish infection in the lungs and are eliminated without causing detectable signs and symptoms of disease. Therefore, a non-specific defence system that can cope with a broad range of pathogens at the interface between lung parenchyma and its ambient space constitutes a critical first line of host defence prior to the participation of innate and adaptive immune cells. This non-specific protection in the respiratory tract can be broadly classified into physical barriers, such as the mucous membrane lining the respiratory tract, and chemical barriers, such as antimicrobial proteins.

Similar to other body surfaces, the conducting airway epithelial cells provide a mechanical barrier that inhibits colonization of the lungs by microorganisms. Protective features of this epithelial cell layer include the production of mucus, which traps small particles including viruses and prevents access to the surface of epithelial cells, and the beating movement of the ciliated epithelial cells which propels the mucus and any trapped particles up and out of the respiratory tract. Pathogens that penetrate these physical barriers encounter various chemical substances that may prevent their growth or directly kill them. Proteins of the complement system and natural antibodies contribute to the body’s non-specific defence system by helping to destroy invading microorganisms. Once activated, complement proteins mediate the lysis, engulfment and destruction of infectious agents. Complement can also cooperates with antibodies, resulting in enhanced pathogen clearance from the airway surfaces. Furthermore, substances such as host cell-derived antimicrobial enzymes and the iron-depriving protein transferrin represent important chemical barriers.

Another important group of proteins that provide protection are those from non-pathogenic microorganisms such as commensal bacteria. Microorganisms dwelling in the upper respiratory tract secrete various proteins that enhance their own survival and concomitantly inhibit the growth of invading pathogenic microorganisms. Recently, evidence has emerged to suggest that commensal bacteria also impact on the induction and expression of the adaptive immune response to lower respiratory tract virus infection. Whether this apparent regulatory effect reflects the action of commensal bacteria in the upper respiratory tract or in gut (or both) has not been formally established.

Respiratory tract epithelial cells are a primary target of infection and propagation by most respiratory viruses. Infection of these cells is first detected by a germline-encoded set of cellular (cytosolic or endosomal) sensors expressed by the infected epithelial cells, which recognize pathogen-associated molecular patterns (PAMPs) present in the virus. These sensors include Toll-like receptor 3 (TLR3), TLR4, TLR7, TLR8, TLR9, retinoic acid inducible gene-I (RIG-I) and melanoma-differentiation-associated gene 5 (MDA5), which recognize evolutionarily conserved nucleic acid motifs within the DNA or RNA genomes of the virus. Recent studies have also suggested an important virus-sensing role for the NOD-like receptor (NLR) family PYD-containing protein 3 (NLRP3) inflammasome in sensing influenza virus infection. Recognition of PAMPs by these innate sensors triggers the synthesis of pro-inflammatory cytokines and the production of type I interferons. Engagement of these receptors on epithelial cells and other cell types present in the lungs (such as plasmacytoid dendritic cells (DCs), γδ T cells and NK cells) following infection triggers a cascade of events that activates adjacent cells, such as fibroblasts, alveolar macrophages and DCs. In addition, these signals also promote the recruitment of inflammatory cells from distal compartments such as the bone marrow via the blood, as well as the initiation of the adaptive immune response.

Supplementary information S1 (table). Infection of these cells is first detected by a germline-encoded set of cellular (cytosolic or endosomal) sensors expressed by the infected epithelial cells, which recognize pathogen-associated molecular patterns (PAMPs) present in the virus. These sensors include Toll-like receptor 3 (TLR3), TLR4, TLR7, TLR8, TLR9, retinoic acid inducible gene-I (RIG-I) and melanoma-differentiation-associated gene 5 (MDA5), which recognize evolutionarily conserved nucleic acid motifs within the DNA or RNA genomes of the virus. Recent studies have also suggested an important virus-sensing role for the NOD-like receptor (NLR) family PYD-containing protein 3 (NLRP3) inflammasome in sensing influenza virus infection. Recognition of PAMPs by these innate sensors triggers the synthesis of pro-inflammatory cytokines and the production of type I interferons.