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REVIEW

A mammalian lung's immune system minimizes tissue damage by initiating five major sequential phases of defense

Kevin Roe[1]

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Abstract
The mammalian lungs encounter several pathogens, but have a sophisticated multi-phase immune defense. Furthermore, several immune responses to suppress pulmonary pathogens can damage the airway epithelial cells, particularly the vital alveolar epithelial cells (pneumocytes). The lungs have a sequentially activated, but overlapping, five phase immune response to suppress most pathogens, while causing minimal damage to the airway epithelial cells. Each phase of the immune response may suppress the pathogens, but if the previous phase proves inadequate, a stronger phase of immune response is activated, but with an increased risk of airway epithelial cell damage. The first phase immune response involves the pulmonary surfactants, which have proteins and phospholipids with potentially sufficient antibacterial, antifungal and antiviral properties to suppress many pathogens. The second phase immune response involves the type III interferons, having pathogen responses with comparatively minimal risk of damage to airway epithelial cells. The third phase immune response involves type I interferons, which implement stronger immune responses against pathogens with an increased risk of damage to airway epithelial cells. The fourth phase immune response involves the type II interferon, interferon-γ, which activates stronger immune responses, but with considerable risk of airway epithelial cell damage. The fifth phase immune response involves antibodies, potentially activating the complement system. In summary, five major phases of immune responses for the lungs are sequentially initiated to create an overlapping immune response which can suppress most pathogens, while usually causing minimal damage to the airway epithelial cells, including the pneumocytes.

Keywords Respiratory system · Alveolar epithelial cells · Pneumocytes · Type III interferons · Type I interferons · Type II interferons

Introduction

This paper will discuss the biochemical and immune cell components of the immune defenses of the mammalian respiratory system, particularly the lungs, but it will not include the more physically associated defenses (e.g., respiratory tract mucus production, movement and expulsion), which is a distinct topic, and which could be classified as a sixth phase of defense. The mammalian lungs, including airway epithelial cells and particularly the squamous type I pneumocytes (i.e., type I alveolar epithelial cells) and pulmonary surfactant secreting type II pneumocytes (i.e., type II alveolar epithelial cells), are continuously exposed to potential pathogens, including bacteria, fungi, viruses and occasionally protozoan parasites. The immune responses of the mammalian lungs need to suppress pathogens with a second equally important goal of minimizing immune cell induced cellular damage to the lungs, in which extensive cellular damage could be fatal.

Discussion

The first phase of immune defense of the mammalian lungs

The type II pneumocytes secrete pulmonary surfactants to biochemically reduce alveolar surface tension [1, 2]. These surfactants include several minor components, even some IgG and IgA antibodies, proteins and lipids, but they are mostly comprised of several phospholipids including the

✉ Kevin Roe
kevin.roe@att.net

[1] United States Patent and Trademark Office, San Jose, CA, USA

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predominant component, phosphatidylcholine (PC), and two lesser components: phosphatidylinositol (PI) and phosphatidylglycerol (PG) [1, 2]. The pulmonary surfactants also comprise hydrophobic proteins, including SP-B and SP-C, to stabilize the roles of PI and PG in the vital surfactant films [1, 2]. In addition, there are important immune components including antibacterial/antifungal/antiviral collagen-like lectin (also called collectin or group II C-type lectin) proteins, including the relatively hydrophilic proteins SP-A and SP-D [2]. Furthermore, there are crucially important phospholipids which also have anti-inflammatory effects and which also bind several viruses to inhibit viral infections, in both the lungs and even the large airways [1].

The surface surfactant components will vary according to the immune status and animal species [2]. In human pulmonary surfactants, the most prevalent PG is palmitoyl-oleoyl-phosphatidylglycerol (POPG), the most prevalent PI is dioleoyl-phosphatidylinositol and the most prevalent PC is dipalmitoyl-phosphatidylcholine (DPPC) [1, 2]. PI and POPG, by direct viral binding and by blocking viral attachment to host cells, have substantial antiviral properties which will inhibit several dangerous RNA viruses, including influenza viruses, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and respiratory syncytial virus (RSV) [1]. Respiratory disease outcomes including potentially fatal acute lung injury (ALI) are frequently associated with impaired or dysfunctional pulmonary surfactant secretions, demonstrating the crucial importance of pulmonary surfactants as a biochemical immune defense of the lungs and the respiratory tract in general [2].

Table 1 summarizes the major human lung surfactant components and their major functions.

These pulmonary surfactant phospholipids also inhibit ligand activation of several pathogen recognition receptors, specifically several Toll-like receptors (TLRs, including TLR2, TLR2/TLR1 complex and TRL2/TLR6 complexes which detect Gram-negative and Gram-positive bacteria, and TLR4, which detects Gram-negative bacteria and viruses) [1]. If not inhibited, these TLRs would activate alveolar macrophages to produce pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) [1]. In summary, these protein and phospholipid pulmonary surfactant components provide a passive and effective first phase of immune defense of the lungs against several pathogens, while reducing the risk of TLR-initiated pro-inflammatory cytokine damage to airway epithelial cells including the pneumocytes.

Furthermore, there is another reason for the inhibition of TLR4 activation by pulmonary surfactants to minimize ALI. Mammals experiencing ALI, especially acute respiratory distress syndome (ARDS), the most severe form of ALI, can die quickly; and this was exemplified by numerous human mortalities from SARS or H5N1 avian influenza virus infections caused by ARDS with its accumulations of immune cells, increased cytokines and pulmonary edema [3–5].

TLR4 can be broadly activated by bacterial lipopolysaccharide (LPS) and several non-bacterial ligands, including certain pathogenic lipids and phospholipids, fibrinogen, fungal mannan, the envelope proteins of RSV and some other ligands [6]. Stimulation of TLR4 can trigger the activation of two downstream signaling pathways to transcription factors: the myeloid differentiation factor 88 (MyD88)-dependent pathway, or the TIR-domain-containing adapter-inducing interferon-β (TRIF)-dependent pathway [6]. Studies have demonstrated that dangerous ALI is mediated by TLR4 triggering through a TRIF intermediary and then a TNF receptor-associated factor 6 (TRAF6) intermediary to eventually activate the NF-κB kinase transcription factor pathway [3, 7]. This pathway will eventually express genes in monocytes and macrophages to release pro-inflammatory cytokines, including IL-1β and IL-6 (the most important) and the chemokine IL-8, and cause oxidative stress by releasing reactive oxidative species (ROS) [3, 7].

One study demonstrated that TLR4 in mouse alveolar macrophages could trigger two separate oxidative stress pathways that cause ALI [3]. The first pathway used hydrochloric acid aspiration to model acute stage ARDS [8] and induced the local generation of ROS and created oxidized

Table 1 Major human lung surfactant components in health and disease

Surfactant component	Predominant human component	Primary function
Phosphatidylcholine (PC)	Dipalmitoyl-phosphatidylcholine (DPPC)	Reduce surface tension
Phosphatidylinositol (PI)	Dioleoyl-phosphatidylinositol	Reduce surface tension
Phosphatidylglycerol (PG)	Palmitoyl-oleoyl-phosphatidylglycerol (POPG)	Reduce surface tension
SP-A (SP-A1 & SP-A2)		Inhibits pathogens
SP-B		Stabilizes PI and PG
SP-C		Stabilizes PI and PG
SP-D		Inhibits pathogens
Oxidized 1-palmitoyl-2-arachidonoyl-phosphatidylcholine (OxPAPC)		Triggers ALI

phospholipids, particularly oxidized 1-palmitoyl-2-arachidonoyl-phosphatidylcholine (OxPAPC), which activated TLR4 and ultimately caused ALI [3]. The second pathway used inactivated H5N1 virus having a conserved hemaglutinin activity which induced ROS and TLR4 surface expression and activated TLR4 and then caused ALI [3, 9]. Furthermore, OxPAPC was identified as an important trigger of ALI in mice and humans; and OxPAPC is known to be produced at sites of inflammation and also present in membranes of apoptotic cells [3, 10]. This study also demonstrated that inactivated influenza A virus could induce rapid activation of the NF-κB transcription factor pathway and pro-inflammatory cytokine production in mouse alveolar macrophages [3]. Normally, TLR4 protein would be distributed throughout the cytoplasm in human peripheral blood mononuclear cells (PBMCs), but exposure of PBMCs with inactivated H5N1 virus induced relocalization and cell membrane association of TLR4, thus inducing TLR4 surface expression and ROS formation in primary human monocytes [3]. This study concluded that the initiation of pro-inflammatory immune responses and dangerous ALI caused by specific pathogens is critically determined by activation of the oxidative stress machinery activated by innate immunity, particularly by activating TLR4 [3].

The second phase of immune defense of the mammalian lungs

If the lung's first phase of immune defense by pulmonary surfactants is inadequate to prevent or suppress a pathogen infection, a second phase of immune defense is quickly activated with a slightly increased risk of lung damage [11]. The second phase involves the use of type III interferons (IFN) [11].

Figure 1 below illustrates various immune cell responses to pathogen lung infections.

Figure 2 below illustrates cellular PRR receptor signaling pathways synthesizing interferon in one cell and cellular interferon pathways in another cell in response to interferon receptor activation.

One influenza virus infection study of murine airway epithelial cells demonstrated that a retinoic acid-inducible gene I (RIG-I)/mitochondrial antiviral-signaling protein (MAVS) signaling pathway is crucial to initiate synthesis of IFNs, and that two transcription factors interferon factor 7 (IRF7) and IRF3 (of lesser importance) were activated for IFN synthesis

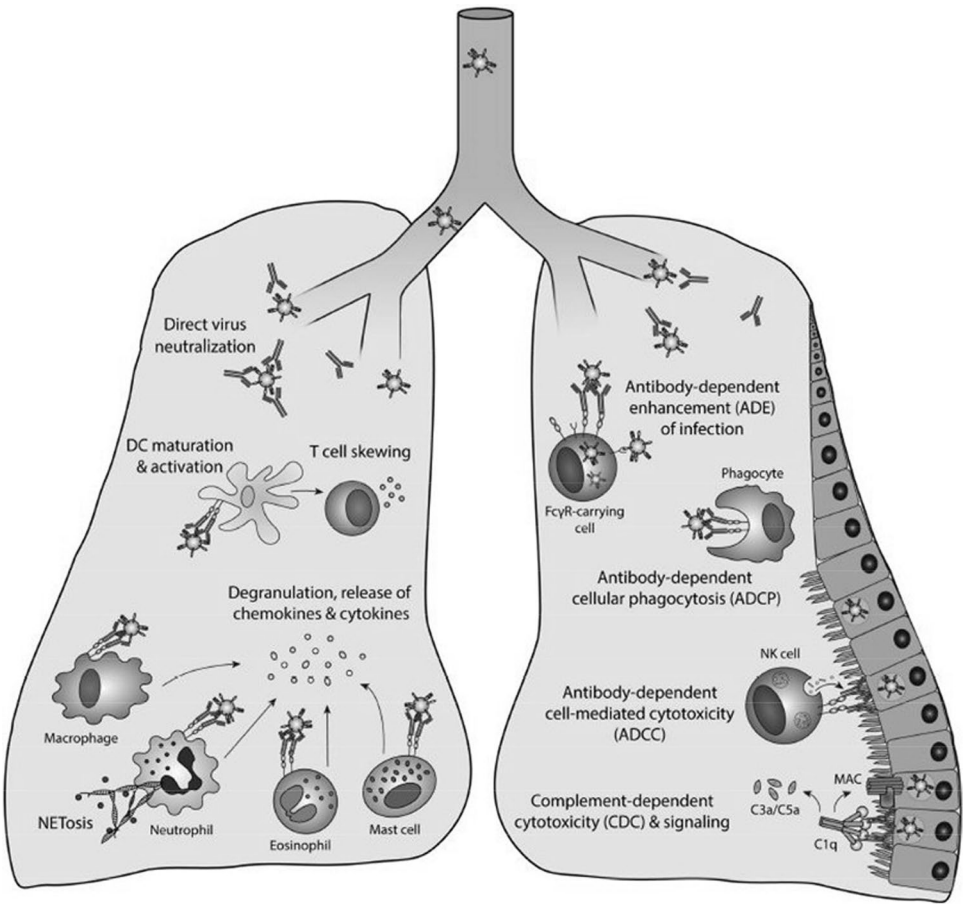

Fig. 1 *DC* dendritic cell, *FcgR* Fc gamma receptor, *MAC* membrane attack complex and *NK cell* natural killer cell. Fig. 1 is reprinted from a Frontiers in Immunology article—entitled "Fc-Mediated Antibody Effector Functions during Respiratory Syncytial Virus Infection and Disease" by van Erp et al. [44]. Fig. 1 is licensed under Creative Commons CC-BY version 4 from Frontiers as the original publisher

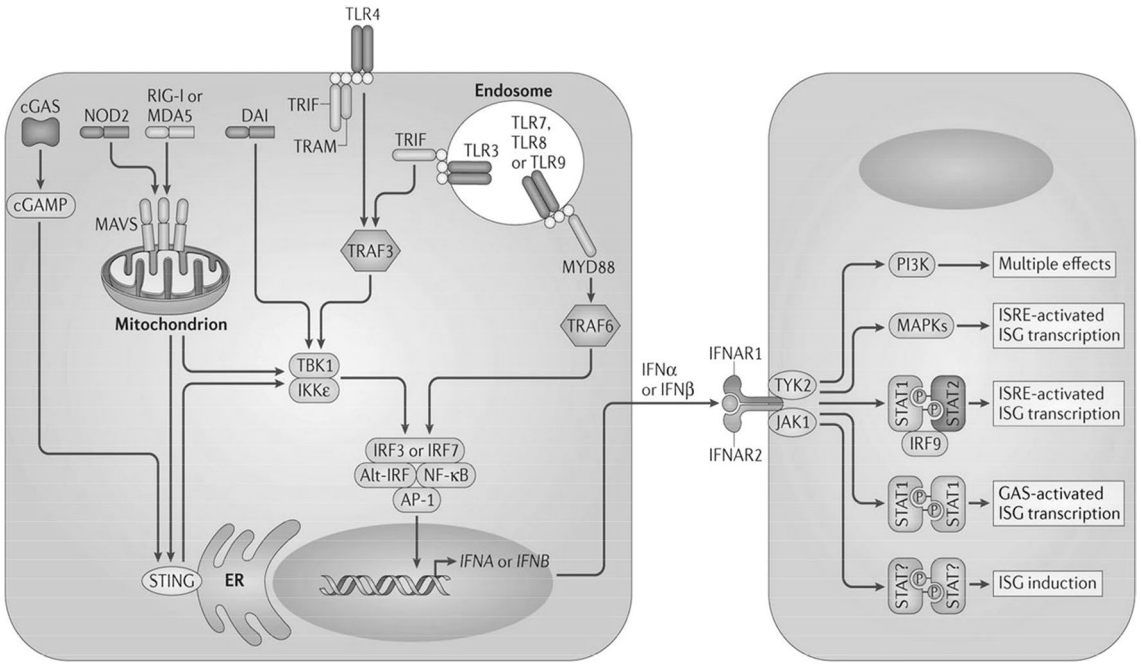

Fig. 2 *cGAS* cyclic GMP-AMP synthase, *cGAMP* cyclic GMP-AMP, *IFN* interferon, *NOD* nucleotide-binding oligomerization domain. RIG-I and MDA5 are RIG-I-like receptors, *MAVS* a mitochondrial antiviral signaling protein, *STING* stimulator of interferon genes, *ER* endoplasmic reticulum, *DAI* DNA-dependent activator of IFN-regulatory factors, *TRIF* TIR-domain-containing adapter-inducing interferon-β, *TRAM* TRIF-related adaptor molecule, *TRAF* TNF receptor-associated factor. *TBK1* TANK binding kinase 1, *IKKε* I-kappa-B kinase epsilon, *TLR* Toll-like receptor, *MYD88* myeloid differentiation factor 88, *NF-κB* nuclear factor 'kappa-light-chain-enhancer' of activated B-cells, *AP-1* activator protein 1, *IFN* interferon, *IRF3* IFN-regulatory factor 3, *IRF7* IFN-regulatory factor 7, *IFNAR* interferon alpha receptor, *JAK1* Janus kinase 1, *TYK2* Tyrosine kinase 2, *PI3K* phosphatidylinositol 3-kinase, *MAPK* mitogen-activated protein kinase, *STAT* signal transducers and activators of transcription. Fig. 2 is reprinted from a Nature Reviews Immunology article—entitled "Type I interferons in infectious disease" by McNab et al. [25]. This reprint is licensed from Springer Nature as the original publisher

[12]. This study also demonstrated that, upon influenza infection, type I IFNs and type III IFNs synthesized by the epithelial cells could independently mediate parallel induction of a completely overlapping set of antiviral interferon-stimulated genes (ISGs) [12]. While there were two redundant IFN loops in epithelial cells, the majority of immune cells responded only to type I IFN, possibly enabling calibrated activation of the epithelial and immune cell defenses [12]. Although high levels of type I IFN would activate both epithelial cells and immune cells, high levels of type III IFN would specifically trigger epithelial cell responses, but immune cell responses would not be triggered; this may explain the comparatively reduced immune-cell mediated pathology in the lungs and other mucosal surfaces from type III IFN synthesis [12].

IFN synthesis after infection by influenza A virus (IAV) requires recognition of viral components by either cytoplasmic receptors or the TLR system, which is determined by the infected cell type [12]. Although plasmacytoid dendritic cells (pDCs) detect influenza virus utilizing TLR7; fibroblasts and conventional DCs synthesize IFN-β after detecting RNA viral genomes by utilizing the cytoplasmic RNA helicase receptors RIG-I [12]. After RNA binding, RIG-I activates the MAVS protein to trigger a signaling cascade which ultimately activates the transcription factors NF-κB and IRF3 and activating protein-1 (AP-1), and the expression of type I IFNs, particularly IFN-β and IFN-α1 in humans [12].

Epithelial cells, including airway epithelial cells and pneumocytes, are primary targets of type III IFN activity, and epithelial cells themselves may also synthesize type III IFN [12, 13]. Using mice lacking functional receptors for type I IFN, type III IFN, or both types of interferons, it was demonstrated in one study that type III IFN provides significant defense against several pathogens capable of infecting the human lungs, including IAV, influenza B virus, RSV, human metapneumovirus, and SARS coronavirus [14].

Four type III IFN (IFN-λ) family members are known to exist at present: IFN-λ1 (IL-29), IFN-λ2 (IL-28A), IFN-λ3 (IL-28B) and IFN-λ4 [15]. IFN-λ1 (IL-29) is the main type III IFN synthesized in human cells, whereas mouse

cells don't synthesize IFN-λ1, but do synthesize IFN-λ2 and IFN-λ3 [15, 16]. All type III IFN family members activate a heterodimeric cellular surface receptor including the subunits: IFN-λR1 (IL-28RA) and IL-10RB [15, 16].

The type III IFN family members separately also have variants with different timings, effects or intensities in their actions. One study found that IFNλ4 and its human variants (e.g., wild type (WT), P70S and K154E) had different antiviral kinetics, compared to IFNλ1 and IFNλ3, and observed that IFNλ4 common (P70S) and rare (K154E) human variants predominantly affected the type III IFN signaling magnitudes, but not their timing [17]. WT IFNλ3 induced stronger and more prolonged signal transducer and activator of transcription 1 (STAT1) phosphorylation, greater ISG expressions, and a stronger antiviral action than WT IFNλ4, which induced a milder and more transient response [17].

The type III IFNs act on infected cells and on nearby uninfected cells to induce the expression of hundreds of ISGs by the activation of pathways including the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway [17]. Phosphorylation of STAT1 after receptor complex activation by IFNλs causes STAT1/2 dimer formation and translocation to the cell nucleus [17]. This then causes ISG transcription, which ultimately expresses immune defense proteins and creates an antiviral environment determined by which members and variants of type III IFN were expressed [17].

In another study, the transcription factor IRF1 was also demonstrated to be involved in another signaling pathway for activating expression of type III IFN to target several pathogens including viruses [18]. Expression of type III IFN has been reported in dendritic cells (DCs), respiratory epithelial cells, keratinocytes, hepatocytes, primary neuronal cells and other cells [13]. The type III IFN, IFN-λ1, was the major IFN type induced by rhinovirus or IAV infections of primary human airway epithelial cells, and particularly produced by type II pneumocytes (alveolar type II epithelial cells) [19, 20].

Compared to type I IFNs discussed in detail below, the type III IFNs induce a more prolonged and lower magnitude response [15]. In murine experiments with various influenza viral exposures, type III IFN was seen as early as one day post-infection after viral infections, while type I IFN was seen after three days post-infection after viral infections [11]. In one study, influenza virus infections in mice induced type III IFNs secretions after significantly smaller viral exposures of influenza and the type III IFN secretions were earlier, compared to type I IFN secretions that were induced by larger viral exposures of influenza [11]. This suggested that the pulmonary immune system response can discern between various viral exposures, and attempt to control smaller viral exposures by using type III IFNs, instead of using the more damaging type I IFNs which have a significant risk of lung damage [11]. Some researchers believe that type III IFNs are an earlier response to smaller respiratory infections to minimize cellular damage, before the more damaging type I IFNs are later induced by larger respiratory infections with consequentially higher risk of lung damage [11, 21].

The significant and comparatively less damaging consequences of type III IFNs compared to other interferons are determined by type III IFN regulation of neutrophil functions [11, 16, 21, 22]. One study concerning murine intestinal tissue demonstrated that neutrophils responded to type III IFN-λ2, and besides inducing ISG transcription, IFN-λ2 (but not type I interferon IFN-β) specifically activated a translation-independent signaling pathway that diminished neutrophil production of reactive oxygen species and secretions, decreasing oxidative stress and intestinal epithelial cell damage without altering neutrophil phagocytosis or cytokine production of tumor necrosis factor (TNF) or IL-6 [22]. Furthermore, type III IFNs (IFN-λ2 in mice) can suppress tissue-damaging neutrophil functions to limit neutrophil-induced oxidation and tissue damage initiated by the cytokine tumor necrosis factor (TNF) [21, 22]. A second study on murine inflammatory arthritis also demonstrated that IFN-λ2 specifically targeted neutrophils, limiting secretions of the inflammatory cytokine IL-1β, and reducing local neutrophil migration capabilities [16]. The first study concluded that IFN-λ2 greatly decreased the activation of the Akt kinase signaling pathway, and this effect depended on the unique ability of IFN-λ2 (not by type I interferons) to utilize a JAK2 kinase pathway [22]. The first study also demonstrated a distinct, translational-independent role for IFN-λ2, in contrast to the role of type I interferons [22].

The type III IFNs were once believed to protect only epithelial cell barriers, a belief based mainly on murine experiments [15]. However, a more recent study using human immune cells examined the regulation of the IFN-λR1 subunit receptor expression and downstream effects of IFN-λ3 stimulation of immune cells in human blood, in comparison to human lung or liver epithelial cells [15]. IFN-λ3 directly bound and upregulated ISG expressions in freshly purified human B-cells and $CD8^+$ T-cells, compared to human monocytes, neutrophils, NK-cells, and $CD4^+$ T-cells [15]. Despite similar IFN-λR1 subunit receptor levels in B-cells and lung epithelial cells, lung epithelial cells bound more IFN-λ3, inducing an ISG expression 50 times larger than the ISG expression induced in B-cells [15]. However, T-cell receptor stimulation upregulated membrane-bound IFN-λR1 subunit receptors in $CD4^+$ T cells, expressed more antiviral genes, and inhibited viral infections, such as human immunodeficiency virus type 1 (HIV-1) [15]. Varied expressions of the soluble form sIFN-λR1 compared to the membrane form mIFN-λR1 were suggested to explain the variable extent of the ISG expression induced by IFN-λ3 in human cells [15].

This study demonstrated that at least IFN-λ3 interacts with human adaptive immune system T-cells and B-cells [15]. Although there is presently no study demonstrating that type III IFNs can interact with the adaptive immune system to create memory lymphocytes, including memory T-cells or B-cells, there is one study which demonstrated that type III IFNs can influence the isotype of antibodies which B-cells produce [23].

This study using murine experiments also demonstrated that murine antibody production by the adaptive immune system is affected by exposure to type III IFNs compared to type I IFNs [23]. This study, which used live attenuated influenza virus and influenza subunit vaccines in mice, observed that type I IFN preferentially promoted the synthesis of antigen-specific IgG2c and IgA antibodies, whereas type III IFN was only effective when applied intranasally to the mucosa, and specifically enhanced synthesis of antigen-specific IgG1 and IgA antibodies [23].

Another study also established that epithelial cells of both lung and gastrointestinal tracts can strongly respond to IFN-λ, and showed that IFN-λ inhibited the replication of viruses including severe acute respiratory syndrome coronavirus (SARS-CoV) in both respiratory and gastrointestinal tracts [14]. Type III IFNs, similar to the type I IFNs to be discussed below, expressed ISGs by activating JAK1 and TYK2, which associate with IFN-λR1 and IL-10RB, respectively, leading to the phosphorylation of STAT1/STAT2 as a pathway to ISG expression [15].

After infection by HSV-2 or influenza virus, macrophages, which are strong type I IFN producers, did not express type III IFN [13]. Therefore, cells synthesizing type I or type III IFNs may partially overlap, but are not identical [13]. Studies using vaginal epithelial cells have shown that the transcription factor pathways leading to type I IFN or type III IFN gene expression are not identical, because genes encoding type I IFNs and III IFNs are regulated by the transcription factors NF-κB and IRF3, but the type III IFN genes depend more on the NF-κB transcription factor pathway than the type I IFN genes, which depend more on the IRF (e.g., IRF3) transcription factor pathways [24].

Several viruses specifically interfere with the IRF transcription factor pathways and will impair type I IFN expression, but the expression of type III IFN will be less impaired and enable a host to resist viral pathogens regardless of their interference with antiviral IFN pathways [24]. However, type I IFNs have broader effects on innate and adaptive cellular immune responses, compared to type III IFNs, which have reduced effects on some cells with limited IFNλR receptor expressions [25].

One group concluded that type III IFN is critical for epithelial barrier integrity in tissues frequently attacked by viruses, and that type I IFN secretions will increase only after the epithelial barrier cannot suppress the virus [26]. This group also suggested that the evolution of such functional compartmentalization was because this defended tissues against comparatively minor viral infections with little risk of cellular damage from a strong activation of immune cells [26].

Table 2 Types of lung interferons and their roles, sources, receptors, actions and consequences

Interferon	Type III	Type I	Type II
Members	IFN-λ1, IFN-λ2, IFN-λ3, IFN-λ4	13 IFN-αs, IFN-β, IFN-ω, IFN-ε, IFN-κ	IFN-γ
PRRs	RIG-I, most endosomal and membrane TLRs	RIG-I, MDA5, NOD1, NOD2 TLRs 2, 3, 4, 7, 8, 9	TLRs, NOD1, NOD2 inflammasones
Main transcription factors	NF-κB, IRF-7, IRF-3 IRF-1	IRF-3, AP-1, NF-κB	AP-1, NF-κB, NFAT, T-bet, Eomesodermin IL-12, IL-18 promote
Cell sources	Epithelial/some immune	Epithelial/immune/most	Immune cells, T-cells NK-cells, iNKT-cells
Receptor	IFN-λR1 & IL-10RB	IFNAR1 & IFNAR2c	IFNγR
Signal paths	STAT1, STAT2, JAK2, JAK1, TYK2	STAT1, STAT2, JAK1, TYK2	JAK1, JAK2, STAT1, STAT4
Acts on lymphocytes	T-cells & B-cells (IFN-λ3)	NK-cells, T-cells, B-cells, myeloid cells	Monocytes, macrophages, myeloid cells
Consequences	Antiviral, less inflammatory compared to type II IFN ISG transcriptions, moderates neutrophils enhance epithelial barriers bacterial pathogens	Increases MHC, IL-12, costimulatory ligands, ISG transcriptions, neutrophils unleashed	Attracts inflammatory monocytes, activates macrophages, causes cellular necroptosis
Epithelial cell destruction risk?	Negligible to moderate	Possibly moderate to medium	Possibly considerable

Table 2 compares the three types of lung cell interferons and their roles, sources, receptors, actions and consequences.

The third phase of immune defense of the mammalian lungs

After the lung's second phase of immune defense is activated, the third phase of immune defense will become involved. This will involve the type I IFNs. Of the type I IFNs, presently 13 IFN-αs are known, whereas there is only a single type known of IFN-β, IFN-ω, IFN-ε or IFN-κ [27].

Type I IFNs, compared to type III IFNs, use a different receptor (IFNAR), which is composed of subunits IFNAR1 and IFNAR2c [13]. However, upon binding their corresponding receptors, type I and type III IFNs trigger JAK-STAT signal transduction pathways leading to the upregulation of hundreds of ISGs, where more than 300 ISGs have been identified [13]. The expressed ISG gene products control viral infection, modulate immune responses or control mitosis, and some ISGs can express factors that participate in the IFN transcription factor pathways and thereby control IFN expression and response through positive or negative feedback loops [13].

Type I IFNs have diverse effects on innate immune cells (macrophages) and adaptive immune cells (T-cells and B-cells) during infection with viruses, bacteria, parasites and fungi, directly and/or through the participation of other mediators. Type I IFNs are important for host defences against viruses, however, they can cause immune pathology in certain acute viral infections, including influenza virus [25]. Type I IFNs can also have detrimental roles during virus infections, either by immune effects which inhibit viral control or by triggering inflammation [25].

Before the lungs experience pathogen infections, alveolar macrophage activations are suppressed by negative regulatory signals secreted by pneumocytes, including signaling proteins (e.g., CD200–CD200R) and inhibitory cytokines including transforming growth factor-β (TGF-β) [28]. During pathogen infections, interference with these negative regulatory signals by loss of pneumocytes will enable alveolar macrophage activations [28].

Almost all cells in mammals can synthesize type I IFNs, typically after activation of pathogen recognition receptors (PRR) by pathogen associated molecular patterns (PAMPs), where PRRs (e.g., TLRs) are located on the cell surface, in cellular cytosol or in cellular endosomes [25]. There is substantial production of type I IFNs by plasmacytoid dendritic cells (pDCs) [25]. These PRRs recognize foreign and self nucleic acids (not normally in the cytosol), and certain other non-nucleic acid PAMPs. The RNA helicases RIG-I and melanoma differentiation-associated gene 5 (MDA5) are the main cytosolic PRRs which detect viral RNA, and may also recognize some viral DNA, and are known to induce synthesis of type I IFNs, especially after detection by TLRs in plasmacytoid dendritic cells and RIG-I-like receptors in alveolar macrophages [25, 28]. Type I IFN synthesis is also induced by other classes of DNA in the cytosol, detected by various receptors, which provide signals to the sensor and signaling intermediate stimulator of IFN genes (STING) to trigger type I IFN synthesis [25]. Furthermore, the molecular sensors nucleotide-binding oligomerization domain containing protein 1 (NOD1) and NOD2 are expressed in the cytosol by several cell types and detect both non-nucleic acid and nucleic acid ligands, thereby inducing type I IFN synthesis [25].

Type I IFNs (IFN-α/β) are induced by infections and play essential roles in innate antiviral defense, and also stimulate the adaptive immune system to enhance antibody and T-cell responses [29]. One study demonstrated with IFN-α/β receptor impaired mice that B-cells and T-cells are direct targets of IFN-α/β during IFN-α mediation of the antibody response against soluble protein antigens [29].

IFN-α/β stimulate myeloid cells, B-cells, T-cells and natural killer (NK) cells to improve immune responses, to more effectively end viral infections and to improve the generation of effector memory cells for future responses targeting repeating pathogen secondary infections [25]. Several studies in both human and murine experiments indicate that IFN-α/β affect adaptive immune cell responses by DCs, either promoting or restricting their responses, according to the needed DC functions [25].

Cross-presentation is a vital function which enables antigen-presenting DCs to present exogenous antigens to $CD8^+$ T-cells, which is an important function in suppressing infections [30]. One study demonstrated that $CD8^+$ T-cell priming for influenza requires antigen presentation by activated DCs which express costimulatory ligand molecules, including CD40, CD80 and CD86, which assist T-cell proliferation and differentiation [31]. Some activated DCs also express costimulatory ligand CD70, the ligand for T-cell receptor CD27, which assists primary and secondary $CD8^+$ T-cell responses [31]. CD27 regulates primary antigen-specific $CD8^+$ T-cell responses by blocking apoptosis of CD8 + T-cells during the later phase of the primary response, thus CD27 is required for optimal quality memory T-cells [32].

However, it was initially uncertain which DCs express CD70, and how CD70 expression facilitates the DC ability to promote $CD8^+$ T-cell proliferation and differentiation [31]. However, a later study demonstrated that IFN-α induces quick differentiation of human monocytes into DCs, known as IFN-DCs, which are very effective in mediating cross-presentation and cross-priming of CD8 + T-cells [30]. It was demonstrated by this later study that, regardless of the route and mechanism of antigen entry, IFN-DCs have

a high capability for preserving internalized proteins from early degradation and also sending antigens toward the MHC class-I processing pathway, enabling long-lasting, cross-priming of T-cells [30].

Treatment with IFN-α/β causes DCs to increase expressions of MHC and costimulatory molecules and to increase the DCs' capabilities for T-cell stimulation [29]. DCs synthesize considerable IL-12, which is essential for driving T helper 1 (Th1)-type responses during certain bacterial and viral infections, and IL-12 is important for IFN-γ production by T-cells and NK-cells [25]. IFN-α/β signaling can be necessary for IL-12 synthesis by DCs after PRR activation, and IL-12 production can be a crucial response during intracellular bacterial and viral infections [25].

The fourth phase of immune defense of the mammalian lungs

After the lung' third phase of immune defense is activated, the fourth phase of immune defense will be initiated as necessary. The fourth phase involves the type II IFN, consisting of one member, IFN-γ, which is predominantly produced by T-cells and NK-cells, and IFN-γ can act on a broad range of cell types that express the IFN-γ receptor (IFNγR) [25].

TLRs expressed by alveolar macrophages and dendritic cells which extend trans-epithelial processes enable early detection of PAMFs in the airway initiating the synthesis of cytokines including IL-12 and IL-23 [28]. Additional pathogen detection via inflammasome sensor activation initiates caspase-1-mediated activation and release of cytokines IL-1β and IL-18 [28]. These cytokines activate tissue-resident cytotoxic T lymphocytes for the elimination of infected cells, and act on innate lymphoid cells (ILCs), NK-cells, NKT-cells, and T-cells to induce synthesis of cytokines including IFN-γ, IL-17, and IL-22 [28]. These cytokines induce pneumocytes and airway epithelial cells (AEC) to initiate synthesis of chemokines and antimicrobial peptides, and also boost pneumocyte and AEC proliferation and/or tight junction formation to strengthen airway epithelial barriers and inhibit pulmonary pathogens [28]. Local and chemokine-recruited phagocytes, including neutrophils and monocytes, are also activated by IFN-γ, to increase their phagocytic targeting of pathogens [28].

In one study using 31 pigs infected with H1N2 swine IAV, pig lungs modelled human lung responses, and the first appearance of pulmonary neutralizing antibodies and influenza virus-specific IFN-γ-producing $CD4^+$ and $CD8^+$ T-cells could be detected in the pig lungs as early as four days post-infection and peaked in numbers in the lungs at six days post-infection [33]. During this study, influenza virus-specific $CD4^+$ and $CD8^+$ T-cells primarily produced IFN-γ, starting at four days post-infection and reaching peak cell numbers in the blood nine days post-infection [33]. Furthermore, influenza virus-specific $CD4^+$ T-cells also produced TNF-α and IL-2 starting at six days post-infection, but these cells did not appear in the lungs until six days (for TNF-α) and nine days (for IL-2) post-infection; $CD8^+$ T-cells produced mainly IFN-γ and/or TNF-α and lacked significant IL-2 production [33].

In the pig lungs, cytokine-producing influenza virus-specific T-cells with CD27 expression were predominant, and CD27 expression was strongest for IFN-γ-producing $CD8^+$ T-cells [33]. An earlier study also correlated CD27 expression with the proliferation of effector CD8 T-cells by showing that the in vivo expansion of influenza virus nucleoprotein-specific $CD8^+$ T-cells was dependent on CD70-CD27 interaction [31]. In the lungs, cytokine-producing influenza virus-specific T-cells with CD27 expression was pronounced, and CD27 expression was strongest for IFN-γ-producing $CD8^+$ T-cells [33]. In summary, type II IFN (IFN-γ) was the most important cytokine to suppress the swine influenza virus in the pig lungs, at the cost of peak numbers of cytotoxic $CD8^+$ T-cells six days post-infection [33].

Influenza experiments in primates are much rarer and difficult, but in a small study of the lungs of non-human primates (rhesus macaques), IFN-γ producing $CD8^+$ T-cells were also essential in suppressing infections with the 2009 pandemic H1N1 influenza virus strain [34]. Separate observations were made of one group of previously uninfected primates inoculated by the 2009 pandemic strain, and a second group of primates primed with an inoculation of a different H1N1 influenza virus strain four months before the 2009 pandemic strain inoculation [34]. In the previously uninfected primates, after infection, both $CD4^+$ and $CD8^+$ T-cells responded [34]. $CD8^+$ T-cells with an activated phenotype (with the proliferation marker Ki-67^+ and adhesion molecule $CD38^+$) appeared in the blood and lungs five to seven days post-inoculation (p.i.) with the 2009 pandemic H1N1 influenza virus strain, and reached peak $CD8^+$ T-cell numbers seven to ten days p.i. [34]. These primate experiment observations, except for an extra one day delay over the cell number timings, were consistent with the previously discussed pig lung experiments, where influenza virus-specific IFN-γ-producing $CD4^+$ and $CD8^+$ T-cells could be detected in lungs as early as four days post-infection and peaked in numbers in the lungs at six days post-infection, and influenza virus-specific $CD4^+$ and $CD8^+$ T-cells primarily produced IFN-γ, starting at four days post-infection and reaching peak cell numbers in the blood nine days post-infection [33].

The previous two studies concerned influenza virus lung infections, but a third study with poxvirus (vaccinia) in murine lungs demonstrated that NK-cells in the lung also produced IFN-γ before the recruitment of $CD4^+$ and $CD8^+$ T-cells [35]. Whereas vaccinia-specific $CD8^+$ T-cells will enter murine lungs at day 4.5 and increase significantly by day 5.5 post-infection [36, 37], the NK-cell population in the

infected lung tissue increased over the first two days post-infection, peaked between the fourth and sixth days, and then decreased [35]. Moreover, lung-resident NK-cells expressed high levels of cytolytic enzymes (perforin and granzyme B) and the NK-cells were the predominant producers of IFN-γ before the $CD8^+$ T-cells arrived [35]. In summary, the experiments are consistent in demonstrating the later arrival of IFN-γ producing $CD8^+$ T-cells, compared to the earlier immune defenses.

The fourth phase of immune defense will be triggered by pulmonary pathogens that were not suppressed by one of the earlier phases of immune defenses. The fourth phase of immune defense will not only be triggered by viral pathogen infections; studies have demonstrated that fungal pathogen and bacterial pathogen infections will also trigger the fourth phase of immune defense [38, 39].

Respiratory fungal infections can be dangerous pulmonary risks, especially involving pathogens belonging to *Aspergillus, Cryptococcus, Pneumocystis*; and these endemic pulmonary fungal pathogens can cause lethal diseases [38]. After fungal pathogen detection, innate myeloid cells including macrophages, neutrophils, and DCs, provide the first immune cell defense through phagocytosis and cytokine secretions [38]. NK-cells inhibit pulmonary fungal infections by direct and indirect killing of fungal pathogens. Adaptive immune cells including Th1 and Th17 T-cells also secrete their signature cytokines, such as IFN-γ, and IL-17 [38].

IFN-γ also plays a critical role in host defense by activating macrophages against dangerous intracellular bacterial pathogens including *Mycobacterium tuberculosis* [39]. In addition, IFN-γ has been shown to be an integral part of other antibacterial actions, including granuloma formation and phagosome-lysosome fusion, both of which control intracellular Mycobacterium [39]. Therefore, the absence of IFN-γ is associated with severe diseases from intracellular bacterial pathogens including *M. tuberculosis* or *Mycobacterium nontuberculosis* [39].

However, IFN-γ is a very dangerous double-edged sword, because IFN-γ can also induce severe damage to airway epithelial cells and pneumocytes, including cellular death [40, 41]. One study identified an interferon (IFN)-γ-regulated subset of monocytes, $CCR2^+$ monocytes, as a major cause of acute lung injury (ALI) during influenza A (IAV) virus infections, where IFN-γ regulated the recruitment of the inflammatory phenotype of $CCR2^+$ monocytes [40]. $CD8^+$ T-cells were the main sources of IFN-γ in IAV-infected lungs, and IFN-γ had a signaling role in the regulation of $CCR2^+$ monocyte-mediated lung pathology during IAV infections [40]. Furthermore, IFN-γ not only attracts lung damaging, inflammatory monocytes, IFN-γ can also cause pneumocyte death by necroptosis [41].

Necroptosis, a type of programmed lytic cell death, has emerged as a fundamental cause for ALI pathogenesis [41]. In one study, mouse primary lung epithelial and endothelial cells pretreated/primed with various inflammatory mediators were examined for their responses to different necroptosis inducers [41]. IFN-γ as low as 1 ng/mL preferentially promoted necroptosis and accelerated damage-associated molecular pattern (DAMP) releases from pneumocytes and airway epithelial cells, but not lung microvascular endothelial cells [41]. Furthermore, IFN-γ was about 50 times more effective at causing necroptosis than type-I IFN-α [41]. Unlike apoptosis, necroptosis ruptures cell membranes, which triggers and amplifies inflammation through the release of DAMPs, including ATP, nucleic acids, IL-1 family cytokines, and other molecules [41, 42].

The fifth phase of immune defense of the mammalian lungs

After the lungs' fourth phase of immune defense is activated, the fifth phase of immune defense will become sequentially involved if necessary. The fifth phase antibody functions can potentially be relatively benign, ranging from direct binding to pathogen surface proteins for neutralizing extracellular pathogens or inducing the direct phagocytosis of extracellular pathogens [43, 44]. Or the fifth phase can dangerously escalate to involve the complement system and potentially cause considerable cell death including cellular destruction of essential pneumocytes and other pulmonary cells [43, 44].

Figure 1 shows antibody actions against pathogens. As can be seen in Fig. 1, antibodies have several potential effector functions, which also substantially assist innate immune cell defenses [44]. Most antibody functions utilize the constant (Fc) region of the antibody, which can interact with complement proteins and specialized Fc-receptors on immune cells, such as the Fc-gamma receptor on NK-cells [44]. The Fc-receptors on immune cells can act in activating or inhibitory pathways, depending on the type of immune cell receptor, and the Fc-receptors are found on B-cells and most innate immune cells [44].

Figure 1 also illustrates cellular destruction by antibody-dependent cell-mediated cytotoxicity (ADCC), where Fc gamma receptors present on natural killer (NK) cells engage antibodies on antibody-bound infected cells and initiate target cell death by releasing cytotoxic granules (not shown) [44]. The most important Fc-mediated antibody functions include ADCC, antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) [44]. There is an increased risk of pneumocyte destruction when immune cell Fc-receptors bind to the Fc contstant regions of antibodies which have bound to infected cells, inducing the killing of intracellular pathogen-infected cells through a variety of

immune cell mechanisms, including ADCC and ADCP, or antibody-mediated complement activation may lead to more dangerous CDC from complement proteins [44]. The antibody facilitated destruction of infected pneumocytes or other pulmonary cells can be considered the fifth phase of pulmonary organ defense by the immune system, and it may potentially be a Pyrrhic victory with dangerous collateral pulmonary cell damage, possibly ALI or ARDS, even if it effectively ends a pathogen infection.

Conclusion

In summary, the mammalian lungs have evolved an impressively sophisticated immune defense with five major phases of immune responses initiated in a staggered and overlapping temporal sequence. The immune defense includes five sequentially activated phases of increasing capabilities, but these phases also have a sequentially increasing risk of causing cellular damage and/or cellular death of airway epithelial cells and pneumocytes. The second through fourth phases of increasing capabilities are also associated with three stages of interferon synthesis and the secretion of interferon members of type III IFN, type I IFN and type II IFN. Type III IFN has been seen as early as one day post-infection by viruses, while type I IFN has been seen after three days post-infection by viruses and type II IFN has been seen after four days post-infection by viruses, such as influenza. Furthermore, while type III IFN can interact with the adaptive immune system to influence the production of antigen-specific antibodies, the creation of memory T-cells appears to begin during the third phase of the respiratory system immune defense. The involvement of antibodies can be considered to be the fifth major phase of defense against pulmonary pathogens, with potential risks of considerable pulmonary cellular destruction and possibly ALI or ARDS.

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