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REVIEW

Unravelling the networks dictating host resistance versus tolerance during pulmonary infections

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Abstract The appearance of single cell microorganisms on earth dates back to more than 3.5 billion years ago, ultimately leading to the development of multicellular organisms approximately 3 billion years later. The evolutionary burst of species diversity and the "struggle for existence", as proposed by Darwin, generated a complex host defense system. Host survival during infection in vital organs, such as the lung, requires a delicate balance between host defense, which is essential for the detection and elimination of pathogens and host tolerance, which is critical for minimizing collateral tissue damage. Whereas the cellular and molecular mechanisms of host defense against many invading pathogens have been extensively studied, our understanding of host tolerance as a key mechanism in maintaining host fitness is extremely limited. This may also explain why current therapeutic and preventive approaches targeting only host defense mechanisms have failed to provide full protection against severe infectious diseases, including pulmonary influenza virus and *Mycobacterium tuberculosis* infections. In this review, we aim to outline various host strategies of resistance and tolerance for effective protection against acute or chronic pulmonary infections.

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> Nothing in biology makes sense except in the light of evolution.
> Theodosius Dobzhnansky

Introduction

For a long time, immunologists considered host defense as the hallmark of immunity, through the detection and destruction of pathogens. However, we now recognize that the host may also provide protection against infections by tolerating them and controlling tissue damage caused either directly via pathogen-derived toxins or indirectly by the immune response. Host tolerance was initially studied in plants (Kover and Schaal 2002; Ayres and Schneider 2012) and then in *Drosophila* (Ayres et al. 2008; Ayres and Schneider 2008, 2009) and the concept has recently been introduced in animals (Raberg et al. 2007; Read et al. 2008; Schneider and Ayres 2008; Raberg et al. 2009; Medzhitov et al. 2012; Fig. 1).

During an infection, the host protects itself by two major mechanisms, namely resistance and tolerance and these mechanisms are not mutually exclusive. Resistance mechanisms are typically associated with a decrease in microbial burden through innate mechanisms, including pathogen detection by various sensors, such as Toll-like receptors (TLR), NOD-like receptors and C-type lectins, or phagocytosis and neutralization by macrophages and adaptive mechanisms via the killing of infected cells by T cell-mediated immunity.

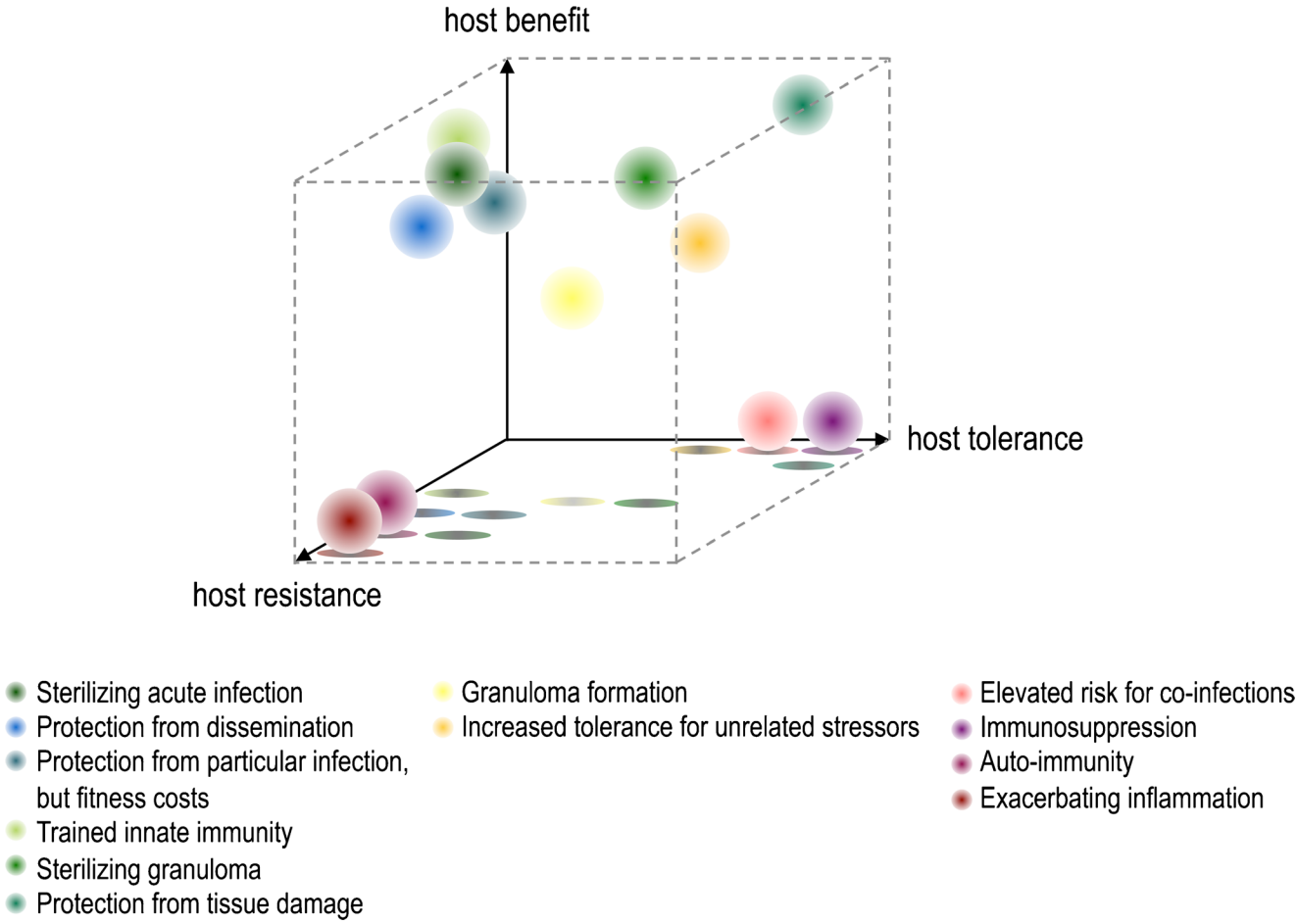

Fig. 1 Three-dimensional representation of host resistance and host tolerance and their beneficial impact on the organism. Each dot represents a major type of immune response in its general placement between host resistance and host tolerance and its contribution to the host benefit. Contribution to the host benefit can vary because of host and pathogen factors. The different placements are not mutually exclusive and the transition is fluid

Although the host's resistance response is essential in controlling the infection and preventing further dissemination, it is frequently associated with significant fitness costs, as it also induces tissue damage. For instance, lung infections often result in mucus production, increased airway permeability, alterations in vascular function, and thereby, impaired lung function. Therefore, a balance between decreasing the microbial burden and restricting tissue damage is required. In this vein, the collateral damage caused by the resistive immune response can be dampened by host tolerance. Disease tolerance is defined as the mechanisms that "decrease host susceptibility to tissue damage, or other fitness costs caused by pathogens or by the immune response" (Medzhitov et al. 2012). Common tolerance mechanisms include the activation of the stress response to eliminate reactive oxygen species (ROS) and the secretion of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). An additional major tolerance mechanism is the tissue repair response, which has been classically associated with the production of type 2 cytokines (e.g., IL-4 and IL-13) that share a STAT6-dependent signaling pathway (Martinez et al. 2009) and the induction of alternatively activated macrophages (AAMφ).

Pulmonary infections are usually associated with alterations in vascular function and increased permeability of the airways, which lead to lung dysfunction. For example, influenza A virus (IAV) induces type 2 cytokines such as IL-33, IL-4 and IL-13 early during infection, driving goblet cell hyperplasia, mucus production and airway hyperreactivity (Chang et al. 2011). However, production of these cytokines upon viral clearance is associated with the restoration of lung function and tissue remodeling (Monticelli et al. 2011). Alternatively, slow growing pathogens such as *Mycobacterium tuberculosis* (Mtb) may exploit type 2 cytokine production for its own benefit to favor the invasion of the lungs and to establish a chronic infection (Heitmann et al. 2014). Mechanistically, IL-4 and IL-13 have been shown to stimulate macrophage fusion and giant cell formation (Helming and Gordon 2007), leading to granulomas, a hallmark of chronic tuberculosis (TB) and an important mechanism of immune evasion and chronicity. Pairing the formation of granulomas with the

increased lifespan of AAMφ may provide an important reservoir for Mtb to facilitate bacterial persistence. Although some groups have found that the inhibition of type 2 cytokine production via antibody blockade or deletion of the IL-4/13 signaling pathway confers enhanced resistance to Mtb infection (Buccheri et al. 2007; Roy et al. 2008), this topic remains controversial (Jung et al. 2002). Undoubtedly though, during pulmonary infection, both resistance to the pathogen, by mounting an effective immune response and tolerance of its presence to control immunopathology have a direct impact on host protection and fitness. In this review, we explore the cost-benefit trade-offs of the immune response and immune-mediated pathology with a particular focus on respiratory infections.

Host resistance in pulmonary infections

Most acute infections in the lungs cause excessive tissue damage that needs to be rapidly controlled and repaired for host survival. During an acute pulmonary infection, the pathogen burden and the magnitude of the immune response that will ultimately determine the extent of the tissue damage are directly correlated. Thus, the extent of the initial resistance mechanisms is an important determinant of host tolerance to infection.

Both pulmonary epithelial and immune cells express a wide range pattern-recognition receptors (PRRs) that identify pathogen-associated molecular patterns (PAMPs) originating from the invading pathogen and of damage-associated molecular patterns (DAMPs) released from infected cells (Holt et al. 2008; Takeuchi and Akira 2009; Braciale et al. 2012). In 1989, Charles Janeway brilliantly predicted the importance of PRRs in the recognition of pathogens by macrophages and their potential link to adaptive immunity (Janeway 1989). This hypothesis led to an explosion of research in the field of innate immunity, beginning with the discovery of the Toll pathway in anti-microbial defense in the plant (Whitham et al. 1994) and the fruit fly (*Drosophila melanogaster*; Lemaitre et al. 1996). This work was followed by Medzhitov and Janeway describing the first mammalian Toll-like receptor (TLR4; Medzhitov et al. 1997) that recognizes lipopolysaccharide (LPS) on gram-negative bacteria (Poltorak et al. 1998). In the last 15 years, more than 13 TLR family members have been discovered that localize to the cell surface or endosome and that recognize diverse bacterial or viral components. Whereas several TLRs detect conserved PAMPs present on bacteria (e.g., LPS, flagellin, or peptidoglycans), a PRR that directly recognizes viruses has yet to be identified. As most structural components of viruses are derived from the host, recognition is necessarily limited to viral nucleic acids. Thus, TLRs involved in sensing viruses are unsurprisingly localized to the endosome and detect extracellular viral particles by stripping and exposing their genome (RNA/DNA) via endosomal acidification. In addition to TLR family members that have evolved to recognize microbial components in the extracellular microenvironment, there are also cytosolic PRRs including Nod-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and others that play a crucial role in recognition of PAMPs within infected cells (Kumar et al. 2011). The evolution of this second layer of PRRs is essential for host survival as the role of TLRs in host defense against intracellular pathogens is less pronounced. Indeed, NLRs are highly conserved (Rast et al. 2006) and crucial in the recognition of various intracellular bacteria including Mtb (Guirado et al. 2013). For example, NOD2 is an NLR family member that recognizes the bacterial peptidoglycan fragment muramyl dipeptide (MDP) and activates nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways (Inohara et al. 2005). Macrophages from NOD2-deficient mice or humans are impaired in cytokine production (e.g., TNF-α and IL-12) following Mtb infection (Ferwerda et al. 2005; Divangahi et al. 2008). In addition, NOD2-deficient mice are more susceptible to the late stages of Mtb infection (Gandotra et al. 2007; Divangahi et al. 2008) emphasizing a potential role for NOD2 in adaptive immunity (Divangahi et al. 2008; Philpott et al. 2014). Whereas most bacteria express an N-acetylated form of MDP, mycobacteria produce an N-glycolylated form, converted via N-acetyl muramic acid hydroxylase activity. N-glycolylated MDP is more potent in inducing NOD2-mediated innate and adaptive immune responses (Coulombe et al. 2009; Behr and Divangahi 2015). Thus, PAMP localization and post-transcriptional modifications can diversify the outcome of the immune response.

Particularly relevant to anti-viral immunity are RLRs, such as RIG-I and melanoma differentiated-associated gene 5 (MDA5), which detect viral single-stranded RNA/short double-stranded RNA (<300 bp) and long double-stranded RNA (>1000 bp), respectively, in infected cells (Iwasaki and Pillai 2014). Additionally, mitochondrial antiviral signaling protein (MAVS), an essential adaptor protein downstream of RIG-I/MDA5, activates NF-κB and interferon (IFN) regulatory factor 3 (IRF3)-dependent signaling pathways and is localized to the mitochondrial outer membrane (Seth et al. 2005). Recognition of a virus by these sensors potently induces type I IFN. Type I IFN is a critical mediator of host resistance to viral infection, as it rapidly induces more than 300 known IFN-stimulated genes (ISG) within infected and neighboring cells rapidly to restrict viral replication (Doly et al. 1998; Schneider et al. 2014). Viruses have also evolved several mechanisms to inhibit RIG-I/MDA5 signaling and to paralyze antiviral responses. For instance, the NS1 protein expressed by IAV inhibits RIG-I signaling, hinting at the crucial role of RLRs in innate immunity to viral infections. Furthermore, type I IFN also promotes the cytotoxic activity of $CD8^+$ T cells by inducing granzyme B expression (Kohlmeier et al.

2010), highlighting a role for type I IFN in orchestrating adaptive immunity. Apart from type I IFN, type II IFN (IFN-γ) and type III IFN (IFN-λ) have also been shown to induce overlapping sets of ISG, which promote viral clearance (Der et al. 1998). Interestingly, influenza PB1-F2 is encoded by an alternate reading frame within the viral polymerase PB1 gene segment and selectively targets the mitochondria of macrophages but not epithelial cells, to inhibit type I IFN production and induce apoptosis, enhancing IAV virulence in mice (Chen et al. 2001; McAuley et al. 2007). Moreover, non-pathogenic influenza viruses engineered to express the PB1 gene from virulent H5N1 or 1918 pandemic influenza strains become highly pathogenic in mice (McAuley et al. 2007, 2010). Mechanistically, PB1-F2 interacts with the permeability transition pore (PTP) complex, containing the adenine nucleotide translocator 3 (ANT3) and voltage-dependent anion channel 1 (VDAC1), both of which have been implicated in mitochondrial-dependent apoptosis (Varga et al. 2011). Recently, we have shown that NLR-family member NLRX1 interacts with PB1-F2 in the mitochondria to disarm its pro-apoptotic effect and to promote the capacity of macrophages to produce type I IFN (Jaworska et al. 2014). It will be interesting to discover other viral or bacterial proteins with similar functions. In this regard, part of the Mtb genome called Region of Difference 1 (RD1), which encompasses a system essential for the secretion of bacterial proteins including Early Secretory Antigenic Target 6 (ESAT6), has the ability to target mitochondria in macrophages and to induce mitochondrial inner membrane potential dissipation, leading to necrosis (Welin et al. 2011) and increased bacterial invasiveness (Hsu et al. 2003). However, the role of NLRX1 in Mtb infection and its potential interaction with ESAT6 remains to be determined.

Host tolerance in acute pulmonary infection

Although immune cells are the critical component of host resistance to infection, the integrity of structural cells (e.g., lung parenchymal epithelial cells) is essential in mitigating tissue damage and promoting host tolerance. While a robust host resistance may result in the complete elimination of the pathogen, collateral tissue damage caused by such a response must be controlled in order to avoid jeopardizing host survival. Several mechanisms contribute to host tolerance:

(1) PRRs: Because the cost of tissue damage is high and may result in the permanent loss of physiological function, repair mechanisms must be initiated from the onset of the infection. Interestingly, the overall effects of single nucleotide polymorphisms in genes encoding TLRs or their signaling components appear to have only a modest effect on host resistance to infectious diseases, thus suggesting a potentially important role in host tolerance (Neagos et al. 2015). Matzinger (2002) initially suggested that the activation of TLRs via DAMPs would serve as an early "alarm signal" of tissue damage for the initiation of the repair process. For example, during *Pseudomonas aeruginosa* infection, high-mobility group box 1 (HMGB1) has been demonstrated to contribute to the inflammation in the lungs of patients suffering from cystic fibrosis (CF) through recognition by TLR2 and TLR4. Indeed, the neutralization of HMGB1 in a mouse model of *Pseudomonas aeruginosa* infection dampens lung inflammation (Entezari et al. 2012). Furthermore, C-type lectin receptors (CLRs) can function as PPRs by recognizing glycan structures expressed by various pathogens (Davicino et al. 2011). For instance, in macrophages, galactose-type lectin-1 recognizes galactose and/or its monosaccharide derivative on *Klebsiella pneumonia* and orchestrates the immune response in the lungs by triggering the recruitment of neutrophils (Jondle et al. 2016). However, conversely, HMGB1 recognition through TLR4 and the receptor for advanced glycated end products (RAGE) on bronchial epithelial cells promotes extracellular matrix synthesis and wound repair (Ojo et al. 2015). Thus, the initial recognition of PAMPs via PRRs in immune cells initiates host resistance, whereas the recognition of DAMPs via PRRs in structural cells may potentially initiate host tolerance by activating tissue repair mechanisms at a very early stage of infection.

(2) Stress response: The cellular stress response has evolved to provide rapid metabolic adaptation to environmental changes including oxygen, glucose, cellular redox, or local ADP/ATP concentrations. This adaptation is required for the maintenance of tissue integrity and for functionality during infection (Soares et al. 2014). During pulmonary infection with IAV or respiratory syncytial virus (RSV), large amounts of ROS are produced by neutrophils and macrophages; this creates oxidative stress in the surrounding tissue. The actin-anchored protein Keap-1 senses the oxidative stress and liberates the transcription factor Nrf2 to induce multiple proteins to scavenge free radicals, eliminate damaged proteins, metabolize oxidized membrane lipids, and repair damaged DNA (Thimmulappa et al. 2006; Kensler et al. 2007; Garofalo et al. 2013). Stress response pathways are complex and have been extensively reviewed with regard to disease tolerance elsewhere (Soares et al. 2014).

(3) Th2 response: Type 2 immunity has been extensively studied in the context of host resistance to metazoan parasites and a remarkable overlap occurs between pathways regulating host resistance to parasites and tissue repair (Allen and Maizels 2011). Type 2 immunity is characterized by Th2 cells secreting IL-4, IL-5, IL-10

and IL-13 and host Th2 immunity has been proposed to have evolved mainly to control tissue damage in the host resulting from parasitic infections (e.g. worms; Allen and Sutherland 2014). Additionally, type 2 cytokines, including IL-10, are produced by regulatory T cells (T_{reg}) and effector $CD4^+$ or $CD8^+$ T cells in the lungs of humans and mice following infection with IAV or RSV (Sun et al. 2009, 2011; Palmer et al. 2010). Blockade of IL-10 signaling by using an IL-10R neutralizing antibody during sublethal IAV infection results in increased morbidity and mortality in mice. Similarly, IL-10-deficient mice are more susceptible to Th17-mediated immunopathology following a challenge with a lethal dose of IAV (McKinstry et al. 2009). However, the role of IL-10 during RSV infection is less clear. Although some studies have demonstrated that IL-10 reduces immunopathology by decreasing T cell responses in mice, other groups have observed that the overexpression of IL-10 augments pathology (Loebbermann et al. 2012; Sun et al. 2013). TGF-β is another important cytokine whose role in resistance versus tolerance has been evaluated in a mouse model of acute IAV infection. TGF-β is expressed in an inactive form by most cell types and needs to be cleaved to become activated (Khalil 1999). Interestingly, IAV neuraminidase can also cleave TGF-β into its active form during infection (Schultz-Cherry and Hinshaw 1996). Whereas some groups have demonstrated that an in vivo blockade of TGF-β increases the mortality of mice infected with the 2009 H1N1 or H5N1 IAV without affecting viral titres, others have observed that the overexpression of the protein by the injection of plasmid DNA reduces inflammation but impairs viral clearance of a H3N1 virus (Williams et al. 2005; Carlson et al. 2010). Collectively, these studies highlight the importance of a balance between host resistance and tolerance mechanisms in a pathogen-specific manner.

(4) Efferocytosis: Considering the high turnover of cells in our body under physiological conditions (~ one million cells die/second), the removal of this cumbersome number of dying cells is essential for host survival. Recent studies have identified efferocytosis (from the Latin "to bury") as a critical mechanism for the disposal of cell corpses, a mechanism that differs from classical phagocytosis (Ravichandran 2010). Interestingly, this disposal is mandatory in both host resistance and tolerance to infection. For instance, during Mtb infection, efferocytosis is a crucial promoter of macrophage bactericidal activity following the engulfment of Mtb-infected apoptotic cells (Martin et al. 2012). We have also recently demonstrated that efferocytosis by dendritic cells is required for cross-presentation to enhance adaptive immunity during Mtb infection (Tzelepis et al. 2015). TGF-β, together with IL-10 and prostaglandins, have furthermore been shown to be produced by dendritic cells following the efferocytosis of apoptotic cells in order to decrease lung inflammation (Voll et al. 1997; Fadok et al. 1998; Huynh et al. 2002). During IAV infection, alveolar macrophages (aMφ) are critical for the clearance of apoptotic bodies during the resolution phase of infection and thereby contribute importantly to the resolution of inflammation (Kosmider et al. 2012; Nelson et al. 2014). Similarly, the depletion of aMφ during *Streptococcus pneumoniae* infection is associated with a poor outcome, because of impaired apoptotic cell clearance (Knapp et al. 2003). The removal of these apoptotic bodies by aMφ has been shown to limit the release of cellular content that may further enhance the inflammation. This anti-inflammatory effect is mediated by the activation of the peroxisome proliferator-activated receptor γ (PPARγ) following the interaction of apoptotic cells with aMφ. It consequently contributes to the AAMφ macrophage phenotype to foster wound healing and the resolution of inflammation (Sica and Mantovani 2012; Mantovani et al. 2013; Novak and Koh 2013; von Knethen et al. 2013).

(5) CD200 signaling pathway: Another mechanism promoting tolerance in the lungs is mediated by CD200R, which is expressed by aMφ and dampens their inflammatory state following the interaction with CD200 expressed by epithelial cells. Studies in CD200-null or $CD200R^{-/-}$ mice have demonstrated that the absence of this signaling pathway leads to the delayed resolution of inflammation and subsequently enhances host morbidity and mortality after IAV infection. The absence of CD200R-CD200 signaling has also been associated with the enhanced influx of both $CD4^+$ and $CD8^+$ T cells in the lungs, further augmenting lung immunopathology (Snelgrove et al. 2008; Rygiel et al. 2009). Whether this interesting lung tolerance strategy is relevant to other infections remains to be determined.

(6) Innate lymphoid cells (ILCs): ILCs represent a family of cells that are of lymphoid origin and that do not express traditional lineage markers (e.g., CD3, CD19, CD11b). Based on the expression of cell surface markers and transcription factors, they are divided into three major subsets (ILC1-3), each with unique functions (Saenz et al. 2010; Spits and Di Santo 2011). During IAV infection, epithelial cells produce IL-33 to induce the secretion of amphiregulin by ILC2 to promote tissue repair mechanisms. Although the depletion of ILC2 does not impair host resistance to IAV, it significantly affects host tolerance as determined by the loss of airway epithelial integrity, decreased lung function, and impaired restoration of airway homeostasis and repair (Monticelli et al. 2011; Zaiss et al. 2015). In addition, a recent study demonstrated that multiple pathogenic strains of RSV induce

the production of IL-13 (downstream of IL-33) by ILC2 in mice (Stier et al. 2016). Conversely, rhinovirus-infected epithelial cells have been shown to produce IL-33 to trigger the production of type 2 cytokines by ILC2, which subsequently promotes airway inflammation and exacerbates asthma (Jackson et al. 2014), suggesting a potentially dichotomous role for ILC2 in immunity to acute viral infections.

Although host tolerance is essential during primary infection, it may increase susceptibility to other pathogens. For example, the induction of a tolerant state in the lungs following IAV infection elevates vulnerability to subsequent bacterial infections (Didierlaurent et al. 2008). IAV infection has been shown to desensitize aMφ, rendering them irresponsive to subsequent TLR stimulation by inhibiting the nuclear translocation of NF-κB-p65 (Didierlaurent et al. 2008). This impaired TLR signaling allows invading bacteria to remain undetected by the innate immune response, promoting pathogenicity. Moreover, the induction of pulmonary tolerance through the CD200-CD200R axis has also been associated with increased susceptibility to secondary bacterial infections (Goulding et al. 2011). Similarly, infection with rhinovirus predisposes mice for subsequent infection with the bacterium *Haemophilus influenzae* by desensitizing aMφ and bronchial epithelial cells to TLR stimuli (Unger et al. 2012). Furthermore, mice stimulated intranasally with the TLR3 agonist poly I:C also exhibit more severe prognosis to secondary infection (Tian et al. 2012). Interestingly, in the case of IAV infection, this susceptibility appears to be mediated by type I IFN (Tian et al. 2012). Although the anti-viral role of type I IFN is well defined, its role in promoting secondary bacterial infections is less clear. However, the increase in host susceptibility to primary bacterial infections including *Francisella tularensis* (Freudenberg et al. 2002), *Listeria monocytogenes* (Fehr et al. 1997) and Mtb (Manca et al. 2005) via type I IFN induction is well documented, signifying a permissive role of type I IFN in secondary bacterial infection. We have previously reviewed this concept (Divangahi et al. 2015).

Inefficiency of host tolerance mechanisms in vital organs is catastrophic and often leads to mortality. The consequences of the replication of the pathogen and a robust immune response in the lungs are severe epithelial loss, increased airway resistance, diminished gas exchange and ultimately, respiratory failure. Highly pathogenic strains of IAV (e.g., 1918 Spanish H1N1 or H5N1), severe acute respiratory syndrome (SARS), or hantavirus infections can induce considerable inflammation in the lungs resulting in death (de Jong et al. 2006; Macneil et al. 2011; Gralinski and Baric 2015). The sequential events and factors contributing to such exacerbated immune responses and the breakdown of host tolerance processes are still not well understood. However, both host and pathogen factors have been shown to contribute to this effect. Indeed, pathogen-intrinsic characteristics, such as the expression of virulence factors, replication rate and tissue tropism, markedly affect the host response. Additionally, the host itself can express genes that will either favor resistance and survival to infection or predispose it to severe immunopathology (Keynan et al. 2013; Arcanjo et al. 2014; Charbonnel et al. 2014). For instance, IL-17A, IL-17F and TNF-α are rapidly secreted following IAV infection and animals deficient in these cytokines show reduced morbidity compared with wild-type animals (Szretter et al. 2007; Crowe et al. 2009). Interestingly, others have observed that TNF-α deficiency during IAV infection leads to increased immunopathology characterized by elevated cellular infiltration and cytokine production in the airways. Thus, depending on the phase of infection, TNF-α may play a dual role by also acting as a negative regulator of inflammatory responses to control immunopathology (Damjanovic et al. 2011). A delay in type I IFN production during SARS infection promotes the accumulation of inflammatory monocytes-macrophages in the lungs, which in turn leads to elevated cytokine and chemokine levels (cytokine storm), increased vascular leakage and decreased survival (Channappanavar et al. 2016). Thus, an understanding of the underlying cellular and molecular mechanisms involved in the induction and maintenance of host tolerance during pulmonary viral infection may provide new avenues for developing therapeutic approaches.

Host tolerance in chronic pulmonary infection

Although host tolerance aims to reduce or control tissue damage inflicted by acute infection, it may also be a powerful defense strategy for host survival in chronic infections. This adaptation strategy is a reflection of the co-evolutionary dynamics of host–pathogen interactions (Best et al. 2014). The best example of this unique interaction between a pathogen and human is perhaps Mtb, as humans are the only reservoir for this bacterium (Comas et al. 2010). Exposure to Mtb leads to two broad outcomes: elimination of the bacteria or its persistence. It has long been recognized that, even among close household contacts of TB cases and despite ample exposure, nearly half of the exposed individuals are negative for the tuberculin skin test (TST), which demonstrates that they are disease-free (Morrison et al. 2008). This finding indicates that some people are naturally resistant to Mtb, because of an efficient immune response (Cobat et al. 2009). However, if Mtb is not eliminated, the pathogen can persist in a quiescent or latent state and typically, the individual develops latent tuberculosis infection (LTBI). Although one third of the world population is infected with Mtb and approximately 1.5 million people die from this pathogen each year (Barry et al. 2009), only 5–15% of individuals with LTBI progress (over months to years) to active TB (Vynnycky

and Fine 1997). The specific mechanisms leading to this protection are still elusive in the vast majority of Mtb-infected people but several experimental studies in small mammals (mice, guinea pigs, rabbits) and non-human primates have significantly contributed to identifying the importance of early, probably innate, immune events during primary infection (Orme et al. 2015).

The importance of innate immune mechanisms is reflected by its remarkable existence and diversity at almost every level of the evolutionary tree of life. Macrophages are a particularly ancient cellular compartment of innate immunity and are the dominant cell type that Mtb infects. The route of entry of Mtb is mainly via the respiratory tract through the inhalation of bacteria and it passages to the lower respiratory tract, where it encounters aMφ. Mtb is internalized by macrophages via a vacuolar structure called a phagosome. Unlike organisms that are destroyed when the phagosome fuses with the lysosome, Mtb actively blocks phagosomal maturation, ensuring its survival in the phagocytic compartment (Podinovskaia et al. 2013). Next, through an ESX-1 mediated process, Mtb disrupts the phagosomal membrane and translocates into the cytosol (Houben et al. 2012). The advantages for the bacterium being delivered into the cytosol are a matter of ongoing investigation but one possibility is that the activation of the cytosolic surveillance pathway results in the induction of type I IFN, which is beneficial for Mtb (Pandey et al. 2009; Manzanillo et al. 2012). Although type I IFN is a major component of antiviral host defense mechanisms (Coulombe et al. 2014) and most viruses contain genes to block the type I IFN pathway, Mtb expresses genes (Stanley et al. 2007) to activate the type I IFN pathway to promote bacterial growth (Manca et al. 2001; Mayer-Barber et al. 2014). Importantly, a type I IFN gene signature has been directly linked to active human TB (Berry et al. 2010). Thus, Mtb has evolved into a parasite of the intracellular milieu of macrophages, where it not only survives but replicates in a naturally hostile environment. This allows Mtb access to the lung interstitium to initiate granuloma formation, which is the early stage of chronic infection. However, how Mtb is translocated from the airways into the parenchyma for the progression of infection is unknown. Do Mtb-infected macrophages migrate through pneumocytes? Or alternatively, do free bacteria directly infect pneumocytes and reach the lung interstitial tissue where they are phagocytosed by interstitial macrophages? As the success of Mtb in establishing chronic infection is dictated by the initial actions of pulmonary macrophages, early inhibition of macrophage activation and eventually cell death are critical for Mtb survival and replication. Experimental studies of a variety of pathogens have shown that the fate of pulmonary macrophages (i.e., the type of cell death) is critical not only for the innate response to infection (Divangahi et al. 2009; Singh et al. 2012) but also for the ensuing adaptive immune response to Mtb infection (Schaible et al. 2003; Behar et al. 2010; Divangahi et al. 2010, 2015; Coulombe et al. 2014; Tzelepis et al. 2015).

Once the primary infection is established, inflammatory monocytes transport Mtb to pulmonary lymph nodes and transfer Mtb antigens to classic dendritic cells for T cell priming (Samstein et al. 2013). T cell responses are essential in immunity to Mtb infection by restricting bacterial growth. Conversely, through various mechanisms, Mtb actively delays initial T cell priming and their trafficking into the lung (Chackerian et al. 2002; Wolf et al. 2008). HIV infection is a clear risk factor for the progression from Mtb infection to disease, because of the significant reduction of $CD4^+$ T cells. However, for the purposes of vaccination, whether increased T cell responses above the population norm provide better protection is unclear. Indeed, recent studies in the experimental murine model of TB have shown that unleashing $CD4^+$ T cell responses in a PD1-dependent manner leads to reduced protection and enhanced mortality (Aubert et al. 2011; Barber et al. 2011). Thus, an understanding of the regulatory mechanisms involved in immunity to TB is fundamental for generating a strong host defense to hinder bacterial growth, while maintaining host tolerance.

One can hypothesize that, during Mtb infection, the initiation of granuloma formation represents the transition of host defense mechanisms from resistance to tolerance. Granulomas have long been thought of as a critical component of host protective immunity to Mtb infection (Davis et al. 2002). However, they have recently been shown also to be beneficial to pathogens (Kaplan et al. 2003; Hunter 2011; Davis and Ramakrishnan 2009; Cronan et al. 2016). For instance, Mtb requires complex granuloma formation at various stages of disease progression for a more efficient spread within individuals (Hunter 2011). The extracellular location of bacteria in chronic granulomas is associated with highly elevated replication rates (Kaplan et al. 2003). In contrast, immunocompromised individuals usually only display poorly formed granulomas and have lower extracellular bacterial burdens (Hunter 2011). Interestingly, a recent study demonstrated that immune responses are geographically segregated, with the center of the granuloma being pro-inflammatory, while the surrounding tissue is anti-inflammatory (Marakalala et al. 2016). In addition, Mtb can initiate a type I IFN response, which has been directly linked to the recruitment of a unique myeloid population ($CD11b^+F4/80^+Gr1^{int}$) to the nascent granuloma; this population is highly permissive for Mtb infection (Antonelli et al. 2010).

Similar to monocytes and macrophages, the protective role of T cells during Mtb infection has recently been scrutinized. Conventionally, the identification of immunodominant Mtb antigens for the generation of a repertoire of Mtb-specific T cells was thought to be the foundation for T cell-mediated protective immunity and, hence, an effective vaccine-based strategy against TB. However, despite inducing enhanced T-cell-mediated responses, one such vaccine has failed to

improve protection in a human trial (Tameris et al. 2013). After more than half a century of BCG vaccination, we still do not know the precise way in which BCG provides protection in children and to what extent this protection is mediated via $CD4^+$ T cells. An emerging hypothesis is that BCG protection is mainly mediated through innate immune pathways, as reviewed elsewhere (Blankley et al. 2014). In addition, the finding that Mtb genes involved in the production of immunodominant $CD4^+$ T cell antigens are hyper-conserved suggests that Mtb may paradoxically benefit from antigen-specific $CD4^+$ T cell activation in humans (Comas et al. 2010). This theory derives further indirect support from the HIV-TB syndemic: whereas HIV is clearly a risk factor for individual progression from Mtb infection to disease, HIV/AIDS is negatively associated with contagion (Corbett et al. 2006). Furthermore, the risk of active TB is enhanced during the early stage of HIV infection, when the number of $CD4^+$ T cells is still in the normal range (Sonnenberg et al. 2005). Together, these observations argue that Mtb depends on the elaboration of a T-cell-mediated immune response for the development of pathology that enables it to be transmitted to other humans.

Concluding remarks

Whereas the concept of host tolerance has been well established in plant biology, an appreciation of this phenomenon in the animal kingdom is just emerging. This delay is mainly attributable to the dominant conventional concept of host resistance to infectious diseases. The cellular and regulatory mechanisms of host tolerance appear to be pathogen-specific, which is mainly reflected by the mode of pathogen transmission. For instance, during an IAV pandemic (e.g., with the 1918 Spanish strain), the success of the influenza virus depends on rapid replication and early transmission. This kinetic of infection ultimately generates a dysregulated immune response, in terms of both the intensity and the duration, which leads to a breakdown of host tolerance. Although this massive immune response completely eliminates the pathogen, host survival will still be significantly compromised in the absence of tolerance. In sharp contrast to the influenza virus, Mtb survival depends on host tolerance. Death from tuberculosis was initially known as "consumption" as this chronic infection causes dramatic cachexia (wasting). Interestingly, a study examining *Mycobacterium marinum* infection in the fruit fly *Drosophila melanogaster* showed that the increased mortality is independent of bacterial load and is mediated by altered host metabolism and increased body wasting (Lazzaro and Galac 2006). This result indicates that, in the absence of tolerance, host resistance is not sufficient to control the infection. Therefore, when human resistance mechanisms fail to reduce the fitness of Mtb and to eliminate the bacteria during the early phase of infection, the host alters its defense strategy from antagonism to symbiosis, which leads to tolerance of the bacteria and chronic, if not lifelong, infection. However, unraveling the cellular and molecular mechanisms involved in the regulation of host tolerance is essential for a better understanding of the pathogenesis of any infectious disease.

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