Mini review

Microbial pathogenesis and type III interferons

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ABSTRACT

The innate immune system possesses a multitude of pathways to sense and respond to microbial pathogens. One such family are the interferons (IFNs), a family of cytokines that are involved in several cellular functions. Type I IFNs are appreciated to be important in several viral and bacterial diseases, while the recently identified type III IFNs (IFNL1, IFNL2, IFNL3, IFNL4) have been studied primarily in the context of viral infection. Viral and bacterial infections however are not mutually exclusive, and often the presence of a viral pathogen increases the pathogenesis of bacterial infection. The role of type III IFN in bacterial and viral-bacterial co-infections has just begun to be explored. In this mini review we discuss type III IFN signaling and its role in microbial pathogenesis with an emphasis on the work that has been conducted with bacterial pathogens.

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1. Introduction

The advent of the antibiotic-era promised to significantly reduce the incidence and negative outcomes associated with infectious disease; however pathogenic bacteria still play a significant role in our lives. Infectious diseases are one of the most common worldwide causes of death and are the leading cause of disease burden as assessed by disability-adjusted-life-years by the World Health Organization (WHO) [1]. The growing number of antimicrobial resistant bacteria is of increasing concern, prompting the WHO in 2014 to release a report on the global burden of antimicrobial resistance, with high levels of resistance present in common pathogens that cause health-care and community-acquired infections [2]. One way of potentially combating resistant organisms is to gain a better understanding of the innate immune host pathways involved in their clearance, with the aim of potentially modulating signaling activation to improve clearance and reduce host damage.

The interferons are a family of cytokines that perform a variety of immune and cellular functions. The type I interferon (IFN) family of cytokines consists of 13 IFNα subtypes, IFNβ, IFNε, and IFNω and the type II IFN family is represented by IFNγ. Initially identified as *IL29,IL28A* and *IL28B*, the type III IFN family (IFNλ), consisting of IFNL1 (IL-29), IFNL2 (IL-28A), IFNL3 (IL-28B) was discovered in

2003 by Sheppard and Kotenko [3,4]. More recently, the type III IFN family expanded when IFNL4 was identified in 2013 through genetic studies of patients infected with hepatitis C virus [5]. Originally thought to be a pseudogene, it became clear that a significant percentage of the human population has a functional *IFNL4* gene, while a single nucleotide polymorphism (SNP) in the majority of the population results in a frameshift mutation inhibiting IFNL4 production [6]. There is high sequence identity between the type III interferon family members, 96% between IL-28A and IL-28B, and approximately 81% with IL-29 and IL-28A/B [3,4]. Interestingly, the type III IFN family is more closely related to IL-10 as opposed to either type I or type II IFNs, which explains why they were initially named as being part of the interleukin family [7]. The genes of the IFN lambda family contain four introns, like IL-10, while the type I IFN genes do not contain any introns [8]. The type III IFNs have 12 and 17% amino acid similarity with IL-10 and type I IFN families respectively.

2. Type III IFN signaling

Type III IFNs are induced in response to a range of viral and bacterial stimuli, with almost complete overlap with the type I IFN pathway [9–11]. Type I and III IFN signaling has traditionally been associated with viral infection but it is now appreciated that bacteria and their products are also able to activate this pathway. Many bacterial pathogens, both intra- and extracellular are able to induce a type I IFN response via recognition of PAMPs and messengers such as DNA, RNA, peptidoglycan, LPS and cyclic diadenosine monophosphate (c-di-AMP) [12–14]. TLR2, 3, 4, 7, 8, 9,

NOD, RNA polymerase III and stimulator of interferon genes (STING) are among the many sensors involved in activating the I IFN response [14,15]. Similarly, diverse pathogens activate the type III IFN response, and it appears that the type I vs. type III balance in signaling is mediated by the cellular location of the receptor, as most receptors can activate both pathways [16]. Currently, the DNA sensor Ku708 is the only identified receptor capable of activating type III not type I IFN [17].

Type III IFNs signal through a receptor dimer consisting of IL-28R and IL-10RB. IL-28R responds exclusively to type III IFN, while IL-10RB is shared with IL-10 family members [4,18]. This raises interesting, and currently unaddressed questions of potential regulation of IL-10 signaling by type III IFN or visa versa. IFNλ signaling is thought to be inhibited by IL-10 but enhanced by IL-22, which also signals through IL-10RB [19,20]. It is unclear if IL-10 and IL-22 influence IFNλ signaling through receptor sequestration or through affects on interferon signaling pathways. Binding of IFNλ to the IL-28R-IL-10RB dimer induces JAK-STAT signaling (Fig. 1), similar to type I IFN signaling, resulting in expression of over 300 interferon responsive genes [21–23]. These genes have been integrated into a searchable database known as the Interferome (v 2.0 http://interferome.its.monash.edu.au). The information from this database has identified over two thousand interferon regulated genes (IRG) and can be used to identify a specific interferon gene signature associated with a particular disease state or species of microbial infection.

While the type I and type III pathways activate a very similar gene set, there are significant differences between the pathways. First and foremost, tissue expression of IFNAR and IL-28R differ significantly. While IFNAR is ubiquitously expressed, IL-28R expression is restricted to a subset of cell types, primarily epithelial cells and keratinocytes however some dendritic cell and neutrophil populations have also been reported to respond to type III IFN [22,24–27]. The specific localization of the IFNλ receptor may allow for a more tightly regulated immune response, such as the expression of signaling inhibitors like the suppressor of cytokine signaling (SOCS) proteins in resident cells such as the epithelium. At the same time, maintaining immune activation in IFNλ insensitive hematopoietic cell populations while type I IFN induces signaling suppression in all cells perhaps resulting in immune tolerance [28].

Type III IFN induction kinetics also differ from type I IFN [29]. Type I IFNs induce a more rapid and higher magnitude response compared to type III IFNs, while type III IFNs induce a more sustained response of gene induction [30–32]. Influenza induces a more robust type III IFN response from epithelial cells, and STAT activation by type III IFN is significantly more prolonged as compared with the response to type I IFN [33–35]. Type I IFN induction of downstream genes is dependent on interferon regulatory factor (IRF) dependent, interferon-responsive sequence element (IRSE) transcription factors. Antiviral signaling downstream of type III IFNs is partially dependent on NF-κB and MAPK signaling activation, which could explain why in human airway epithelial culture type I IFN signaling was the primary contributor to anti-viral signaling in response to RSV [30,36,37]. Recently, transcription factor Med23 was shown to selectively upregulate type III not type I IFN, while type III IFN was selectively downregulated by ZEB1 [38,39]. Therefore, while the type III IFN family is capable of activating the same genes as other IFN families, restricted receptor expression and dependence on other signaling pathways for optimal gene induction limit the influence of type III IFNs on immunity however, once activated the type III IFN family can have a more prolonged role in host defense.

3. Type III IFN in human disease

The role of type III IFN in human disease in not yet completely understood, however, initial studies have uncovered an association between mutations in IL-28B and the response to hepatitis C virus. Polymorphisms upstream of *IFNL3* can predict the response of chronically infected hepatitis C virus (HCV) patients to type I IFN therapy [40–42]. This polymorphism also correlates with natural clearance of the virus. An additional polymorphism in *IFNL3*, TT/ΔG, was found to be an even better predictor of HCV clearance, due to increased expression of *IFNL4* [43,44]. GlaxoSmithKline is currently developing IFNλ therapy based on these findings, with the hypothesis that these treatments will not only boost clearance of HCV, but will reduced negative side effects associated with PEG-
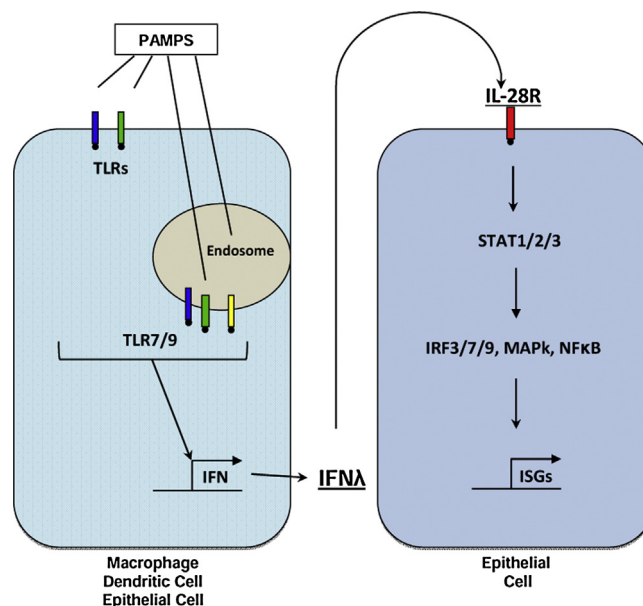

Fig. 1. Type III IFN signaling pathway.

IFN (type I IFN) therapies due to the limited locations of IFNL receptor expression.

Other diseases have been linked to excessive activation of type I IFN and have been termed "interferonopathies". The first to be identified was Aicardi–Goutières syndrome (AGS), an inflammatory disorder of the brain and skin, patients exhibit raised interferon levels and a type I IFN gene signature [45]. Other examples include SAVI (STING-associated vasculopathy with onset in infancy), global proteosome disorder, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) as well as spondyloenchondrodysplasia and systemic lupus erythematosus with complement deficiency have also been identified as interferonopathies [46–48]. IFN signaling has been linked to exacerbation of asthmatics, in which an inverse correlation between IFNL and severity of allergic asthma in humans has been reported [49,50]. These diseases have been associated with type I IFN, however because type I and type III IFN activate the same downstream genes the contribution of type III IFN to these diseases cannot be ruled out.

4. Role in viral infections

Much of the early work towards identifying the role of type III IFN in infectious disease has focused on viral infection. Interferon knockout mice and in vitro experimental systems have been developed to better understand the immune implications of type III IFN. Data generated utilizing these models and data suggesting a potential role for type III IFN in cancer and autoimmunity are reviewed in detail in a recent article by Lazear et al. [51], and therefore they will only be briefly summarized here.

The vast majority of research has focused on its contribution of type III IFN to anti-viral host defense. In mice, type III IFN is produced at significantly higher levels than type I IFNs in response to influenza virus, and the produced type III IFN is able to protect mice from severe influenza infection even in $Ifnar^{-/-}$ mice [33]. The presence of either a functional type I or type III IFN pathway is sufficient to mount a host defense response against influenza infection, while increased viral titer is observed in mice lacking both the type I and type III IFN receptors, as well as in $Stat1^{-/-}$ mice in which both type I and type III IFN pathways are inhibited [33,52,53]. Similarly, clearance of SARS-CoV was found to be dependent on STAT1, but not type I, II, or III IFN receptors, suggesting that these pathways can compensate for each other in their response to some viral pathogens. Host defense against other viruses in the murine system is more dependent on the type III IFN pathway. For example, herpes simplex virus (HSV) clearance requires activation of type III IFN and systemic elimination of murine norovirus requires IFN lambda [38,54]. Treatment with type III IFN is also progressing for the treatment of viral infections.

Phase 2b studies on patients with chronic hepatitis C showed improved viral suppression and fewer side effects with type III versus type 1 IFN therapy [55]. As of now it is unclear why the dependence on type III IFN differs between these viral infections, however it could be due to the type of cell involved in clearing these infections and their relative level of type III IFN receptor expression.

5. Role in bacterial infections

Type III IFN has also been implicated in anti-bacterial immune responses. The type III pathway was first shown to be activated by live *Salmonella enterica* Typhimurium or purified lipopolysaccharide (LPS) in human dendritic cells [56]. Induction of type III IFN was then correlated with *L. monocytogenes* clearance by Lebreton et al. in 2011 [57]. They demonstrated that the *Listeria* virulence factor LntA targets the chromatin repressor BAHD1 preventing its interaction with interferon stimulated genes (ISGs), and therefore increases interferon signaling. These studies were the first to indicate that bacteria could not only activate the type III IFN pathway, but that bacterial virulence factors modulate chromatin remodeling to affect this pathway. To date, only one study has directly tested the contribution of type III IFN to the clearance of bacterial pathogens [22]. In this study both *S. aureus* and *P. aeruginosa* were found to activate type III IFN signaling in the lung. Both organisms activated type III IFN to different degrees, but in either case loss of the type III IFN receptor improved bacterial clearance and reduced lung pathology during acute infection. The contribution of type III IFN to clearance of other bacterial pathogens has not been directly studied, however we can attempt to extend the results of studies aimed at the type I IFN pathway. These results are summarized below (see Table 1).

5.1. Salmonella enterica

S. Typhimurium has been shown to activate type III IFN production. *S.* Typhimurium activates a robust type III IFN response in phagocytic cells (dendritic cells) but not in intestinal epithelial cells [56,58]. The activation of type III IFN signaling by *S.* Typhimurium can occur with both live and heat-killed organism, as well as via its purified LPS, akin to the type I IFN response [59]. The in vitro response of human cells to *S.* Typhimurium occurs rapidly within 2–4 h after infection and is maintained over a 24 h period. This transcription still occurs even in the presence of a protein synthesis inhibitor. To gain a better understanding of the pathway Pietila et al. [56] showed that type III IFN production was inhibited with inhibitors to p38 kinase, PI3K and NF-κB, but not ERK or JNK kinase. Interferon stimulated genes such as *CXCL10* were also inhibited. Consistent with LPS inducing the activation of

Table 1
Summary of data on bacterial pathogens known to activate type III IFNs.

Pathogen.	Receptor	Cell/tissue types induced in	Role in pathogenesis/clinical disease	References
Borrelia burgdorferi	TLR7	PBMC	Induction correlative to infectivity	64, 65
Enterococcus faecalis	n/a	Epithelial	n/a	58
Lactococcus lactis	n/a	BMDC	n/a	70
Listeria monocytogenes	MAVS	Epithelial, placenta	n/a	16, 57, 58
Mycobacterium tuberculosis	n/a	Epithelial	Higher induction in active infection	58, 61
Pseudomonas aeruginosa	n/a	BMDC, epithelial, lung	Pneumonia, decrease in CF epithelium	22, 68
Staphylococcus aureus	n/a	BMDC, epithelial, lung	Pneumonia, superinfection colonization	22,58, 85
Staphylococcus epidermidis	n/a	Epithelial	n/a	58
Salmonella Typhimurium	n/a	moDC, Epithelial	n/a	56, 58

PBMC-peripheral blood mononuclear cells, BMDC-bone marrow derived dendritic cell, moDC-human monocyte derived dendritic cell, CF-cystic fibrosis, n/a-not analyzed/unknown.

type III IFN, inhibition of dynamin-dependent endocytosis abolishment secretion, presumably by interfering with the TRIF-TRAM signal. While it is known that type I IFN plays an inhibitory role in infection [60], a role is yet to be identified in *Salmonella* infection.

5.2. Listeria monocytogenes

Listeria monocytogenes was one of the original organisms studied in the context of bacterial activation of type I IFNs and remains heavily studied in this area and now more recently in the type III IFN field. Type III IFN induction by *L. monocytogenes* has so far been shown to occur in intestinal epithelial cells, hepatocytes and placental trophoblasts [57,58], with no induction observed in HEK or THP-1 cells [58]. Activation of type III IFN in intestinal epithelial cells occurs in multiple stages. An initial induction occurs as the bacteria are internalized then a later phase that corresponds to escape from the vacuole. Internalization of *L. monocytogenes* and hence type III IFN induction requires the expression of the invasion proteins LnlA and LnlB, while listeriolysin that mediates escape into the cytosol is also required for type III IFNs to be induced [58].

L. monocytogenes produces another secreted factor that directly effects type III IFN production. The LntA (*Listeria* nuclear targeted protein A) protein is able to target the protein BAHD1 in the cell nucleus [57]. BAHD1 is a chromatin repressor that is capable of repressing interferon stimulated genes (ISGs). Intestinal epithelial cells are able to activate type III IFN when stimulated with *L. monocytogenes* but not in the absence of LntA [57,58]. Under normal conditions, the targeting of BAHD1 by LntA facilitates production of type III IFNs. The role of LntA and type III IFN in infection is a perfect example of a pathogen fine tuning expression of a virulence factor. Inactivation of LntA leads to improved clearance in animal models, while constitutive expression of LntA that leads to higher type III production also leads to enhanced clearance.

The RIG-I like receptors (RLR) are involved in type III induction by *L. monocytogenes*. Signaling via the RLR adaptor protein mitochondrial antiviral signaling (MAVS) is sufficient for type III IFN induction. Specifically, MAVS present in the signaling organelles, peroxisomes, was sufficient to signal [16]. While the role of type III in infection with *L. monocytogenes* has not been tested in vivo, activation of type III IFN has been shown in a model of fetoplacental listeriosis as well as induction of interferon responsive genes [58].

5.3. Mycobacterium tuberculosis

The ability for *M. tuberculosis* to activate type III IFN has been observed clinically. Comparison of sputum from healthy, latent and actively infected patients showed significantly higher levels of type III IFN (IL-28A) in actively infected samples [61]. The levels of IL-28A also correlated well with the bacterial load present in the sputum. The ability of *M. tuberculosis* to induce type III IFN was further corroborated by observations that as patients initiated therapy, reduced bacterial loads led to reduced IL-28A levels. The signaling involved in type III IFN induction by *M. tuberculosis* has not yet been investigated other than the observation it can active type III IFN in A549 cells in vitro [58]. Hopefully a greater understanding of type III IFN signaling proves as useful as it has for type I IFN signaling. A type I IFN signature has been identified for *M. tuberculosis* that is detectable in both actively infected patients and those with latent infections [62], and presents itself as having excellent diagnostic potential.

5.4. Borrelia burgdorferi

The causative agent of Lyme disease, *Borrelia burgdorferi*, induces type III IFN production in a similar manner as type I IFN. Type I IFN is induced by nucleic acids (DNA or RNA) through TLR7/9 and TLR8 in monocytes [63]. Type III IFN has been shown to be induced by live organisms and purified RNA through TLR7 in human peripheral blood mononuclear cells [64]. The ability to induce type III IFN appears to correlate with clinical isolates. Clinical isolates typically induce a much more robust interferon (type I or III) response than isolates less frequently associated with infection [65]. The ability of *B. burgdorferi* to activate type III IFN appears to be dependent on the plasmid lp36. Strains lacking the plasmid have reduced adherence and uptake by phagocytes, this ultimately leads to a blunted type III IFN response. The physiological significance of the type III IFN pathway in *B. burgdorferi* pathogenesis is yet to be determined.

5.5. Staphylococcus aureus

S. aureus is able to differentially activate interferons through a variety of receptors and transcription factors [66,67]. While the precise receptors involved in the activation of type III IFN are not known, much has been learned through the use of IL-28R knockout mice. *S. aureus* is able to activate type III IFN in both myeloid and stromal cells when alive and when heat killed [22]. Prompt activation is observed in vivo in a model of acute pneumonia. Mice lacking IL-28R have significantly improved outcomes to infection with improved bacterial clearance from the airway and lung tissue, improved pulmonary pathology and reduced proinflammatory cytokine production compared to equally infected control mice. One cytokine reduced in this model is IL-1β, which when the IL1-R is antagonized in vivo, improved clearance of *S. aureus* is also observed. Type I IFN is known to influence the activation of PDCD4 that influences proinflammatory cytokine production. PDCD4 is regulated by miR-21. Cohen et al. [22] showed miR-21 to be increased after infection that concomitantly reduced PDCD4, attributing the reduced cytokine production observed in *Il28r*$^{-/-}$ mice to this result. Mice lacking PDCD4 also had improved outcomes to *S. aureus* infection. These data provide evidence for a host pathway that negatively contributes to bacterial pathogenesis.

5.6. Pseudomonas aeruginosa

The role of type III IFN in *P. aeruginosa* infection is similar to that described for *S. aureus*. *P. aeruginosa* is able to rapidly activate type III IFN production in dendritic cells, epithelial cells and in vivo before levels decline to baseline after 18 h of infection in the lung [22,68]. Induction of type III IFN was observed to be decreased in cystic fibrosis compared to control airway epithelial cells [68]. *Il28r*$^{-/-}$ mice when intranasally infected with *P. aeruginosa* are able to more effectively clear the infection from the airway and lung tissue, with the associated improvement in pulmonary pathology and reduction in proinflammatory cytokine production [22]. As observed with *S. aureus*, Cohen et al. [22] found miR-21 to be increased and PDCD4 to be decreased in the *Il28r*$^{-/-}$ infected mice compared to wild-type mice. An additional mechanism to explain the ability of type III IFN signaling to aid bacterial persistence is biofilm formation. In an in vitro cell culture model, respiratory syncytial virus (RSV) infection was observed to increase *P. aeruginosa* biofilm formation [69]. This biofilm formation was shown to be both type I and type III IFN dependent, with knockdown or antibody neutralization of the receptors reducing *P. aeruginosa* biofilm formation in the presence of RSV infection [69].

Several other bacterial species have been studied and shown to induce type III IFN (such *Lactococcus lactis, S. epidermidis* and *Enterococcus*) [58,70] however, this is the extent of what is known about their ability to activate this pathway.

6. Bacterial superinfection

The history of influenza suggests that secondary bacterial infection significantly contributes to the mortality associated with severe influenza infection [reviewed in detail [71,72]]. Originally bacterial co-infection was observed in lung tissue saved from victims of the 1918 influenza pandemic. Principle bacteria found in these lung samples were *S. pneumoniae*, *S. aureus*, and *H. influenzae* [73]. Morbidity and morbidity in subsequent influenza pandemics has also been correlated with the presence of a co-infecting bacterial pathogen. In 1957 and 1968 *S. aureus* emerged as the most common co-infecting pathogen and once again in 2009–2010 *S. aureus*, especially the USA300 strain, was associated with severe influenza associated pneumonia [74]. Further contributing to the emergence of *S. aureus*, vaccines have reduced the occurrence of *H. influenzae* type B and *S. pneumoniae* [75,76], therefore the rate of co-infection with these bacteria has dropped while the rates of *S. aureus* co-infection have increased, specifically multi-drug resistant MRSA strains.

Murine studies of influenza associated bacterial infection have also demonstrated that interferon signaling contributes to enhanced disease associated with these infections. Type II interferon acts on resident macrophages in the lung, suppressing expression of the surface protein MARCO, which is essential for phagocytosis of bacteria [77]. Type I interferon appears to influence the role of several immune functions in this model of superinfection. Type I IFN has been implicated in the development of *S. aureus* and *S. pneumoniae* superinfection [78,79]. Impairment of anti-bacterial host defence by type I interferon occurs through decreased CCL2 production and inhibition of the IL-17 antimicrobial pathway [80–82]. It is worth noting that the studies analysing the type I IFN pathway in bacterial superinfection did not examine the role of type III IFNs, and it is quite possible that due the parallel nature of these pathways the type III IFNs also contribute to the enhanced disease phenotype.

In addition to retrospective studies of pandemic influenza infections, evidence is emerging of an association between the live attenuated influenza vaccine and bacterial nasal carriage. Live attenuated influenza vaccine was found to enhance the carriage levels of *S. pneumoniae* and *S. aureus* in the nasopharynx [83]. Likewise in humans, vaccine administration was found to alter the nasal microbiome with an increase in IFN gene signatures and elevated carriage of *Staphylococcal* species [84]. In this study, interferon induction was responsible for the increased susceptibility to bacterial infection in a murine model, as induction of IFN signaling with poly(I:C) resulted in increased bacterial carriage [84].

Influenza infection has also been shown to increase and restructure the mouse nasal microbiome [85]. While in many cases the overall diversity remained unchanged increases in commensal staphylococci were observed. This change in microbiota was shown to be type III IFN and STAT1 dependent. Influenza infected mice were also more susceptible to *S. aureus* colonization and subsequent aspiration of organisms into the lung. This susceptibility was dependent upon type III IFN signaling. In a model of acute *S. aureus* lung infection post-influenza, mice previously infected with influenza had higher bacterial burdens in the lung that were reduced in the absence of type III IFN signaling [85]. Therefore the type III IFN pathway promotes both colonization of the airway and subsequent infection of the lower airway.

7. Conclusions

Although only recently discovered compared to the rest of the interferon family, type III IFNs have already shown to play roles in viral and bacterial infections. Type III IFN therapy is undergoing clinical trials with hepatitis C infection and polymorphisms in human in IFNL3 can predict improved outcomes to therapy. Type III IFN induces a similar repertoire of genes as type I IFN over a prolonged period of time. Several studies have identified that bacterial pathogens can activate the type III IFNs. Clinical data and the use of knockout mice have identified several pathogens that appear to flourish when type III IFN is induced. These data indicate type III IFN signaling as a novel pathway for potential host immunomodulation in an era where antibiotic resistance is of increasing concern and over exuberant host responses contribute to morbidity and mortality.

Acknowledgements

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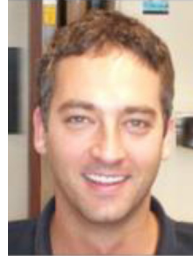
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