# Type I Interferons in Immune Defense Against Streptococci

**Pavel Kovarik, Virginia Castiglia, and Marton Janos**

## Type I Interferons in Bacterial Infections

The function of type I interferons (IFNs) in viral infections is well established and can be almost uniformly described as protective. In contrast, their role in the context of bacterial infections is much less clear, as both beneficial and detrimental effects of type I IFN signaling have been reported in animal models [1, 2]. Examples where type I IFNs confer a protective role can be found in cases of infection with *Salmonella typhimurium*, Group B Streptococcus (GBS), *Legionella pneumophila*, and *Streptococcus pneumoniae* [3–6]. The molecular mechanisms underlying type I IFN function in the context of these infections range from the induction of cytokines and iNOS, to the enhanced differentiation of inflammatory macrophages, and may also include more complex processes, which orchestrate innate and adaptive immune responses. On the other hand, in cases of infection with *Listeria monocytogenes* and *Francisella tularensis*, type I IFNs exert unfavorable functions [7–11]. Various mechanisms can explain these harmful effects, such as type I IFN-mediated apoptosis of infected lymphocytes and macrophages, IFN-dependent reduction of IL-17 production by γδT cells, or diminished neutrophil activity. In summary, it is currently not possible to identify the denominator of either beneficial or detrimental effects of type I IFNs. Given the profound effects of these immunomodulatory cytokines on the outcome of bacterial infections, elucidating their incompletely understood induction by bacteria is of immense importance [12]. In the following, we will review the current understanding of the role of type I IFNs, as well as of the mechanisms of their induction in host defense against *Streptococcus pyogenes* (Group A Streptococcus, GAS), *Streptococcus agalactiae* (GBS), and *S. pneumoniae*.

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These streptococcal species are major human pathogens which, despite a long history of intense research, continue to pose a serious health threat worldwide. In this context, new therapies employing modulation of cytokine activities are attractive yet underexplored strategies.

## Group A Streptococcus (*S. pyogenes*)

### *Pathogenicity*

GAS, also called *S. pyogenes*, is a leading Gram-positive human pathogen. GAS causes a broad range of mostly self-limiting diseases including pharyngitis (strep throat), scarlet fever or impetigo [13, 14]. It may however establish invasive and life-threatening infections, such as necrotizing fasciitis and toxic shock, which result in mortality rates of more than 30 % [13]. GAS accounts for over 700 million mild and more than 650,000 severe invasive infections worldwide annually [15]. GAS and *S. pneumoniae* are the most frequently found coinfecting bacteria in specimens of the 1918 influenza pandemic and in patients of the recent H1N1 influenza outbreak [16, 17]. Analysis of patient samples and animal studies reveal that the exceptionally wide range of GAS-caused diseases along with the transition from contained to invasive infections is determined by the virulence factor armament of a particular bacterial strain and by the genetic inventory of the host immune system [13, 18–20]. The underlying host–pathogen interactions are not well understood. Virulence factors include T cell-activating superantigens, surface-localized proteins such as the serotype-determining M protein interfering with the complement system and phagocytosis, the internalization-inhibiting hyaluronic acid capsule, secreted proteases with cytokine/chemokine-inactivating properties, secreted DNases that help bacterial dissemination, and the cytolysins SLO and SLS [19, 21–23]. Horizontal bacteriophage-mediated genetic transfer and the counteracting CRISPR system contribute to the virulence diversity observed between GAS strains [24–26]. On the host side, animal studies demonstrated that innate immune cells, most notably macrophages, dendritic cells, and neutrophils, play an essential role in successful defense during subcutaneous infection, a model of invasive GAS infection [27–29]. In models of upper respiratory tract infections, mucosal Th17 cells have been found to exert protective effects although the specific effector function of these cells in GAS infections remain to be identified [30, 31]. IL-17-mediated activation of antibacterial innate immune mechanisms could be involved in the Th17-dependent defense. Interestingly, in mice the variability of individual innate immune responses contributes to differences in susceptibility to GAS infections more than the variability in T cell-mediated responses [32].

Despite the fact that GAS is a human-specific pathogen, and mice are resistant against GAS outside of laboratory conditions [33, 34], animal infection models are invaluable for understanding GAS diseases and improvements of current therapies. Consistently, much of what is known about host–pathogen interactions in GAS

infections has been established from studies using gene-targeted mice. In future studies, the use of humanized mice [35] will be helpful for functional and mechanistic assessment of GAS virulence factors that target human but not murine defense systems.

## *Type I IFN Induction*

GAS activates type I IFN production by both human and mouse innate immune cells [4, 36–38]. In addition, GAS infection of primary human macrophages triggers an IFN signaling signature resulting, among others, in the activation of the transcription factor STAT1 [37]. This signaling signature is prevented by antibodies neutralizing IFN-α and IFN-β; however, the precise nature of type I IFNs induced by GAS in human cells remains unclear. In mice, primary bone marrow-derived macrophages (BMDMs) and conventional dendritic cells (cDCs), but not plasmacytoid dendritic cells (pDCs), were shown to produce IFN-β upon GAS infection [36, 38]. In fact, GAS-derived DNA triggers IFN-β in macrophages, whereas GAS RNA stimulates IFN-β in cDCs [38] (Table 1). Generally, IFN-β is the primary type I IFN

**Table 1** Ligands, host cell signaling proteins, and cell types inducing type I IFNs in streptococcal infections

| Pathogen | Ligand | Signaling proteins | Host cells | References |
|---|---|---|---|---|
| GAS | DNA<br>RNA<br>Live bacteria<br>Live bacteria | MyD88, STING, TBK1, IRF3<br>MyD88, IRF5<br>TLR7, MyD88, IRF1<br>STAT1, IRF1, MxA | BMDMs (mice)<br>cDCs (mice)<br>cDCs (mice)<br>Human primary macrophages | [36, 38]<br>[36, 38]<br>[4]<br>[37] |
| GBS | DNA<br>RNA | TBK1, IRF3<br>TLR7, MyD88 | BMDMs (mice)<br>Peritoneal macrophages (mice)<br>cDCs (mice) | [75]<br>[74]<br>[4] |
| *S. pneumoniae* | DNA | DAI, TBK1, STING, IRF3 | Nasal epithelial cells, epithelial cell of the respiratory tract cDCs (mice)<br>Nasal lymphoid associated tissues (mice)<br>Alveolar macrophages (humans, mice),<br>BMDMs (mice) | [6, 55]<br>[91]<br>[92] |

*IFN* interferon, *MyD88* myeloid differentiation primary-response protein 88, *TBK1* TANK-binding kinase, *STING* stimulator of IFN genes, *IRF* IFN regulatory factor, *STAT1* signal inducer and activator of transcription 1, *TLR7* toll-like receptor 7, *DAI* DNA-dependent activator of IRFs, *BMDMs* bone marrow-derived macrophages, *cDCs* conventional dendritic cells

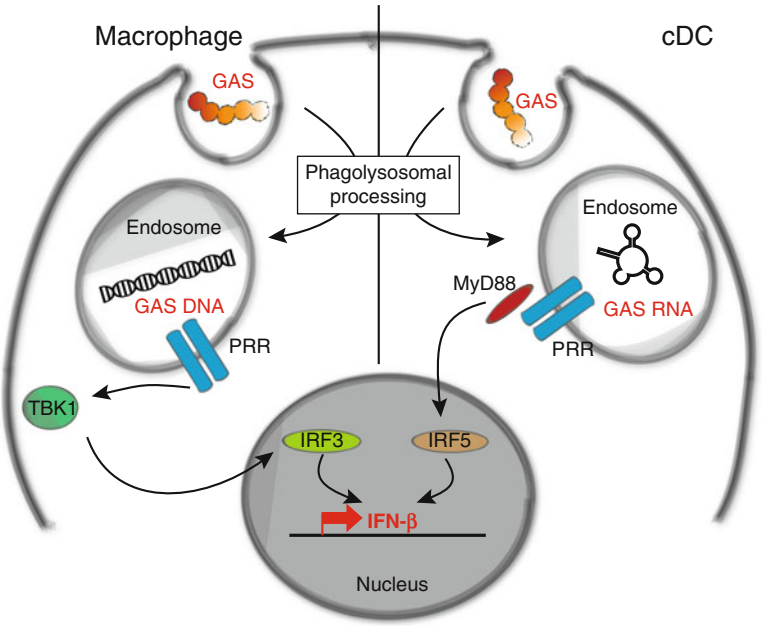


**Fig. 1** Type IFN signaling and induction by GAS. GAS-derived DNA induces IFN-β in macrophages in a TBK1- and IRF3-dependent way. GAS-derived RNA induces IFN-β in cDCs via MyD88 and IRF5. Both pathways require functional phagocytosis and endosomal signaling

produced upon infection—it up-regulates the transcription factor IRF7 which then triggers IFN-α genes [39].

GAS-induced IFN-β activates the transcription factor STAT1 and STAT1 target genes in an IFNAR (type I IFN receptor)-dependent manner, confirming and clarifying a functional involvement of IFN signaling downstream of type I IFN production [36]. In contrast, the mechanism of type I IFN induction by GAS is incompletely understood (Fig. 1). Most importantly, the pattern recognition receptors (PRRs) triggering the IFN-β gene are not known [38]. In general, the identity of PRRs able to sense GAS remains one of the most challenging questions. The sole involvement of TLR2, the PRR recognizing cell wall components of Gram-positive bacteria, as well as of TLR1, TLR4, and TLR6 have been excluded [36, 38, 40]. Similarly, nucleic acid-recognizing TLR3, TLR7, and TLR9 are dispensable for production of inflammatory cytokines and type I IFNs by GAS-infected innate immune cells [36, 38, 40]. Further, type I IFNs are induced independently of the cytosolic PRRs NOD1 and NOD2 [38], which were shown to be required for IFN-β stimulation in several viral and bacterial infection models [41, 42]. Attempts at identifying the proximal GAS sensor have been performed employing cells derived from mice deficient in multiple TLRs. TLR2/TLR4 and TLR2/TLR6 double-deficient BMDMs and cDCs were not impaired in GAS recognition. It remains to be elucidated

whether and how the newly characterized TLR13 is involved in GAS recognition and type I IFN induction. TLR13 is activated by a conserved sequence within the 23S rRNA of both Gram-negative and -positive bacteria [43, 44]. TLR13 stimulation causes production of inflammatory cytokines including TNF, IL-6, and IL-1β, but its role in type I IFN induction has not been clarified yet. Similarly, the role of TLR13 in host defense against bacterial pathogens remains to be investigated despite the ability of this PRR to recognize RNA of important pathogens such as *S. aureus* or GAS [43, 45]. The fact that TLR13 is expressed in mice but not humans raises the question whether humans possess an alternative route of bacterial RNA recognition. Yet another receptor that could potentially play a role in type I IFN induction by GAS is the recently characterized cyclic GMP-AMP synthase (cGAS) which acts as a cytosolic DNA sensor [46, 47]. cGAS is a danger recognition receptor which upon binding to DNA synthesizes the second messenger cyclic GMP-AMP (cGAMP). cGAMP binds and activates the ER protein STING to trigger IRF3 and IFN-β gene expression [48, 49]. While cGAS is involved in cellular defense against viruses [50–53], a role of cGAS in bacterial infections and/or in induction of type I IFNs by bacteria has not been demonstrated yet.

Signaling events downstream of the type I IFN-inducing GAS-specific PRRs are better understood (Fig. 1 and Table 1). Activation of *Ifnb* gene expression by GAS-derived DNA in macrophages is dependent on the TBK1 kinase and the transcription factor IRF3 [38]. In contrast, the IFN-β-inducing pathway triggered by GAS RNA in cDCs requires the adaptor MyD88 as well as the transcription factor IRF5, but not IRF3 [38]. Uptake of GAS is needed for triggering IFN-β production suggesting that phagolysosomal processing of internalized GAS liberates the bacterial IFN-β inducers. Whether both BMDMs and cDCs are involved in IFN-β production in vivo and whether these cell types play a redundant or distinct roles have yet to be examined.

## *Type I IFN Functions*

Mice lacking the type I IFN receptor IFNAR1 are more susceptible to subcutaneous GAS infection [38], a standard model of severe invasive cellulitis [20]. The mortality rate of GAS-infected IFNAR1-deficient mice is 70 % whereas it is only 25 % in WT mice. IFNAR1 knockouts were shown to exhibit increased recruitment of neutrophils to the site of infection but the molecular and cellular basis of the beneficial effects of type I IFNs in GAS infection remain to be elucidated. The high neutrophil number observed in mice lacking type I IFN signaling is consistent with previous observations demonstrating inhibitory effects of type I IFNs on macrophage production of the chemokines CXCL1, CXCL2, and CCL2 during *S. pneumoniae* infections [54, 55]. These chemokines play a key role in attracting neutrophils to the site of infection. It is at present unclear how the increased neutrophil recruitment in GAS-infected IFNAR knockout mice could evoke more detrimental disease.

One can speculate that an exaggerated inflammatory response elicited by recruited neutrophils causes severe tissue damage, thereby allowing better dissemination of the pathogen. Such scenario is conceivable as GAS expresses several DNases that help liberate it from neutrophil extracellular traps (NETs) [56, 57]. Consistently, the DNase *Sda*1 is a potent virulence factor which promotes GAS to acquire an invasive infection phenotype [58]. GAS exhibits a profound propensity to induce NETs, structures that contain large amounts of inflammation-promoting material such as neutrophil DNA, histones, and other chromatin-associated proteins [59, 60]. Interestingly, TLR9, a PRR able to sense self DNA [61], might be involved in sensing GAS-induced NETs as it is beneficial in an intraperitoneal model of GAS infection [62]. This indirect role of TLR9 in GAS infections is supported by the lack of effect of TLR9 knockout on direct GAS recognition by BMDMs and cDCs [4, 38, 40]. Thus, the enhanced neutrophil recruitment in IFNAR1-deficient mice might result in more intense, hence lethal inflammation. Effects of type I IFNs on other immune reactions such as recruitment of macrophages by GAS-induced TNF [63], or IL-1β production by the GAS-activated NLRP3 inflammasome [64], should be addressed in future studies to reveal the precise role of type I IFN signaling.

## Group B Streptococcus (*S. agalactiae*)

### *Pathogenicity*

GBS, also called *S. agalactiae*, is a Gram-positive human pathogen and leading infectious agent in neonatal sepsis worldwide [65]. Neonatal sepsis causes over two million deaths annually, with decreasing incidence largely due to improved prophylactic measures [66]. In early onset neonatal disease (within 6 days after birth), GBS is transmitted vertically from mothers vaginally colonized by the pathogen. In late onset disease (7–89 days after birth), GBS infection is usually a consequence of horizontal transfer in communities. GBS is also a significant cause of maternal morbidity (bacteremia, endometritis) [67]. GBS virulence factors include the polysaccharide capsule, membrane damaging exotoxins, and adherence molecules which enable evasion of the immune system and colonization of the host [68]. Innate immune system-derived TNF, IL-1β, and nitric oxide are key defense factors in host protection [69–71]. The vulnerability of neonates to GBS results in part from underdeveloped adaptive immunity but more importantly from deficiencies in innate immunity, including limited capacity of neutrophil production and increased risk of bone marrow exhaustion [67, 72]. The neonate immune insufficiency allows colonization and infection by GBS resulting mostly in meningitis or pneumonia. Prophylactic vaccination and immunomodulation appear the most promising approaches to eradicate GBS disease [67, 73].

## *Type I IFN Induction and Function*

Type I IFN signaling has a protective function in GBS infections: mice deficient in either type I IFN receptor or IFN-β exhibit increased mortality in a neonatal infection model, both after intravenous or intraperitoneal GBS administration [74]. This lethal infection outcome is caused by uncontrolled bacteremia, suggesting that type I IFN signaling is required for launching a complete immune and antibacterial response. Both macrophages and cDCs, but not pDCs, were identified as the source of type I IFNs [4, 74, 75] (Table 1). A direct comparison of type I IFN amounts indicate that cDCs are the major producers in vitro [4] but the principle type I IFN-producing cell in vivo has yet to be confirmed. Type I IFN production is dependent on uptake and phagolysosomal processing of GBS [4, 75] (Fig. 2). In macrophages, GBS DNA was identified as type I IFN inducer that acts along the TBK1 and IRF3 axis [75] (Fig. 2 and Table 1). GBS DNA was proposed to escape phagosomes into the cytosol where it is detected by an unknown cytosolic DNA receptor, which is different from the double-stranded DNA sensor DAI [75, 76]. The inducer of type I IFNs in cDCs was shown to be GBS RNA, which was sensed in a MyD88-dependent manner in phagosomes of infected cells [4] (Fig. 2 and Table 1). The endosomal

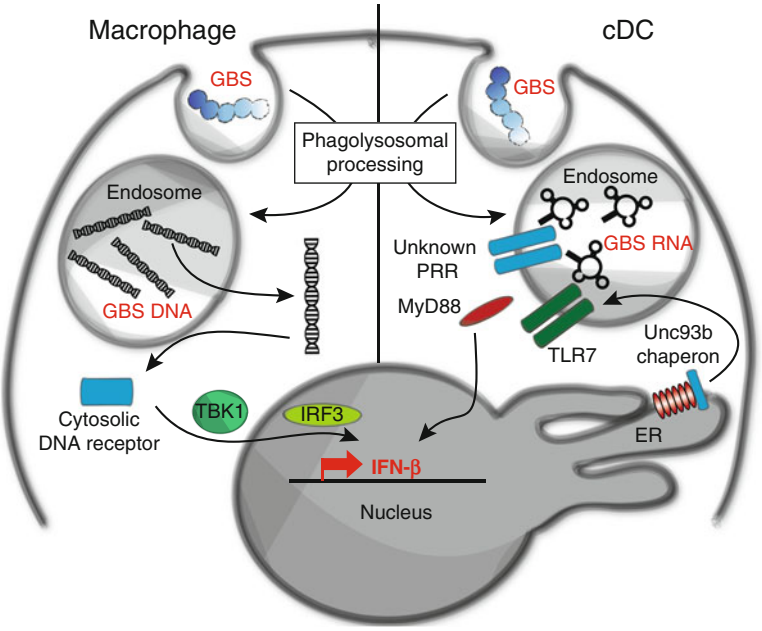


**Fig. 2** Type IFN signaling and induction by GBS. Induction of type I IFNs by GBS requires uptake and phagolysosomal processing of the pathogen. In macrophages, GBS-derived DNA triggers a cytosolic sensor which signals via TBK1 and IRF3 to induce IFN-β gene expression. In cDCs, GAS-derived RNA triggers the in Unc93b-dependent way the endosomal TLR7 which signals via MyD88 toward the IFN-β gene

TLR7 was found to be involved in sensing of GBS RNA. Interestingly, GBS RNA was reported to induce TNF in macrophages independently of TLR3, TLR7, and TLR8, but it required MyD88 [77]. This RNA recognition occurs in endosomal compartments as it is dependent on Unc93b, a chaperon fundamentally involved in trafficking of endosomal TLRs. Together, these studies indicate that recognition of GBS is cell type-specific, and that GBS RNA induces type I IFNs in cDCs but not in macrophages. The molecular basis of the different outcome of GBS RNA sensing in macrophages and cDCs remains to be deciphered. As is the case with GAS, the analysis of the recently identified sensors TLR13 and cGAS might be helpful in resolving the open questions.

## *Streptococcus pneumoniae*

### *Pathogenesis*

*S. pneumoniae* (pneumococcus) is a Gram-positive human pathogen regarded as the most frequent cause of community-acquired pneumonia [78, 79]. Pneumonia is the leading lethal infectious disease in developed countries [78, 79]. *S. pneumoniae* is one of the most prominent examples of a human-specific commensal microbe that frequently turns into an infectious agent. *S. pneumoniae* asymptomatically colonizes the nasopharynx in up to 60 % of all preschool children. Yet, *S. pneumoniae* represents the prime bacterial killer among children below the age of 5 with 1.2 million deaths annually worldwide. *S. pneumoniae* also poses a serious health risk to elderly people as a consequence of age-related immunosenescence. Of particular importance is a secondary *S. pneumoniae* infection of influenza patients, *S. pneumoniae* is one of the most frequent coinfecting pathogens in cases of influenza outbreaks [16, 17]. Both the genetic makeup of the pathogen and the condition of the host immune system play decisive roles in the transition from a commensal microbe into invasive pathogen. However, the exact parameters regulating this shift are not well understood. *S. pneumoniae* occurs in more than 90 serotypes which differ in their virulence. The serotypes are characterized by their polysaccharide capsule, which plays an important role in evasion of the immune system by inhibiting phagocytosis and complement binding [80]. An armament of other virulence factors including pneumolysin, hyaluronidase, neuraminidase, the serine protease PrtA, cholin-binding proteins, etc. contribute to various extents to pneumococcal diseases [81, 82]. The immune response against *S. pneumoniae* is initiated by its interactions with innate immune receptors. TLR2 is triggered by *S. pneumoniae* cell wall components (e.g., LTA), TLR4 can be activated by pneumolysin and TLR9 recognizes pneumococcal DNA [80, 83–86]. Furthermore, the cytosolic receptors NLRP3, NOD2, and AIM2 contribute to *S. pneumoniae*-induced inflammatory cytokine induction [80, 87–90].

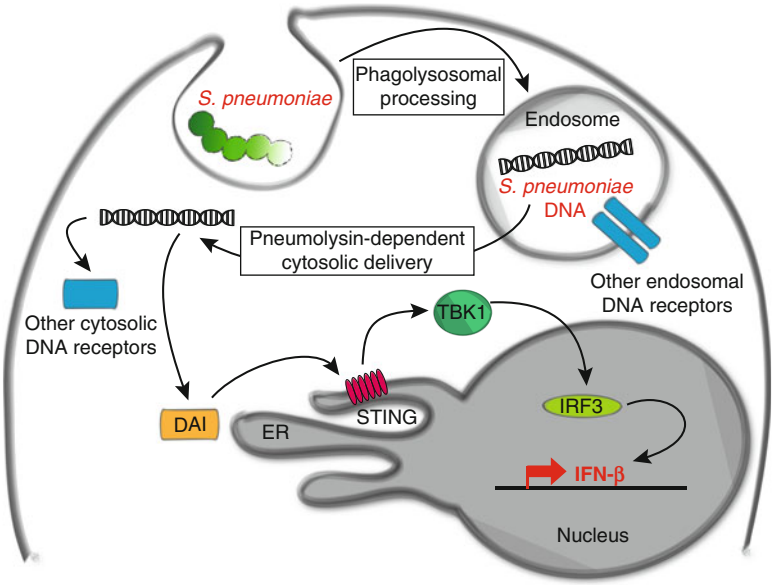


**Fig. 3** Type IFN signaling and induction by *S. pneumoniae*. The cytosolic DNA sensor DAI and other cytosolic DNA receptors are involved in the induction of the IFN-β by *S. pneumoniae*. Induction of IFN-β is dependent on STING, TBK1, and IRF3

## *Type I IFN Induction*

*S. pneumoniae* induces type I IFNs in nasal-associated lymphoid and epithelial tissues, as well as in human and mouse alveolar macrophages and mouse BMDMs [6, 55, 91, 92]. The type I IFN inducer is *S. pneumoniae* DNA, which is recognized upon internalization of the pathogen and/or pneumolysin-dependent cytosolic delivery [6] (Table 1). The double-stranded DNA sensor DAI participates in the detection of *S. pneumoniae* DNA as DAI-deficient cells produce less IFN-β than control cells [6] (Fig. 3). Similar to GAS and GBS, the signaling pathway downstream of the proximal sensor includes TBK1, STING and IRF3, and is possibly indirectly dependent on NOD2 [6, 55] (Fig. 3 and Table 1). Signal transduction toward the IFN-β gene proceeds in the absence of TLR4, MyD88, NOD2, and TRIF. Thus, the IFN-β-inducing properties of *S. pneumoniae*-derived DNA resemble those of GAS and GBS. It remains to be investigated whether *S. pneumoniae* RNA also possesses immunostimulatory capabilities as described for GAS and GBS.

### *Type I IFN Function*

Intravenous infection of type I IFN signaling-deficient mice with *S. pneumoniae* results in increased lethality [74]. Further evidence for a beneficial role of type I IFNs was provided by a study using a more natural route of infection, i.e., intranasal [6]. This particular study reported an impaired clearance of the pathogen from the site of infection, i.e., from the upper respiratory tract, in mice lacking IFNAR1, despite more potent recruitment of monocytes and dendritic cells. The exact mechanism of how type I IFNs elicit protective effects in pneumococcal infections remains to be characterized.

A distinct mode of pneumococcal infection is represented by coinfections with the influenza virus. These coinfections exhibit high morbidity and are life threatening in elderly patients. In animal models of coinfections, mice are first exposed to the influenza virus and a few days later *S. pneumoniae* is delivered intranasally. Both, *S. pneumoniae* and influenza virus are able to induce type I IFNs. Coinfections lead to synergistic induction of type I IFNs and, remarkably, this high level of type I IFN signaling is detrimental to the host [54, 55, 93]. The mechanisms of the harmful effects of type I IFNs on post-influenza bacterial infection include decreased production of the chemokines CCL2, CXCL1, and CXCL2, which act as chemoattractants for monocytes and neutrophils. As a result, less monocytes and neutrophils are recruited to infected tissues, although the precise nature of the most affected leukocytes is a matter of debate [54, 55]. Further studies are needed to clarify the molecular principles of coinfections. Such studies should particularly address the inability to tolerate tissue damage, which has recently been reported to play a critical role in influenza and *L. pneumophila* coinfections [94].

## Type I Interferons in Streptococcal Infections: Unifying Themes and Divergences

Although they share several common features, GAS, GBS, and *S. pneumoniae* cause diverse diseases in humans. They are Gram-positive encapsulated pathogens exhibiting a largely extracellular life cycle. Their key virulence factors are cytolysins, which possess cytotoxic properties and promote intracellular survival and/or phagolysosomal damage. These pathogens' ability to survive and grow within infected cells is very limited, although it has been reported that GAS is capable of acquiring a significant intracellular life span [13, 95]. Nonetheless, most internalized GAS are efficiently killed by the host phagolysosomal lytic and oxidative mechanisms. GAS that has escaped from the hostile phagosomal environment is rapidly recognized in the cytosol by the autophagy machinery and eradicated [96, 97]. The highly successful destruction of streptococci in the phagosomes results in the release of, among others, bacterial nucleic acids, which can act as type I IFN inducers. Consequently, endosomal recognition of GAS and GBS RNA induces

type I IFNs [4, 38]. In this context, the role of *S. pneumoniae* RNA has yet to be investigated. In contrast, all three streptococcal species have been reported to induce type I IFNs by their DNA, which is sensed by cytosolic DNA receptors [6, 38, 75]. Cytolysins are likely to be involved in the passage of DNA through the phagosomal membrane, but the precise mechanisms of streptococcal DNA delivery into the host cell cytosol remain unclear. The issue of type I IFN-inducing receptors also requires further investigation. Whereas TLR7 was identified as the RNA-sensing type I IFN inducer in response to GBS but not GAS [4, 38], the DNA sensor DAI was found to induce type I IFNs in response to *S. pneumoniae* but not GBS [6, 75]. Future studies, now also include newly identified receptors, will show whether there are common type I IFN-inducing pathways in streptococcal infections.

Type I IFNs exhibit protective functions in infections against all three streptococcal species discussed here, yet the precise nature of these beneficial functions are not well explained. As the three streptococcal species cause different diseases and display in part different tissue tropism, the mode of action of type I IFNs will most likely involve multiple possibly non-overlapping mechanisms. Elucidation of type I IFN functions is essential for our better understanding of the surprisingly detrimental effects of these cytokines during viral coinfections [54, 55, 93]. Further, it has yet to be investigated whether the negative impact of type I IFNs during coinfections is restricted to respiratory pathogens.

## Outlook

Despite significant advances in our understating of type I IFNs in bacterial infections, the key questions remain unresolved for most bacterial pathogens. These questions include the identity of type I IFN-inducing sensors and the specific effector functions of type I IFNs. Analyses of a broader range of innate immune receptors, ideally by employing unbiased approaches such as mass spectroscopy or genetic screens, will give us a more comprehensive picture of type I IFN induction. To elucidate the effector functions of type I IFNs, better infection models are needed. These will have to include animals allowing cell type-specific deletion of IFNAR1 [98], analysis of animals lacking different type I IFNs (particularly IFN-β), and in vivo and intravital imaging techniques. A so far unexplored aspect in streptococcal infections is the timing of type I IFN signaling. In the view of recent findings describing an unexpected harmful function of type I IFNs during persistent viral infections [99, 100], time-resolved analysis of type I IFN signaling in streptococcal infections and viral coinfections will need to be conducted in future studies. Another major challenge is the evaluation of the relevance of animal studies for the understanding of streptococcal diseases in humans. Clearly, the use of gene-targeted mice will remain fundamental for mechanistic and proof-of-principle studies. However, the increasingly better understood differences between the human and mouse immune systems, including their partially different repertoires of innate immune

receptors, should be carefully considered when using animal models for human-specific pathogens.

Modulation of immune responses is recognized as a highly promising approach in the treatment of severe infectious diseases, and it may be the sole strategy for the treatment of acute life-threatening conditions such as streptococcal toxic shock syndrome. Type I IFNs are major immune modulators, possessing both immunostimulatory and immunosuppressive properties [101, 102]; as such, the elucidation of their mechanism of action in streptococcal infections could eventually establish type I IFN signaling as a target for novel therapies.

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