

Review Article



Current Understanding and Future Perspective of Bats Antiviral Innate Immunity

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Abstract | Viruses trigger the innate immune system to produce interferons via the Janus kinase/signal transducers and activators of transcription pathway, resulting in the transcription and expression of interferon-stimulated genes (ISGs). Bats and humans share some common ISGs but with some structural and genomic differences, impacting the ability for bats and humans to respond to viral infections. Also, there are fundamental differences in the bat and human innate immunity other than ISGs, including inflammasome activation, stimulator of interferon-stimulated genes protein function, immunological approaches, physiological adaptations, protein kinase R adaptation, and lineage-specific immune responses in bats. However, the incomplete genetic annotation of all the bat species, a lack of understanding of bat-virus interactions and viral co-infection, and biases in bat-virus relationship studies hinders the understanding towards bat antiviral innate immunity. By completing the genetic annotation of bats, developing wild-like environments when studying the bat immune system, improving data collection methods and conducting further studies on bat immunity and viral co-infection would further the understanding on infection dynamics and control as well as the relationship between bats and viruses, allowing a better prevention of future pandemics through a more understanding towards the mechanisms and triggers to viral disease emergence.

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Introduction

The structure of viruses: Viruses are small obligate intracellular parasitical microbes (Summers, 2009; Dimmock *et al.*, 2016). They contain an RNA or DNA genome and aim to deliver its genome to the host cell (Figure 1) (Gelderblom and Baron, 1996), exploiting its cellular mechanisms for replication and survival (Hoenen and Groseth, 2022). The viral

genome is packed in a protein coat formed from capsomers called a capsid (Chappell and Dermody, 2015). Some viruses have an envelope surrounding the viral capsid which is formed from the lipid membranes of the host organism, which includes plasma membrane, endoplasmic reticulum and Golgi apparatus (Navaratnarajah *et al.*, 2008; Louten, 2016b).

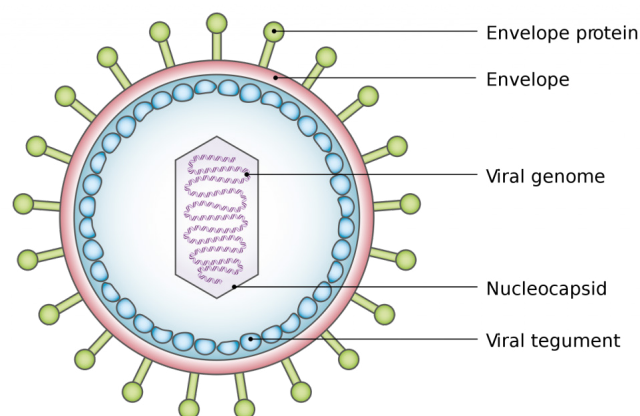


Figure 1: Structure of a virus. From: Taylor, 2010. CCO 1.0 Universal.

Viral infection cycle

The infection cycle of viruses can be divided into three stages: entry, genome replication and exit (Ryu, 2017). Viral entry initiates with attachment of the virus to the host cell attachment factors and viral receptors which are virus-specific via viral attachment proteins on the virion surface (Ryu, 2017). For example, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S-glycoprotein embedded on the virion surface attaches to angiotensin-converting enzyme 2 (ACE2) receptor (Zhou *et al.*, 2020). After attachment, the virus begins to penetrate into the cytoplasm (Carter and Saunders, 2013). For enveloped viruses, penetration can be achieved via direct fusion, where the viral envelope fuses with the host cell membrane (Yamauchi and Helenius, 2013), or by receptor-mediated endocytosis, where virions attached to receptors are clustered and endocytosed to form vesicles which are released into the cytoplasm via mechanisms including clathrin-mediated endocytosis, micropinocytosis, caveolae/lipid rafts and phagocytosis (Mercer *et al.*, 2010; Burrell *et al.*, 2017). For non-enveloped viruses, viral entry is mainly achieved through receptor-mediated endocytic mechanisms (Cann, 2005), with the exception of polioviruses and adenoviruses where the capsid undergoes conformational changes after attachment before internalized via an actin and tyrosin kinase-dependent mechanism (Brandenburg *et al.*, 2007). After viral entry, the viral capsid is uncoated to release the viral genetic material in the form of ribonuclearproteins, with the mechanisms depending on viral genome size (Ryu, 2017; Moreira *et al.*, 2021). The viral genetic material is then replicated, and different mechanisms are employed depending on the type of the genome according to the Baltimore classification system (Louten, 2016a).

The newly transcribed material then assembles and matures to form new virions (Dimmock *et al.*, 2016). The matured virion is ultimately released out of the cell via lysis of the infected cells for naked viruses, and envelopment of the matured capsid followed by exocytosis for enveloped viruses (Ryu, 2017).

Hosts in viral emergence

Hosts are important for the replication and survival of viruses (López-Lastra, 2022), and hence play important roles in viral emergence, with a multitude of factors contributing to promoting viral emergence and spread (Long *et al.*, 2018). These factors include host specificity for viral polymerases and viral attachment, host cell replication machinery and the subversion of host cellular factors for viral exit at the end of the replication cycle (Long *et al.*, 2018; Hoenen and Groseth, 2022). Viral infectious diseases in humans are often spread via zoonoses from bats (Jones *et al.*, 2008), and both species play important roles in viral emergence (Mackenzie *et al.*, 2016; Sudhan and Sharma, 2020), with bats known as the reservoir host for a lot of viral infectious diseases (El-Sayed and Kamel, 2021; Li *et al.*, 2023), due to its evolution to counteract the protein-mediated modulation of antiviral responses by limiting pro-inflammatory responses induced by viral infections whilst maintaining type I interferon (IFN) responses (Banerjee *et al.*, 2020; El-Sayed and Kamel, 2021). It was also suggested that pandemics could be prevented by studying immunological features in bats (Mallapaty, 2023), where by understanding the ecology of bat-borne viruses, the triggers to disease outbreaks and mechanisms for viral emergence, outbreak management plans can be designed, and risk reduction strategies including public education, promoting usage of personal protective equipment, restricting the sales of bushmeat and improved surveillance against potential zoonotic viruses can be implemented (Brown, 2004; Smith and Wang, 2013). In this article, the way humans and bats interact with viruses and the differences between them will be discussed. The future of studying bat antiviral abilities will also be discussed.

Interaction of viruses with hosts

Host organisms interact with viruses via the immune system, which are made of two interconnected systems: innate and adaptive immunity (Punt *et al.*, 2019).

Adaptive immunity

Adaptive immunity is activated after innate immunity (Murphy *et al.*, 2022). It is a highly specific immune response that is triggered rapidly upon re-infection (Moyano and Aguirre, 2019) carried out by lymphocytes, including B cells and T cells (Alberts *et al.*, 2002). B and T cells involve in two different classes of adaptive immunity, which are antibody-mediated and cell-associated immunity (Alberts *et al.*, 2002; Sette and Crotty, 2021).

Antigen presentation

T cells need to be activated in order to further activate other immune cells, including macrophages and B cells (Abbas *et al.*, 2017). However, unlike B cells, which can recognize free antigens, T cells can only recognize cell-associated antigens, so antigens need to be presented to them through antigen-presenting cells (APCs) (Punt *et al.*, 2019), which include macrophages, dendritic cells (DCs) and B cells (Alberts *et al.*, 2002). Antigens are presented to T cells via 2 classes of major histocompatibility complexes (MHCs) which present 2 separate types of antigens: endogenous antigens on MHC class I (MHC-I) and endogenous antigens on MHC class II (MHC-II) (Kotsias *et al.*, 2019).

Antigen presentation on MHC-I: MHC-I presents intracellular antigens to CD8⁺ T cells for initiating the differentiation of CD8⁺ T cells into memory T cells or cytotoxic T cells (Punt *et al.*, 2019). Antigens in the cytosol are degraded by proteasomes into smaller peptides, which then complexes with MHC-I and is transported to the cell membrane (Abbas *et al.*, 2017).

Antigen presentation on MHC-II: MHC-II presents extracellular antigens to CD4⁺ T cells for initiating the differentiation of CD4⁺ T cells into memory T cells and helper T cells (Kotsias *et al.*, 2019). Antigens are endocytosed into the APC, degraded by acidic pH-dependent endosomal and lysosomal enzymes into smaller peptides, complexed with MHC-II and transported to the cell membrane (Punt *et al.*, 2019).

Antigen cross-presentation: For the CD8⁺ cytotoxic T cells to act against invading viruses, exogenous antigens from the infectious agent must be acquired and presented to the naïve CD8⁺ T cells via MHC-I (Kotsias *et al.*, 2019). Since classical pathways described above cannot present exogenous antigens to MHC-I, cross-presentation is required to allow detection and

response to invading pathogens (Rock and Shen, 2005). Cross-presentation is mainly conducted in DCs, and there are two main pathways commonly referred to as the cytosolic and vacuolar pathways (Joffre *et al.*, 2012). The cytosolic pathway involves antigens phagocytosed into the APC as a phagosome, processed by the proteasomes which are then loaded onto MHC-I in the endoplasmic reticulum or in the phagosome after re-importation (Delves and Roitt, 2011), while the vacuolar pathway involves the antigen undergoing phagosomal degradation into peptides which are then loaded onto MHC-I (Joffre *et al.*, 2012).

Cell-associated immunity

Cell-associated immunity is conferred by T cells, and the activation of naïve T cells depends on antigens presented to them via MHCs and 3 other signals: T cell receptor-MHC-peptide interaction, CD28-CD80/86 co-stimulatory signal and a cytokine signal that directs T cell differentiation and proliferation (Punt *et al.*, 2019). There are 2 main subsets of T cells: CD4⁺ and CD8⁺ T cells, which are developed from the positive selection process during T cell development (Abbas *et al.*, 2017). The T cells undergoes differentiation and proliferation to become functional and active (Delves and Roitt, 2011). CD4⁺ T cells differentiate into CD4⁺ memory T cells or CD4⁺ T helper (T_H) cells (Punt *et al.*, 2019). Memory T cells, which can be either CD4⁺ or CD8⁺, are important for providing enhanced immunity against reinvading antigens by rapid conversion into effector T cells (Tungland, 2018; Al-Saihati *et al.*, 2023). T_H cells, on the other hand, help with activating B cells, macrophages and cytotoxic T cells to fully activate adaptive immunity (Alberts *et al.*, 2002).

Antibody-mediated immunity

Antibody-mediated immunity is conferred by B cells, where viral cell surface antigens trigger the release of antibodies from B cells (Nothelfer *et al.*, 2015). Antibodies bind to the antigens to stop them from binding to host cell receptors, inactivate the virus, and mark the invading pathogens to be easily destroyed by phagocytic cells (Alberts *et al.*, 2002). B cells can be activated in a T cell-dependent or T cell-independent manner (Neurath, 2008). For T-dependent B cell activation, antigens are presented to B cell receptors, which are then internalized and processed before interacting with T_H cells to create the suitable conditions for B cell differentiation and memory cell

formation (Punt *et al.*, 2019). For T-independent activation, T-independent antigens TI-1 and TI-2 are involved instead, where TI-1 antigens interact with the B cells via the B cell receptor and innate immune receptors, while TI-2 only interacts with B cell receptors (Punt *et al.*, 2019).

There are 5 classes of antibodies: Immunoglobulin G (IgG), IgA, IgM, IgD and IgE (James, 2022). IgM and IgG are the major antibody subtypes involved in antiviral immunity, with IgM acting as the first line of defence against any invading pathogens due to its low affinity and high avidity (Punt *et al.*, 2019), and IgG which is produced later in the immune response with multiple subclasses (IgG1, IgG2, IgG3 and IgG4) responsible for multiple functions including opsonization, complement activation and mediation of antibody-mediated cellular cytotoxicity by natural killer (NK) cells (Abbas *et al.*, 2017; James, 2022).

Innate immunity

Innate immunity is a rapid non-specific immune response triggered upon the entry of pathogens (Moyano and Aguirre, 2019). It is conferred by physical immunity, which are the natural physical and chemical barriers that stops viral invasion (Riera-Romo *et al.*, 2016), the activation of cellular response to infections resulting in phagocytosis, the release of cytokines and chemokines, and the activation of adaptive immunity via T cell responses and antibodies (Punt *et al.*, 2019).

Cellular innate immunity involves macrophages, granulocytes, neutrophils, NK cells and DCs (Weber, 2021). Macrophages, granulocytes and neutrophils contain cell-surface receptors to recognize and engulf invading viruses via phagocytosis to eradicate them (Alberts *et al.*, 2002). Macrophages and granulocytes act as APCs to present engulfed pathogenic antigens to T cells and B cells to initiate adaptive immunity (Weber, 2021). Neutrophils, on the other hand, die after phagocytosing pathogens (Punt *et al.*, 2019). NK cells carry out antibody-mediated cellular cytotoxicity mediated by IgG to kill invading pathogens (Abbas *et al.*, 2017). DCs bridges innate and adaptive immunity by also acting as an APC to present antigens to T cells to induce adaptive immunity (Punt *et al.*, 2019).

The innate immune response also involves a set of serum proteins called complement (Duval *et al.*, 2023), where the complement system is found

to be capable of direct neutralization of viruses via opsonisation, formation of membrane attack complexes on virion surface and virus-infected cells, and targeting of intracellular viral components for proteasomal degradation (Mellors *et al.*, 2020). The antiviral response is mainly mediated by host pattern recognition receptors (PRRs) recognizing pathogen-associated molecular patterns (PAMPs), stimulating interferon (IFN) release that upregulates interferon-stimulated genes (ISGs) (Yan and Chen, 2012; Schneider *et al.*, 2014; Alandijany, 2019).

Interactions of innate and adaptive immunity

While adaptive immunity has the advantage of flexibility and immunological memory from B and T cells, it is dependent on innate immunity to initiate and direct its actions (Clark and Kupper, 2005). This crucial interaction is achieved by DCs, which are part of the innate immune system and are the only cells capable to activate naïve T cells (Punt *et al.*, 2019). DCs, which are developed in the bone marrow, becomes mature when exposed to PAMPs (Chain, 2003). Mature DCs engulf the antigen on the surface of MHC-I and MHC-II and present it to naïve T cells, aiming to cause T cells to respond (Zanna *et al.*, 2021). DCs provides 4 signals to responding T cells to activate T cell maturation and differentiation: The interaction between the T cell receptor and the antigen-MHC complex on the DC surface (Clark and Kupper, 2005); a co-stimulatory signal between CD80/CD86 on the surface of the DC and CD28 on the T cell surface (Fuse *et al.*, 2006); a stimulatory signal for CD4⁺ T cells to differentiate into either T_H1, T_H2 or T_{reg} cells (Clark and Kupper, 2005); and a poorly characterized signal to T cells for homing receptor production (Campbell and Butcher, 2002). These activated CD4⁺ T cells help with stimulating antibody-mediated and cell-associated immunity (Punt *et al.*, 2019).

Viral immune evasion strategies

Viruses developed methods to escape the immune responses from the host (Alcami and Koszinowski, 2000). These methods include antigenic variability to avoid antibody recognition, expressing homologs of complement regulatory proteins to block complement activation, encoding homologs of MAC inhibitors to prevent from complement lysis, interfering with the IFN system (refer to section 4.8), inhibiting and modulating cytokines and chemokines involved in initiating and regulating innate and adaptive immune responses, blocking cytokine and chemokine

production, activity and signal transduction, inhibiting apoptosis, evading cytotoxic T cell and NK cell activity, and modulating MHC function (Alcami and Koszinowski, 2000).

Innate immune system and viruses

The IFN system is crucial for innate immune responses, acting as the first line of defence against invading viruses (Schneider *et al.*, 2014). PRRs, including toll-like receptors (TLRs), retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs), recognize PAMPs, including viral RNA and DNA, and trigger the release of IFNs and other cytokines (Koyama *et al.*, 2008). IFNs bind to cell surface receptors to initiate a signalling cascade via the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway that upregulates ISG transcription, forming an effective antiviral state against viruses (Stark and Darnell, 2012; Schneider *et al.*, 2014).

Classification and functions of PRRs

There are 5 main types of PRRs: TLRs, RLRs, NLRs, C-type lectin receptors (CLRs) and absent in melanoma-2 (AIM2)-like receptors (ALRs), and each PRR has its specific one or more PAMPs that it binds to (Li and Wu, 2021). PRRs recognize common

molecules on the surface of pathogens, and sends a downstream signal to induce immunoprotective functions provided by the innate immune system and initiating specific immune functions (Abbas *et al.*, 2017). Table 1 summarizes the types of PRRs that associates with viral PAMPs, and the functions of these virus-associated PRRs will be discussed.

TLRs

TLRs are an important family of PRRs that form the cornerstone of the innate immune system (Sadik *et al.*, 2015). There are 10 functional TLRs found in humans (TLR1-10) subdivided into two groups, cell membrane TLRs (composed of TLR1/2 heterodimers, TLR6/2 heterodimers, TLR4, TLR5 and TLR10) and intracellular TLRs (composed of TLR3, TLR7, TLR8 and TLR9) (Gay *et al.*, 2014; Sellge and Kufer, 2015). The main function of TLRs is to recognize PAMPs and mediate immune responses by recruiting adaptor proteins and activating TLR signalling cascades, including the myeloid differentiation primary response 88 (MyD88)-dependent and the Toll/interleukin-1R (IL-1R) homology (TIR)-domain-containing adaptor protein-inducing IFN- β (TRIF)-dependent signalling pathways (Lancaster *et al.*, 2005; Kagan, 2012). Antiviral immunity relies mainly on intracellular TLRs, with the exception of 3 cell membrane TLRs: TLR2, TLR4 and TLR10 (Akira *et al.*, 2006; Lee *et al.*, 2018).

Table 1: Types of PRRs and their associated viral PAMPs.

PRRs		Associated viral PAMPs	References
TLRs	TLR2	Haemagglutinin protein	Akira <i>et al.</i> , 2006
	TLR3	dsRNA	Akira <i>et al.</i> , 2006
	TLR4	Envelope proteins	Akira <i>et al.</i> , 2006
	TLR7	ssRNA	Akira <i>et al.</i> , 2006
	TLR8		Akira <i>et al.</i> , 2006
	TLR9	DNA, CpG DNA motifs	Akira <i>et al.</i> , 2006; Kawai and Akira, 2007
	TLR10	dsRNA	Lee <i>et al.</i> , 2018
NLRs	NOD2	ssRNA	Sundaram <i>et al.</i> , 2024
	NLRC3	DNA	Sundaram <i>et al.</i> , 2024
	NLRC5	Unknown sensing capacity	Kanneganti, 2010
	NLRP1	dsRNA	Sundaram <i>et al.</i> , 2024
	NLRP3	ssRNA	Kanneganti, 2010
	NLRP6	dsRNA	Sundaram <i>et al.</i> , 2024
	NLRP9	dsRNA	Sundaram <i>et al.</i> , 2024
RLRs	NLRX1	Unknown sensing capacity	Kanneganti, 2010
	RIG-I	Short dsRNA (<1000 bp), 5'PPP-RNA	Li and Wu, 2021
ALRs	MDA5	Long dsRNA (>1000 bp)	Li and Wu, 2021
	AIM2	dsDNA, ssRNA	Zhang <i>et al.</i> , 2017; Cui <i>et al.</i> , 2024

Most TLRs are responsible for detecting viral nucleic acids (Chuenchor *et al.*, 2014). TLR3 senses viral dsRNA and induces type I IFN release by activating nuclear factor- κ B (NF- κ B) and MyD88 signalling (Alexopoulou *et al.*, 2001). TLR7 and TLR8 both detect viral ssRNAs and signals via the NF- κ B and MyD88 pathways (Heil *et al.*, 2004). TLR9 detects viral genomes rich in CpG-DNA motifs, activating inflammatory cytokine and type I IFN release (Akira *et al.*, 2006). TLR10, which is found on the cell surface as opposed to being in the endosome like the other nucleic acid-sensing TLRs, senses viral dsRNAs and regulates IFN expression via the interferon regulatory factor 7 (IRF7)-MyD88 axis (Lee *et al.*, 2018). Interestingly, Lee *et al.* (2018) also observed that TLR10 cross-talks with TLR3, and regulates TLR3 expression to inhibit signalling.

Some TLRs, on the other hand, detects viral glycoproteins (Akira *et al.*, 2006). TLR2 detects hemagglutinin protein of measles virus, glycoprotein B on cytomegalovirus and the capsid of hepatitis B virus (Bieback *et al.*, 2002; Oliveira-Nascimento *et al.*, 2012), which activates the mitogen-activated protein kinase (MAPK) signalling cascade via p38, which can lead to IRF3 activation and inducing IFN production as a result (Compton *et al.*, 2003). TLR4 detects envelope proteins of viruses, such as the fusion protein of respiratory syncytial virus (Kurt-Jones *et al.*, 2000), the glycoproteins of ebolavirus and vesicular stomatitis virus (Halajian *et al.*, 2022), and the spike protein of SARS-CoV-2 (Shirato and Kizaki, 2021), activating the TRIF-dependent signalling pathway to induce IFN production (Akira *et al.*, 2006).

NLRs

NLRs are a large, diverse family of proteins that senses a large array of pathogenic triggers to induce multiple innate immune signalling pathways, including NF- κ B signaling, MAPK pathway and cytokine production (Sundaram *et al.*, 2024). The functions of NLRs are determined by their specific domains: Acidic transactivating domain-containing NLR protein (NLRA), baculovirus inhibitor of apoptosis protein repeat-containing NLR protein (NLRB), caspase activation and recruitment domain (CARD)-containing NLR protein (NLRC), pyrin domain-containing NLR protein (NLRP), and NLRs containing a domain with no similarity to known NLR subfamily members (NLRX) (Chou *et al.*, 2023). NLRAs and NLRBs are mainly involved

in antibacterial immunity, while some members of NLRCs, NLRPs and NLRXs are involved in antiviral immunity by detecting viral genetic material (Sundaram *et al.*, 2024).

NLRCs have 5 members: NOD1 (also known as NLRC1), NOD2 (also known as NLRC2), NLRC3, NLRC4 and NLRC5, and they all contain at least a CARD domain, with NOD2, NLRC3 and NLRC5 are involved in antiviral immunity, while NOD1 and NLRC4 are involved in immunity against other microbial pathogens (Sundaram *et al.*, 2024). NOD2 interacts with viral ssRNA, which activates MAPK and NF- κ B signalling pathways via the kinase RICK to activate IRF3 to produce IFNs (Sabbah *et al.*, 2009). NLRC3, on the contrary, negatively regulates NF- κ B and STING-mediated IFN signaling upon detecting viral DNA (Zhang *et al.*, 2014). NLRC5 is also found to interact with invading RNA viruses, but it remains unclear what component of these invading viruses is NLRC5 associating with (Neerincx *et al.*, 2010).

NLRPs are another subfamily of NLRs that shares a similar structure within the subfamily, which includes a pyrin domain at the N-terminal, a central NACHT domain, and a CARD domain at the C terminal (Sundaram *et al.*, 2024). 14 members of NLRPs have been found in humans (NLRP1-14), and they mainly function as the activator of inflammasomes (Sundaram *et al.*, 2024). NLRP1 detects viral dsRNA, leading to inflammasome activation (Bauernfried *et al.*, 2021). NLRP3 is found to detect viral ssRNA and stimulate caspase-1 activation and IL-1 β and IL-18 secretion, but the exact mechanism remains unclear (Kanneganti, 2010). NLRP6 and NLRP9 both detect viral dsRNA and induce inflammasome activation (Sundaram *et al.*, 2024).

NLRX1 is the only protein in the NLRX subfamily which is found in mitochondria, and contains a mitochondrial targeting sequence, which is not found in any other NLRs (Tattoli *et al.*, 2008). It is suggested that NLRX1 is involved in mitochondrial antiviral signalling (MAVS) and can sense viruses, but its exact sensing capability remains unknown (Moore *et al.*, 2008).

RLRs

RLRs are a group of intracellular PRRs that detects viral nucleic acids like TLR7 and TLR9 to induce antiviral immune responses (Li and Wu, 2021). There

are 3 types of RLRs: RIG-I, melanoma differentiation-associated gene 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2) (Yoneyama *et al.*, 2005). LGP2 mainly functions in regulating the recognition of PAMPs by RIG-I and MDA5 to prevent RLR-mediated resistance by facilitating MDA5 and inhibiting RIG-I signalling (Liu and Gack, 2020). RIG-I and MDA5 share similar structures, hence they share a similar function in recognizing viral dsRNA (Li and Wu, 2021). However, their recognition depends on the length of the dsRNA, where RIG-I senses viruses with DNA shorter than 1000 base pairs (bp), while MDA5 recognizes viruses with longer DNA lengths (> 1000 bp) (Wang *et al.*, 2010b; Zou *et al.*, 2013). Activated RIG-I and MDA5 releases the CARD domain, which gets ubiquitinated, and the active RLR moves to the mitochondria to activate MAVS (Thoresen *et al.*, 2021), which then induces IFNs and other cytokines (Yoneyama *et al.*, 2004; Chan and Gack, 2016).

ALRs

ALRs are a group of recently discovered PRRs capable of viral sensing (Feng *et al.*, 2019). It is discovered that AIM2, the most well-established member of ALRs, is capable of sensing viral dsDNA and ssRNA (Zhang *et al.*, 2017; Kumari *et al.*, 2020). After sensing viral nucleic acids, AIM2 activates caspase-1, which leads to the release of IL-1 β and IL-18, as well as activating IRF-dependant IFN release (Kumari *et al.*, 2020).

Signalling pathways of PRRs

There are 4 major signalling pathways adopted by PRRs: NF- κ B signalling, MAPK signalling, TANK-binding kinase 1 (TBK1)-IRF3/7 pathway and inflammasome signalling (Li and Wu, 2021). The ways these signalling pathways are utilized by PRRs in antiviral immunity are discussed below.

NF- κ B signalling

NF- κ B is a transcription factor that plays a key role in cellular inflammation and immune responses, and is often involved in signal transduction initiated by PRRs (Li and Wu, 2021). The NF- κ B signalling system is defined by the NF- κ B dimer (formed from p50 and p65 proteins), inhibitor of nuclear factor kappa B (I κ B) regulators and I κ B kinase (IKK) complexes (Mitchell *et al.*, 2016). The NF- κ B signalling pathway is used by TLRs, NLRs and RLRs, leading to the activation and transcription of ISGs (Li and Wu, 2021).

After TLRs recognize and bind to their respective PAMPs, the toll-IL-1 receptor (TIR) domain conducts signals by binding to different adaptor proteins (Anthoney *et al.*, 2018). TLR signalling is then divided into MyD88-dependent and MyD88-independent signalling dependent on the adaptor proteins (O'Neill and Bowie, 2007). For MyD88-dependent signalling, the TIR domain on MyD88 binds to TIR on TLRs, recruits IL-1R-related kinase 4 (IRAK4), and activates IRAK1 and IRAK2 (De Nardo *et al.*, 2018; Li and Wu, 2021). This leads to the recruitment of tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6), and the formation of a complex with transforming growth factor (TGF)- β -activated kinase 1 (TAK1) and TAK-binding proteins 1 and 4 (TAB1 and TAB4) (O'Neill and Bowie, 2007). TRAF6 is then degraded by self-ubiquitination, while the TAK1-TAB1-TAB4 complex activates the IKK complex (consists of IKK γ , IKK α and IKK β) and activates I κ B in the I κ B/p50/RelA complex via phosphorylation (Li and Wu, 2021). The phosphorylated I κ B is then ubiquitinated and degraded, releasing p50/RelA into the nucleus, leading to NF- κ B release (Lawrence, 2009). Alternatively, NF- κ B can be released independent of MyD88 via a TRIF-dependent pathway, where TRIF recruits TRAF6 or receptor-interacting protein 1 (RIP1) and activates NF- κ B signalling via the recruitment of the TAK1-TAB1-TAB4 complex, the activation of the IKK complex and I κ B (O'Neill and Bowie, 2007). I κ B is then ubiquitinated and degraded, leading to NF- κ B activation (Li and Wu, 2021).

For NLR-mediated signalling, after detecting viral PAMPs on NOD2, NOD2 is activated, then self-dimerizes and recruits RIP2 via its CARD domain (Park *et al.*, 2007). Activated RIP2 recruits TAK1, TAB1 and the NF- κ B essential modulator (NEMO)/IKK α /IKK β complex (Hasegawa *et al.*, 2007). IKK α and IKK β are activated, which activates NF- κ B signalling as a result (Li and Wu, 2021).

For RLRs, when viruses invade cells, RIG-I and MDA5 detects viral dsRNAs and undergoes conformational changes and becomes activated (Zevini *et al.*, 2017), which then binds to MAVS to induce downstream signalling via TRAF3, which then recruits IKK ϵ /TBK1 (Samie *et al.*, 2018), activates I κ B and NF- κ B (Li and Wu, 2021), or TRAF6 (O'Neill and Bowie, 2007).

MAPK signalling

MAPK is a group of serine-threonine protein kinases that can be activated by a range of cytokines, hormones and neurotransmitters, as well as cell stress and cell adhesion (Johnson and Lapadat, 2002). It is important for antiviral signalling by TLRs and NLRs.

In the MyD88-dependent signalling pathway for TLRs, activated IRAK1 interacts with TRAF6, which recruits via the TAK1-TAB1-TAB4 complex (refer to section 3.2.1). Apart from activating the IKK complex, TAK1 can also activate 2 MAPK pathways: The p38 pathway and c-Jun N-terminal kinase (JNK) pathway (Alexopoulou *et al.*, 2001). For the p38 pathway, TAK1 phosphorylates MAPK kinase 3 and 6 (MKK3/6), which phosphorylates p38 (Kumar *et al.*, 2018). p38 then either activates p53 to initiate inflammatory responses, NF- κ B to initiate inflammatory gene transcription, or MAPK-interacting protein kinase 1 (MNK1) to activate Sprouty 2 (Spry2) to induce IFN production (Kumar *et al.*, 2018; Li and Wu, 2021). For the JNK pathway, TAK1 phosphorylates MAPK kinase 4 and 7 (MEK4/7), which phosphorylates JNK, which activates NF- κ B and signal transducers and activators of transcription 1 (STAT1) to initiate inflammatory responses (Kumar *et al.*, 2018).

For NLRs, when activated by viral components, NLRs recruit downstream CARD9, which activates p38 and JNK pathways as mentioned above (Hsu *et al.*, 2007).

TBK1-IRF3/7 pathway

IRF3 and IRF7 are important transcription factors that are crucial for the production of type I and type III IFNs (Dalskov *et al.*, 2020). The TBK1-IRF3/7 pathway can be activated by TLRs and RLRs (Liu *et al.*, 2015).

In the MyD88-independent signalling pathway of TLR3 and TLR4, after binding to their respective viral PAMPs, TRIF is recruited, which then recruits TRAF3 and the IKK ϵ /TBK1 complex (Samie *et al.*, 2018), leading to the phosphorylation of IRF3 and IRF7, which induces the activation and transcription of IFN genes, leading to the production of IFNs (Li and Wu, 2021).

For RLRs, when RIG-I and MDA5 detects viral nucleic acids, they interact with their shared caspase recruitment domain to induce MAVS dimerization and TRAF3 binding, leading to the recruitment of

TANK, nucleosome assembly protein 1 (NAP1) and similar to NAP1 TBK1 adaptor (SINTBAD) (Li and Wu, 2021). TANK activates TBK1 to phosphorylate IRF3 and IRF7, ultimately leading to IFN production.

Apart from PRRs, cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) signalling pathway can also activate the TBK1-IRF3/7 signalling pathway (Decout *et al.*, 2021). cGAS responds to viral dsDNA to catalyze the formation of cyclic GMP-AMP (cGAMP), which activates STING and induce the translocation of STING from the endoplasmic reticulum to the Golgi apparatus, activating the TBK1-IRF3 signalling pathway, triggering the production of IFNs as a result (Hopfner and Hornung, 2020).

Inflammasome signalling

Inflammasomes are a multi-protein complex assembled by PRRs that are capable to recognize PAMPs, which then recruits and activates caspase-1, and the activated caspase-1 splices pro-IL-1 β and pro-IL-18 into IL-1 β and IL-18 respectively (Schroder and Tschopp, 2010). There are 3 inflammasomes involved in antiviral immunity: The NLRP1 inflammasome, the NLRP3 inflammasome and the AIM2 inflammasome, and they all contain apoptosis-associated speck-like protein containing CARD (ASC) and caspase protease (Li and Wu, 2021).

IFN system

Classification of IFNs

There are three types of IFNs: types I, II and III (Cao *et al.*, 2022). Type I IFNs are mainly expressed in innate immune cells (Negishi *et al.*, 2017), and include IFN- α , IFN- β , IFN- ϵ , IFN- κ , and IFN- ω subtypes, with other species-specific subtypes being identified (Walter, 2020; Cao *et al.*, 2022). IFN- α has 13 subtypes (IFN- α 1, IFN- α 2, IFN- α 4, IFN- α 5, IFN- α 6, IFN- α 7, IFN- α 8, IFN- α 10, IFN- α 13, IFN- α 14, IFN- α 16, IFN- α 17 and IFN- α 21), and although belonging to the same subtype, they have slightly different antiviral activities, where the subtypes are not equally expressed against different viral invasions (Moreau *et al.*, 2023). IFN- α is produced under induction by IRF3/7, which then signals via the IFN system to induce the transcription of ISGs, which promotes antiviral, antiproliferative and immunomodulation activities (Moreau *et al.*, 2023), as well as activating monocytes, APCs, DCs,

macrophages, NK cells, B and T cells, and promoting antibody class switching (Cha *et al.*, 2014). IFN- β plays an important role in macrophages by synergizing with TLR downstream signalling pathways to induce optimal inflammatory cytokine production, in the differentiation of immune effector cells, which helps establish the critical link between innate and adaptive immune responses, in the activation and priming of T cells, and the induction and activation of B cells to promote long-lived antibody production and antibody class switching (Sin *et al.*, 2012). IFN- ϵ plays a unique role in antiviral immunity on mucosal surfaces by inducing a localized short-lived mucosal immune response and to promote gut-specific CD8⁺ T-cell immunity by promoting antigen-specific CD8⁺ T cell migration to the gut (Xi *et al.*, 2012). IFN- κ possibly functions as the first line of type I IFNs produced by inducing ISG responses more quickly than IFN- κ but with a lower intensity and a shorter duration (Fu *et al.*, 2021). Fu *et al.* (2021) also showed that ISGs are only induced by the membrane-bound IFN- κ , but not by the secreted form, suggesting that the antiviral effects exhibited by IFN- κ are cell-associated. IFN- κ also induces ISG transcription, inhibits viral replication, prevent cell proliferation, and modulates innate immune responses by increasing cell survival time and acute-phase proteins, promoting phagocytosis and NK cell activities, and reducing viral excretion (Li *et al.*, 2017).

Type II IFNs contain IFN- κ as the only subtype (Schneider *et al.*, 2014), and are produced in NK cells (Lee and Ashkar, 2018). IFN- κ interferes with multiple stages of the viral life cycle, including inhibiting viral invasion by controlling the expression and distribution of receptors required for viral entry or stopping the transfer of the invading virus from the endosome into the cytoplasm, inhibiting the replication process by disrupting the replication niche, hindering translation to prevent viral gene expression, lowering stability by impeding the assembly of the nucleocapsid, stopping viral release by cleaving disulphide bonds in CD63, and prevent virus reactivation by suppressing the transcription of viral master regulators (Kang *et al.*, 2018).

Type III IFNs are produced in primary hematopoietic lineage cells and epithelial cells (Wack *et al.*, 2015), and include IFN- λ 1, IFN- λ 2, IFN- λ 3, and IFN- λ 4 subtypes (Lazear *et al.*, 2019). IFN- λ activates antiviral responses and induce ISGs, recruit and

activate immune cells, exerting a localized antiviral effect and inhibits initial viral transmission without activating inflammation and initiates early infection control at the barrier surface (Liu *et al.*, 2024).

IFN receptors

Each class of IFNs have a different cell surface receptor complex (Figure 2) (Cao *et al.*, 2022). IFNs bind to their respective receptors to initiate the signalling cascade (Negishi *et al.*, 2017).

All type I IFNs bind to interferon-alpha receptor 1 (IFNAR1) and IFNAR2 complex (Takaoka and Yanai, 2006). IFNAR1 and IFNAR2 are transmembrane proteins of the class II helical cytokine receptors, and they form ternary complexes with the ligand upon binding (Uzé *et al.*, 2007). The ectodomain of the high-affinity IFNAR2 subunit consists of 2 fibronectin type III (FNIII)-like subdomains (D1-2) (Novick *et al.*, 1994), while the low affinity IFNAR1 subunit comprises 4 FNIII-like subdomains (SD1-4) (Uzé *et al.*, 1990). When type I IFNs are bound to the IFNAR1/2 heterodimer, IFNAR1 undergoes a conformational change, with the movement of the SD4 subunit suggesting the role of SD4 in signalling since it is not needed for ligand binding (Piehler *et al.*, 2012), which was suggested to play a role in IFN activity regulation, allowing rapid IFN-mediated ISG activation and expression (Sharma *et al.*, 2016; Walter, 2020). However, the regulation of type I IFN was said to be driven by the dimerization of IFNAR1/2 mediated by IFNs, which activates Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2), subsequently inducing ISG expression (Walter, 2020). Despite the 17 subtypes of type I IFNs, they all share to the same IFNAR1/2 complex, and activates different signals, leading to different biological activities (de Weerd *et al.*, 2007). This is achieved by the utilization of different regions of the intracellular domain of the IFNAR β_L subunit possibly by promoting distinct conformational changes in the receptor to affect signalling (Domanski *et al.*, 1998). It is also found that type I IFNs all have different affinities to the receptor complex, and they all bind competitively to both receptors, which correlates with the differential signal activation and biological activities displayed by different type I IFN subtypes (Jaks *et al.*, 2007). IFNARs are generally found in almost all cell types, except for the low expression level of IFNAR2 in the brain, which suggests that either IFNAR2 is not required for type I IFN signalling in the brain, or that

IFNAR2 expression is reduced to downregulated type I IFN signalling in the brain to protect the brain from pro-inflammatory cytokines (de Weerd and Nguyen, 2012).

Type II IFNs bind to interferon-gamma receptor (IFNGR) complex containing 2 IFNGR1 and 2 IFNGR2 chains (Schroder *et al.*, 2003). IFNGR1 functions majorly in ligand binding and signal transduction, while IFNGR2 serves to support IFNGR1 in its functions (Alspach *et al.*, 2018; Shi *et al.*, 2023). Also, the IFNGR complex consists of 2 IFNGR1 and IFNGR2 chains each is due to IFN- γ being a homodimeric molecule, and stoichiometry experiments showing that the IFNGR-IFN- γ complex is at a 2:1 ratio, meaning that for IFN- γ signalling to occur, multiple heterodimeric IFNGRs (i.e. IFNGR1/2 complexes) are required (Fountoulakis *et al.*, 1992). The dimerization of IFNGR complex is important in the signalling pathway by IFN- γ , where upon binding of IFN- γ , the association between IFNGR1 and IFNGR2 tightens and the intracellular domains of the receptors reorientates, allowing associated JAK1 and JAK2 to be in close proximity to phosphorylate the tyrosine 440 on the intracellular domain of IFNGR1 to create a binding site for STAT1, which forms an active STAT1 homodimer to activate transcription of gamma-activated site (GAS) element-mediated ISGs (Bach *et al.*, 1997; Alspach *et al.*, 2018). Like type I IFN receptors, IFNGRs are found in almost all cell types, with one exception where IFNGR2 is absent from T_H1 cells, which may allow selective inhibition of T_H2 cell proliferation whilst allowing T_H1 cells to escape the antiproliferative effects of IFN- γ (Pernis *et al.*, 1995).

Type III IFNs bind to interferon-lambda receptor (IFNLR) complex containing IFNLR1 and IL-10 receptor 2 (IL-10R2), where IL-10R2 is a shared receptor of IL-10, IL-22 and IL-26 (Wack *et al.*, 2015). Similar to type I IFN receptors, there is a high-affinity receptor chain (IFNLR1) and a low-affinity receptor chain (IL-10R2), but type III IFNs show weaker affinities to their receptors than type I IFNs, allowing IFN- λ s to be more sensitive to the expression levels of receptors on cells (de Weerd *et al.*, 2024). IL-10R2, like type I and II IFN receptors, can be found in all cell types, possibly due to its function as a shared receptor with other ILs (de Weerd and Nguyen, 2012). However, IFNLR1 expression is almost exclusive to epithelial cells (Zheng *et al.*, 2008; Ouyang *et al.*,

2011), particularly in keratinocytes and cells from the kidney, lung and the gastrointestinal tract (Ank *et al.*, 2008), suggesting that IFN- λ signalling may be specialized in antiviral activities at epithelial barrier surfaces (Kotenko *et al.*, 2019).

Evolution of IFNs

The IFN system is generally thought to have evolved from a class II helical cytokine ancestor and the IL-10 cytokine family (Secombes and Zou, 2017). Two rounds of whole genome duplication between invertebrates and vertebrates led to the formation of the IL-10 ancestor and IFN ancestor, which have further duplicated to form the 2 loci containing the IL-10 family genes, as well as the types I and III IFN loci (Nakatani *et al.*, 2007; Siupka *et al.*, 2014). The locus for type II IFN is also said to have diverged from the IL-10 family genes as an early event in vertebrate evolution (Secombes and Zou, 2017). Retrotransposition events also occurred on type I and type III IFN genes, giving rise to further IFN loci and the production of more IFN subtypes (Secombes and Zou, 2017). The evolution of some IFNs, including IFN- α 6, IFN- α 8, IFN- α 13, IFN- α 14 and IFN- γ occurred under strong purifying selection, bringing about their essential and non-redundant function in immunity, while that of other IFNs, especially IFN- α 10 and IFN- ϵ , occurred under more relaxed selective constraints, leading to redundancy in host defense against viral infections (Manry *et al.*, 2011).

IFN signalling

Canonical IFN signalling pathway: Type I and III IFNs share a similar signalling mechanism due to their structural similarity (Figure 2) (Pestka *et al.*, 2004; Mesev *et al.*, 2019). After binding to their respective receptor complexes, type I and III IFNs initiate the cross-phosphorylation of JAK1/TYK2, which subsequently trigger signal transducers and activators of transcription 1 and 2 (STAT1 and STAT2) phosphorylation (Lazear *et al.*, 2019). The phosphorylated STAT1/STAT2 heterodimer recruits IFN-regulatory factor 9 (IRF9) to form IFN-stimulated gene factor 3 (ISGF3) (Schneider *et al.*, 2014). ISGF3 translocate into the nucleus to induce IFN-stimulated response elements (ISRE)-regulated ISG expression (Dumoutier *et al.*, 2003).

ISGF3 also engages with proteins subunits of the SWI/SNF complex, including BAF47, BAF200 and BRG1, which are involved in chromatin remodelling

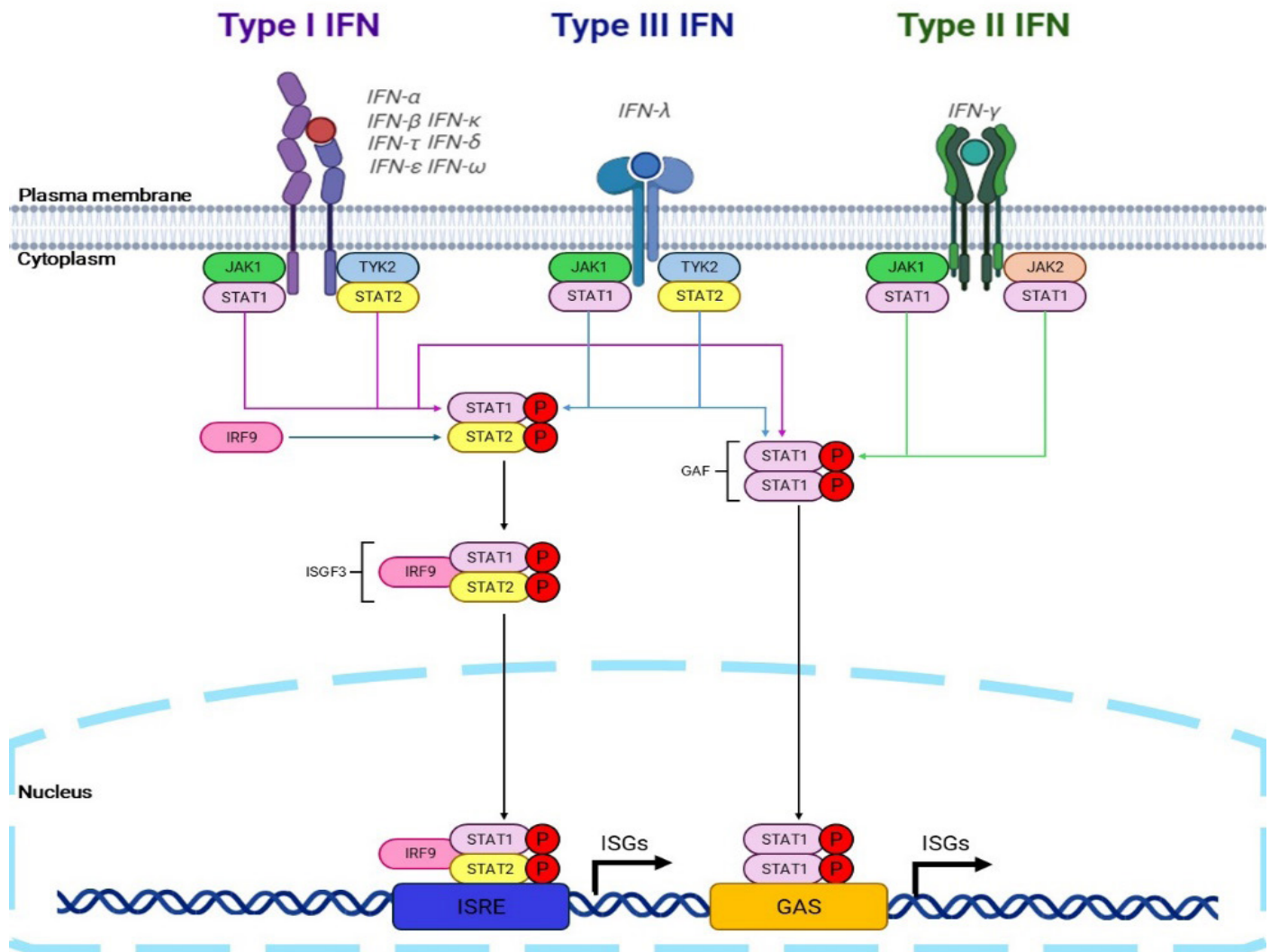


Figure 2: Canonical IFN signalling cascade.

and are required for ISG transcription (Au-Yeung and Horvath, 2018b). The ISG promoter region has core histones present without IFN binding, namely H2A.Z and H3.3 (Tamura *et al.*, 2009; Au-Yeung and Horvath, 2018a). IFN stimulation leads to the loss of H2A.Z from the promoter, leading to ISGF3 occupancy of the region, resulting in ISG transcription (Au-Yeung and Horvath, 2018b). H3.3, on the other hand, persists after IFN stimulation to inhibit histone H1 from occupying the region, which would lead to a decrease in response to IFN stimulation (Braunschweig *et al.*, 2009; Kadota and Nagata, 2014). These chromatin remodelling events allow better DNA accessibility and transcription for ISGs (Au-Yeung and Horvath, 2018b).

Type II IFNs use a distinct signalling mechanism (Figure 2). They form a homodimer that binds to the 2 IFNGR1 subunits initially, resulting in the binding to the 2 IFNGR2 subunits, activating the receptor

(Walter *et al.*, 1995; Schneider *et al.*, 2014). The activated receptor phosphorylates JAK1 and JAK2, which then phosphorylates STAT1 (Negishi *et al.*, 2017). Phosphorylated STAT1 forms a homodimer called interferon gamma activation factor (GAF) that undergoes nuclear translocation to initiate GAS-regulated ISG transcription (Cao *et al.*, 2022).

Non-canonical IFN signalling pathways

Apart from phosphorylating and activating STAT1 and STAT2 to promote ISG transcription and expression, JAKs and TYKs can activate other non-canonical IFN signalling pathways. These pathways include the MAPK pathway, the phosphoinositide 3-kinases (PI3K)/mammalian target of rapamycin (mTOR) pathway and the Unc-51-like kinase 1 (ULK1) pathway (Saleiro and Platanias, 2019; Mazewski *et al.*, 2020).

MAPK pathway in IFN signalling: The p38 MAPK

pathway is activated by all 3 types of IFNs, and is essential for the optimal transcription of ISGs (Fish and Platanias, 2014). IFN-activated JAKs can activate VAV and other guanine-nucleotide-exchange factors to activate RAC1 and small G proteins, leading to the activation of a MAPK kinase kinase, which phosphorylates MKK3/6 to activate p38 (Platanias, 2005). p38 activates MNK1 and MNK2, which are essential for the mRNA translation of ISGs (Saleiro and Platanias, 2019), as well as Spry1, Spry2 and Spry4, which negatively regulates IFN signalling and IFN-inducible biological responses, including antiviral effects of type I IFNs (Sharma *et al.*, 2012). Mitogen- and stress-activated kinases 1 and 2 (MSK1 and MSK2) are also activated by p38, which are required for histone H3 phosphorylation, and is important for immediate early gene expression (Clayton and Mahadevan, 2003).

Apart from p38, the MEK-ERK pathway is also activated by type I and II IFNs in response to viral infections, and is important in regulating the activation of IRF3 and IFNs (Platanias, 2005). JNK is also thought to regulate signal induction during IFN responses to viral infections, leading to the removal of infected cells by apoptosis (Li *et al.*, 2004).

PI3K/mTOR pathway in IFN signalling: mTOR is important in regulating signals for mRNA translation, cell metabolism and cell proliferation (Saleiro and Platanias, 2019), and it acts as a sensor to environmental and cellular changes, which then integrates these signals to control the fate of different immune cells, affecting both innate and adaptive immune responses (Powell *et al.*, 2012). The mTOR pathway occurs downstream of the PI3K/AKT pathway, and plays critical roles in the mRNA translation of IFN-sensitive genes (Kaur *et al.*, 2007). mTOR is present as the common catalytic subunit in 2 complexes, mTORC1 and mTORC2 (Saleiro and Platanias, 2015). mTORC2 is found to be activated by both type I and II IFN receptors, which is crucial in controlling ISG transcription and mRNA translation (Kaur *et al.*, 2012; Kroczyńska *et al.*, 2016).

ULK1 pathway in IFN signalling: ULK1 is found to control innate immune responses. For example, in the cGAS-STING-TBK1-IRF3/7 pathway which leads to type I IFN production, the synthesis of cGAMP mediated by cGAS triggers the dephosphorylation of ULK1, igniting downstream phosphorylation of

STING, leading to STING degradation and type I IFN production suppression, suggesting that ULK1 acts as a negative feedback control mechanism (Konno *et al.*, 2013). ULK1 also plays a central role in type I and II IFN signalling, activating the p38 and MLK3/ERK5 MAPK pathways respectively (Saleiro and Platanias, 2019).

Regulation of IFN signalling

The IFN signalling cascade is regulated by post-translational modifications (PTMs) and epigenetic modifications to ensure prompt activation upon infection to provide first line of immunity, and appropriately controlled after clearance of the infection to prevent tissue damage (Chen *et al.*, 2017).

PTMs

PTMs alters protein activity, stability and sub-cellular localization to alter the components of the IFN signalling cascade, playing a critical role in regulating IFN activity (Mowen and David, 2014). PTMs include phosphorylation, ubiquitylation, SUMOylation, ISGylation, acetylation and methylation (Chen *et al.*, 2017).

Phosphorylation: The phosphorylations of JAK1, JAK2, TYK2, STAT1 and STAT2 are crucial for the activation of the canonical IFN signalling and induction of ISG expression (Levy and Darnell, 2002). Once binded to IFNs, IFN receptors phosphorylate their respective associated JAKs and TYKs, then JAK1 and JAK2 phosphorylates STAT1, phosphorylating a tyrosine residue (Chen *et al.*, 2017). A serine residue on STAT1 is also phosphorylated via the MAPK pathway in response to IFNs (Wen *et al.*, 1995). Other kinases, including protein kinase C-delta (PKC δ), cyclin-dependent kinase 8 (CDK8) and IKK ϵ , have been found to phosphorylate serine residues of STAT1 to augment IFN responses, restrain cytotoxicity of NK cells and promote DNA binding activity of STAT1 respectively (Uddin *et al.*, 2002; Tenover *et al.*, 2007; Putz *et al.*, 2013). STAT2 is regulated via tyrosine phosphorylation to trigger STAT dimerization, nuclear translocation and transcriptional activation of ISGs (Steen and Gamero, 2013).

IFN signalling is negatively regulated via phosphatase families (Chen *et al.*, 2017). For example, the suppressor of cytokine signalling (SOCS) family phosphatase SOCS1 binds to JAKs to decrease the tyrosine kinase activity of JAKs (Shuai and Liu, 2003), and to IFNAR1 to prevent STAT1 phosphorylation,

weakening cellular responses to type I IFNs as a result (Fenner *et al.*, 2005). SH2 domain-containing phosphatase 1 and 2 (SHP1) dephosphorylates JAK1 and STAT1 to impair IFN signalling (Shuai and Liu, 2003; Du *et al.*, 2005). Protein tyrosine phosphatase, non-receptor type 2 (PTPN2) is also found to dephosphorylate STAT1 in the nucleus (Mustelin *et al.*, 2005).

Ubiquitylation: Ubiquitylation is important for controlling innate signalling-dependent type I IFN production by inducing protein degradation or disrupting signal transduction (Chen *et al.*, 2017). Ubiquitylation can occur on the receptor level, where the Skp1-Cullin1-HOS-Roc1 ubiquitin ligase acts on IFNAR1, promoting its ubiquitylation and degradation (Kumar *et al.*, 2003), as well as on the ligand level, where STATs are targeted for proteasome-mediated degradation to downregulate STAT-mediated transcriptional activation (Chen *et al.*, 2017).

To sustain IFN signalling, USP2a and natural killer lytic-associated molecule (NKLAM) acts as deubiquitinases to promote phosphorylation and transcriptional activity of STAT1 (Lawrence and Kornbluth, 2016; Chen *et al.*, 2017).

Ubiquitylation-like modifications: Ubiquitin-like molecules, including small ubiquitin-related modifier (SUMO) and ISG15, can also be conjugated onto substrate proteins in a similar mechanism as ubiquitylation, termed as SUMOylation and ISGylation respectively (Melchior, 2000; Durfee *et al.*, 2010). STAT1 can be SUMOylated by protein inhibitors of activated STAT 1 (PIAS1), leading to IFN signalling attenuation and ISG expression downregulation (Ungureanu *et al.*, 2005). On the other hand, ISGylation of JAK1 and STAT1 by ISG15 is a positive regulator of signalling and antiviral function, resulting in prolonged phosphorylation and activation of JAK1 and STAT1, and DNA binding of STAT1 (Chen *et al.*, 2017). USP18 is specific for deISGylation, which hinders the antiviral function of the IFN system (Skaug and Chen, 2010).

Acetylation and methylation: Apart from histones, many non-histone proteins are subject to acetylation and methylation, which is critical for the regulation of multiple biological processes and cell signalling (Yang and Seto, 2008; Chen *et al.*, 2017). For example, histone

deacetylase 9 (HDAC9) deacetylates TBK1 to allow phosphorylation of TBK1, activating the TBK1-IRF3/7 pathway for IFN induction (Li *et al.*, 2016). HDAC3 deacetylates STAT1 upon IFN stimulation to allow phosphorylation of STAT1 (Krämer *et al.*, 2009). IFNAR2 recruits a histone acetyltransferase CREB-binding protein (CBP), which acetylates IFNAR2, STAT2 and IRF9 to ensure the formation of the ISGF3 complex (Chen *et al.*, 2017). On the other hand, STAT1 is methylated by protein arginine methyltransferase 1 (PRMT1) upon type I IFN transduction to prevent PIAS1 from interacting with STAT1 to promote DNA binding activity of STAT1 (Mowen *et al.*, 2001).

Epigenetic regulation

Epigenetic regulation controls immune responses against viruses by controlling gene expression and repression via histone modification, DNA methylation and non-coding RNAs (Chen *et al.*, 2017).

Histone modification

Multiple histone modifiers have been found or suggested to have effects on the induction or repression of IFN signalling by mediating the modifications of IFN and ISG gene loci (Chen *et al.*, 2017). For example, the expression and activity of *IFNB* are controlled by modifications including SUMOylation and deacetylation mediated by HDAC1 and HDAC8 (Decque *et al.*, 2015; Meng *et al.*, 2016). Type I IFNs can stimulate ISG expression by inducing ubiquitylation on lysine 120 of histone H2B, leading to transcriptional activation (Fonseca *et al.*, 2012). Methylation of histones at multiple lysine and arginine sites have also shown to participate in IFN-induced ISG expression (Chen *et al.*, 2017). Histone modifications can also act as molecular markers for recruiting chromatin remodelling enzymes, leading to local chromatin loosening by sliding nucleosomes on DNA (Trotter and Archer, 2007). For example, under IFN- α induction, chromatin remodelling factor BRG1 associates with STAT2, promoting the recruitment of the SWI2/SNF2 chromatin remodelling complex, leading to selective upregulation of ISGs (Huang *et al.*, 2002).

DNA methylation

DNA methylation of 5'-C is closely involved in the regulation of IFN signalling, and hypomethylation of DNA may lead to the hyperresponsiveness of IFNs, which causes overexpression of ISGs, resulting

in autoimmune diseases, such as systemic lupus erythematosus (Chen *et al.*, 2017).

Non-coding RNAs

microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are induced by IFNs to act as feedback regulators in modulating IFN signalling (Chen *et al.*, 2017). miRNAs targets protein-coding transcripts, resulting in RNA silencing (Ha and Kim, 2014). miRNAs can inhibit IFNAR1 expression in thymic epithelial cells, leading to impairment in IFN-mediated thymic involution (Papadopoulou *et al.*, 2012), or indirectly promote IFN signalling by targeting the suppressor SOCS1 (Wang *et al.*, 2010a), or weaken IFN responses by directly suppressing STAT1/2 expression (Kohanbash and Okada, 2012), or downregulate ISG expression by repressing JAK1 and IRF9 transcription (Mukherjee *et al.*, 2015). On the other hand, lncRNAs mediates regulation of IFN response via direct promotion of expression of IFNs (Gomez *et al.*, 2013), or by mediating crosstalk between TLRs and the IFN system (Chen *et al.*, 2017).

IFN crosstalk with other signalling pathways

Crosstalk refers to how biological signals are integrated from multiple inputs in a response network affects a biological output (Vert and Chory, 2011). The IFN system crosstalks with inflammatory signalling, including the NF- κ B and the inflammasome pathways to achieve better antiviral immunity (Dai *et al.*, 2022).

Crosstalk between IFN and NF- κ B signalling pathways: After NF- κ B/RelA enters the nucleus, it binds to the enhancer of an IFN promoter, promoting the transcription of *IFNA* and *IFNB* genes to induce IFN- α and IFN- β production (Dong *et al.*, 2013). IKK α and IKK β in the IKK complex also crosstalks with components of the MAPK and TBK1-IRF3/7 pathways, regulating ISG transcription (Oeckinghaus *et al.*, 2011). The expression of *PKR*, which is an ISG, produces PKR that reduces host cell translation and I κ B degradation, inducing NF- κ B signalling activation (Dai *et al.*, 2022). PKR overexpression under viral infection also activates NF- κ B and IFN responses, enhancing type I IFN and proinflammatory cytokine expression, preventing viral replication as a result (Zhu *et al.*, 2021). In summary, the IFN signalling pathway regulates NF- κ B signalling via the induction of ISG expression, while the NF- κ B pathway strongly affects IFN pathway activation via NF- κ B/RelA (Dai *et al.*, 2022).

Crosstalk between IFN and inflammasome signalling pathways: As mentioned previously, the cGAS-STING-TBK1-IRF3/7 pathway can induce IFN production in cells (refer to section 3.2.3). During inflammasome signalling, activated caspase-1 not only can splice pro-IL-1 β and pro-IL-18 (Schroder and Tschopp, 2010), it can also cleave cGAS, exerting a negative effect on IFN activation during DNA viral infection (Wang *et al.*, 2017). Also, RIG-I and MDA-5 activates MAVS upon binding to viral ssRNA, promoting the signalling of the NLRP3 inflammasome, not only to increase caspase-1 activation and NLRP3 inflammasome downstream molecule production, but also to promote the recruitment of the inflammasome to mitochondria, where mitochondrial reactive oxygen species and mitochondrial DNA (mtDNA) act as damage-associated molecular patterns to promote NLRP3 oligomerization and activation (Marchi *et al.*, 2022). mtDNA can also act as an agonist for cGAS, which promotes the cGAS-STING-TBK1-IRF3/7 pathway to promote type I IFN production (Dai *et al.*, 2022).

Effects of IFN signalling

IFNs induce the expression of ISGs, which increases the antiviral state of cells by increasing viral replication resistance and viral RNA translation suppression (Murphy *et al.*, 2017). IFNs also increase major histocompatibility complex class I expression, activate DCs, macrophages and NK cells to increase antigen presentation in cells and to kill infected cells (Murphy *et al.*, 2017).

Viral evasion of IFN responses

Despite the IFN system being part of the innate immune system, invading pathogens can still find ways to thwart or divert IFN responses (Zhu *et al.*, 2023). Firstly, viruses inhibit sensor proteins and their adaptors, such as directly disabling PRRs and blocking MAVS and STING (Andrejeva *et al.*, 2004; Varga *et al.*, 2012; Ma *et al.*, 2015). Viruses also target the activity of RLRs, cGAS and IFI16, which are regulated by multiple PTMs including phosphorylation, deamidation, ubiquitylation and ISGylation (Chiang and Gack, 2017; Song *et al.*, 2021) by targeting the responsible PTM enzymes or actively removing and adding regulatory PTMs, disrupting regulatory mechanisms required for their activation (Zhu *et al.*, 2023). Secondly, viruses shield their genetic material in membranous structures or vesicles, or modify the viral nucleic acids to remove

some key features that stimulates PRR activation, escaping immune detection by PRRs as a result (Wang *et al.*, 2011; Reynard *et al.*, 2014). Thirdly, virus destroy proteins that are critical in the innate immune response by inducing proteasomal, lysosomal or autophagy-based degradation (Meylan *et al.*, 2005; Han *et al.*, 2021; Zeng *et al.*, 2021), or by cleaving key regulators or elicit specific miRNA expression to “silence” the expression of innate immune factors (Hou *et al.*, 2016; Zhu *et al.*, 2023). Fourthly, viruses relocalize or seize innate signalling proteins instead of degrading them, preventing host proteins from performing their normal duties at the proper sites (Lifland *et al.*, 2012; Riedl *et al.*, 2019). Finally, viruses inhibit IFNAR signals by blocking STAT1 from binding to IFNARs (Talbot-Cooper *et al.*, 2022), inhibiting surface expression of IFNAR1 (Lubick *et al.*, 2015), promoting IFNAR1 degradation (Xia *et al.*, 2016), or sequestering IFNs prior to IFNAR binding (Symons *et al.*, 1995). Viruses can also suppress the JAK-STAT pathway by manipulating negative feedback inhibitory proteins of the SOCS family, or by impeding STAT1/2 phosphorylation or translocation (Zhu *et al.*, 2023).

ISG induction and expression in humans and bats

Invading viruses induce IFN production in cells, which upregulates ISG expression (Aso *et al.*, 2019). Mammal species, including humans and bats, have a set of common ISGs that is shared among all mammals and a set of species-specific ISGs (Shaw *et al.*, 2017). Here, the major differences between human and bat ISGs will be discussed.

Comparison of human and bat ISGs

There are over a hundred ISGs identified in humans, but while a number of bat ISGs have been identified in the past, the total number of bat ISGs remain undetermined (Zhang and Irving, 2023). Most human and bat ISGs share similar structures and functions, but notable differences are observed (Fuchs *et al.*, 2017; Benfield *et al.*, 2015; Jacquet *et al.*, 2022). Identified bat ISGs are summarized below (Figure 3), and a few will be highlighted.

MX genes

Exclusively induced by type I and III IFNs (Holzinger *et al.*, 2007), MX genes produce myxovirus resistance (MX) proteins, which are GTPases that inhibit IAV replication (Haller *et al.*, 2015). Bats have 2 MX paralogs, MX1 and MX2, while their human

counterparts are MXA and MXB respectively (Fuchs *et al.*, 2017). Although there were structural differences, where bat MX1 were found to be positively selected at both the N- and C-terminus, which was not found in human MXA (Fuchs *et al.*, 2017), human MXA and bat MX1 shared a mostly similar structure of a dynamin-like GTPase, with a globular GTP-binding domain at the N-terminal and a stalk-like C-terminal connected by a bundle-signalling element (Gao *et al.*, 2011), and conserved cis-acting ISRE motifs (Zhou *et al.*, 2013). Also, both human MXA and bat MX1 were functionally similar to each other in terms of antiviral capacity against influenza A virus (IAV), Indiana vesiculovirus (VSV) and La Crosse Virus (Zhang and Irving, 2023). This suggests MX genes are evolutionarily conserved in mammals due to high structural and functional resemblance. However, Fuchs *et al.* (2017) noticed species-specific MX protein antiviral effector function levels across six bat species. It could hence be estimated MX proteins of different bat species act differently on the same viruses. Also, only a few viruses were tested against MX1 proteins, so while bat MX1 proteins share conserved structures across varied species, its full functional capacity remains unknown. Besides, Zhou *et al.* (2016) reported a constitutively elevated expression of IFN- α in *Pteropus alecto*, which was not observed in humans, meaning that MX1 should be highly expressed at bat cellular level. However, Fuchs *et al.* (2017) demonstrated that MX1 was not highly expressed in normal bat cells, and the expression was only boosted upon IFN- α treatment. Yet, the role of IFN- γ was not examined in the study, and type III IFNs can induce MX protein expression (Holzinger *et al.*, 2007; Fuchs *et al.*, 2017). Therefore, it is possible that virus-induced type III IFN production in bats is more important for bat MX gene expression regulation while type I IFN production during viral infection in humans alone can control human MX gene expression.

IFITM3

IFITM3 gene belongs to the family of IFITM genes that encode for interferon induced transmembrane (IFITM) proteins (Shi *et al.*, 2021), which uses an amphipathic helix domain to mechanically change the membrane lipid arrangement of enveloped viruses, blocking membrane fusion and stopping viral infections as a result (Li *et al.*, 2013). Benfield *et al.* (2015, 2019) discovered human and bat IFITM3 had conserved antiviral functions, which may be

ISG	Species	Function
IRF1		Induction of IFN production and ISGs, regulation of ISGs, modification of JAK1 and STAT1 (Zhou et al., 2022)
IRF3/7		Formation of the IRF3/7 heterodimer to initiate IFN-I and IFN-III production and regulation (Ma et al., 2023)
DDX58		Sensing cytoplasmic viral nucleic acids and initiating IFN-I production (Yoneyama et al., 2004)
BST2		Blocking the release of enveloped viruses by tethering virions to infected cell membranes (Neil et al., 2008)
IFIH1		Sensing viral infection and inducing IFN-I and pro-inflammatory cytokines (Meng et al., 2017)
IFIT1		Sensing viral ssRNA and inhibit viral mRNA expression by binding specifically to PPP-RNA (Abbas et al., 2013)
IFITM3		Blocking membrane fusion by viruses by changing the membrane lipid arrangement of viruses (Li et al., 2013)
ADAR		Destabilizing viral dsRNA by RNA editing to deaminate adenosine to inosine (Szymczak et al., 2022)
APOBECs		Inducing viral ssDNA mutations during reverse transcription to ablate infection (Salter et al., 2016)
MORC3		Derepressing IFN-β upon degradation by virulence factor ICP0 (Fox & Lenschow, 2022)
Bats	MX1	 Inhibiting viral replication by acting as GTPases (Haller et al., 2015)
	MX2	 Inhibiting viral replication by acting as GTPases (Haller et al., 2015)
	OAS1a/b	 Sensing viral dsRNA and activating the innate immunity to exert antiviral effects (Yang et al., 2023)
	OAS3	 Catalysing the 2' and 5' oligomers of adenosine to activate RNase L (Gene, 2004-)
	PKR	 Sensing cell stress and arresting viral replication by phosphorylating eIF2 (Sadler & Williams, 2007)
	TRIM6/34/5/22 gene cluster	 Degrading retroviral capsids, signalling through polyubiquitination and direct autophagy (Vunjak & Versteeg, 2019)
	USP18	 Inhibiting IFN-I signalling to enforce viral replication, hence activating adaptive immunity (Honke et al., 2016)
	RNASEL	 Degrading viral and cellular ssRNA in bats upon IFN signalling activation (Zhou et al., 2005)
	RTP4	 Decreasing association between viral polymerase and helicase to viral RNA (Boys et al., 2021)
	ISG15	 Inhibiting viral replication and controlling IFN release and host signalling pathways (Perng & Lenschow, 2018)

Figure 3: Antiviral effector ISGs in bats. Adapted from: Zhang and Irving, 2023.

explained by the conserved functionally important amino acid residues at the CD225 domain, including 3 S-palmitoylated cysteine residues, ubiquitinated lysine residues, residues crucial for endosomal targeting, oligomerization control and viral restriction mediation. However, this experiment was conducted on microbats only, and it is unknown if the same phenomenon will be observed in other bat species.

Also, codon 70 of *IFITM3* is not conserved between 4 species of microbats, and mutations in codon 70 of microbats had shown reduced antiviral restriction against Zika virus (ZikaV) and an increased restriction against Semliki Forest virus (SFV) and IAV (Benfield et al., 2019). This shows that *IFITM3* function in antiviral restriction may vary across different mammal species and the viral species also has an impact on the

antiviral function displayed by IFITM3, meaning the functionality of ISGs in general may be affected by the pathogen itself, and that the reason bats showing a higher ability in harbouring viruses whilst remaining asymptomatic may be explained by multiple bats ISGs having a stronger antiviral restriction due to mutations in bat ISGs that are not found in the human analogues. The combined antiviral effect displayed in bat ISGs may hence be higher than human ISGs as a result of these small differences in the sequence of the ISGs between bats and humans.

ISG15

ISG15 encodes for interferon stimulated gene 15 ubiquitin-like modifier (ISG15), a ubiquitin-like protein that directly inhibits viral replication via conjugating viral proteins, inhibiting virus egress and modulating viral latency (Perng and Lenschow, 2018). ISG15 also regulates immune responses by controlling IFN release, host damage and repair pathways, and host signalling pathway that inhibits viral infection (Perng and Lenschow, 2018). Although human and bat ISG15 shared a conserved anionic patch between the two ubiquitin-like β -grasp folded domains, human and bat *ISG15* only share a 58% sequence identity, and the affinity of bat ISG15 was lower than the human analogue (Langley *et al.*, 2019). Also, the hinge region composition of the bat ISG15 allows the formation of a type I reverse turn which is absent in the human analogue (Dzimianski *et al.*, 2019). These structural differences between bat and human ISG15 had been shown to impact virus protein-protein interactions, where the non-structural protein 1 of influenza B viruses (NS1B) only interact with human and non-human primate ISG15, but not bat ISG15 (Sridharan *et al.*, 2010). Mutations in the hinge regions of human ISG15 have also been found to have drastic impacts in the binding of NS1B to ISG15 (Jiang and Wang, 2018). This therefore suggests that ISG structural differences may have an impact on host susceptibility towards certain viruses, which may make bats good asymptomatic reservoirs for viruses due to its lower susceptibility towards more viruses compared to humans. Also, Langley *et al.* (2019) observed differences in the structures of ISG15 in the whole Chiroptera order that is limited to the genus level, indicating possible variations in the antiviral functions and levels displayed by ISG15 across different bat species. This further suggests that the antiviral abilities shown by ISGs across different bat species are varied.

RNASEL

RNASEL encodes for the protein ribonuclease L (RNase L), a ubiquitous endoribonuclease that degrades viral and cellular ssRNA upon IFN signalling activation (Zhou *et al.*, 2005) in bats (De La Cruz-Rivera *et al.*, 2018). Bat RNase L was highly inducible by IFNs, but human RNase L was not (De La Cruz-Rivera *et al.*, 2018). Also, the induction kinetics of human and bat RNase L were different at the ending stages, where a decline was found in bats but not in humans (De La Cruz-Rivera *et al.*, 2018). This resulted in a slower 2'-5'-oligoadenylate synthetase (OAS)-RNase L pathway activation in bats (Li *et al.*, 2019), leading to a slower type I and III IFN activation and thus a slower *OAS* gene induction and expression in bats (Banerjee *et al.*, 2019). However, whether bats have an alternate method to compensate the reduced levels of IFN production via the OAS-RNase L pathway remains unknown. One possible mechanism is other positive regulators, such as PKR, IRF3 and IRF7, have a higher expression levels in bats than in humans upon induction of the initial wave of IFN production after detection of viral PAMPs, leading to more production of IFNs, forming a stronger positive feedback loop in IFN production and ISG induction in bats.

TRIM5 α

TRIM5 α encodes for tripartite motif-protein 5 α (TRIM5 α), a retroviral capsid-targeting protein family that stops viral infection before or during reverse transcription (Ohkura *et al.*, 2023). It is part of the *TRIM6/34/5/22* gene cluster, which are heavily involved in antiviral innate immune responses (Bharaj *et al.*, 2016; Fernandes *et al.*, 2022). TRIM5 α could act against human immunodeficiency viruses (HIV) and murine leukaemia virus (MLV) in humans but could only act against MLV in bats (Morrison *et al.*, 2020; Ohkura *et al.*, 2023). Morrison *et al.* (2020) found viral restriction against HIV in bats was done by MX2 and a non-TRIM5 α cyclophilin A-based ISG product. Also, the makeup of the *TRIM6/34/5/22* gene cluster in humans and bats are different, where humans only have one copy of *TRIM5 α* in the cluster while some bat species do not have *TRIM5 α* , and others contain multiple copies, and that the gene arrangements in the cluster is different across multiple bat species and humans (Fernandes *et al.*, 2022). Besides, the PRYSPRY domain of TRIM5 α , which is crucial for recognition of viral capsids and restriction of virus function (James *et al.*, 2007), differed strongly in

humans and bats, which is caused by evolution from the strong selective pressure ensued by the viruses on bat *TRIM5α* (Fernandes *et al.*, 2022). This suggests that due to higher exposure of bats to viruses as a reservoir host, bat ISGs are more rapidly evolved to defend against a variety of viruses. Moreover, bats having multiple copies of *TRIM5α* may be beneficial in adapting against newly exposed viruses without dampening restriction against known viruses by allowing independent mutations (Fernandes *et al.*, 2022). This phenomenon may extend beyond other ISGs, hence creating a more all-rounded immune defence against viruses compared to humans.

Fundamental differences between human and bat innate immune system

DNA sensing and inflammasome activation

The pyrin and HIN domain (PYHIN)-containing gene family are the only found DNA sensors in the innate immune system that can activate inflammasomes (Härtlova *et al.*, 2015), which is important in initiating an inflammatory response in the host via IL-1 β and IL-18, leading to pyroptosis and removal of the infected cell (Jacobs and Damania, 2012). Ahn *et al.* (2019) discovered the entire PYHIN gene family appeared evolutionarily lost despite finding its locus across multiple bat species, and NLR family pyrin domain containing protein 3 (NLRP3) inflammasome activation was therefore severely dampened, reducing IFN production (Figure 4). Clayton and Munir (2020) suggested this was due to metabolic adaptations for flight, which limited excessive inflammation activation and IFN production regulation normally initiated by PYHIN gene family proteins. Therefore, bat cells may be able to activate inflammasomes via a non-PYHIN-containing DNA sensor. Alternatively, the inflammasome may be activated by other activators, including ion fluxes, mitochondrial reactive oxygen species and lysosomal damage (Blevins *et al.*, 2022). Viral entry into bats may trigger the bat cells to release more ions and mitochondrial reactive oxygen species and to activate lysosomes, leading to the activation of the NLRP3 inflammasome. Also, the expression of positive regulators to IFN production normally induced by PYHIN genes, such as IRF3 and PKR, may be induced by other mechanisms, resulting in a rise in IFN level. One possible mechanism is TANK-binding kinase 1 (TBK1), which phosphorylates IRF3 to drive IFN- β production, may be activated via autophosphorylation

(Clark *et al.*, 2011). The self-activation of TBK1 may be a common phenomenon in bat cells, promoting IFN production. Another mechanism is through the post-translational modifications of lysine residues in TBK1 by K63-linked polyubiquitin chains in bat cells, which drives IFN release (Li *et al.*, 2011).

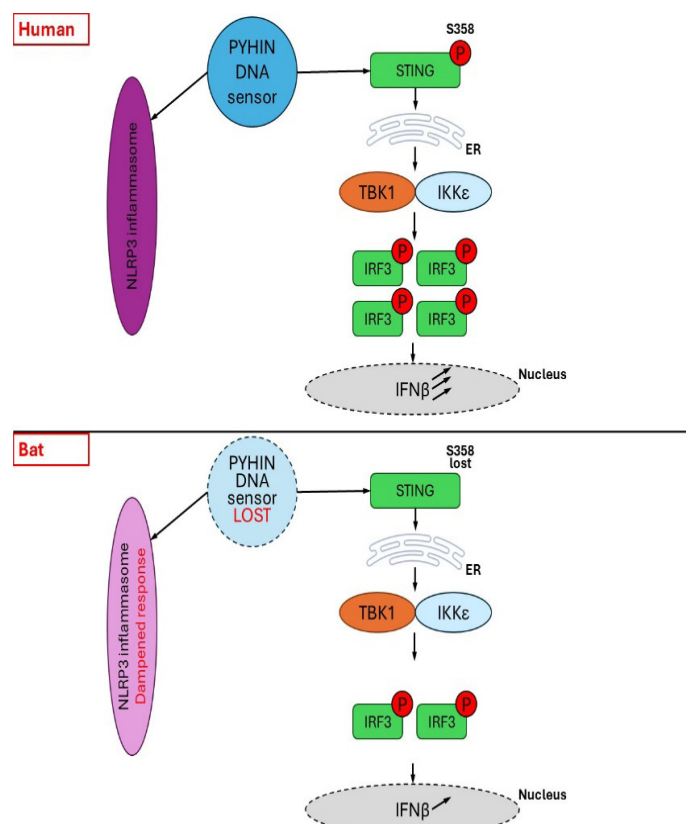


Figure 4: The comparison of human and bat STING and inflammasome activities within a cell. The lost PYHIN gene family DNA sensor in bats leads to a dampened NLRP3-mediated inflammasome response, which also impacts the action of STING, which in bats lacks a serine residue, reducing its functionality (Clayton and Munir, 2020).

STING in humans and bats

Part of the cGAS-STING-TBK1-IRF3/7 pathway, STING is an adaptor protein which recognizes self and pathogenic DNA in the cytosol and regulates IFN production (Barber, 2015; Zhang *et al.*, 2022). Xie *et al.* (2018) found the loss of the PYHIN gene family DNA sensor not only dampened NLRP3 inflammasome activation, but also the function of STING due to a replaced S358 serine residue. As a result, less TBK1 and inhibitor of nuclear factor kappa-B kinase subunit epsilon (IKK ϵ) were activated to phosphorylate IRF3 (Ding *et al.*, 2020), leading to less IFN activated in bats via this pathway (Figure 4) (Liu *et al.*, 2015). However, Fu *et al.* (2023) found in *Tadarida brasiliensis*

1 lung (TB1 Lu) cells that under cGAS stimulation, STING proteins in TB1 Lu cells were activated, inducing IFN- β production and ISG activation upon infection by Newcastle disease virus (NDV), VSV and avian influenza virus (AIV), suggesting that either the loss of function of STING proteins in bats may only be limited to certain bat species, and STING proteins still play a role in bats to combat against viruses, or the effect of the loss of the S358 serine residue on the function of the STING protein in bats is not as large as estimated in other bat species.

Human and bat immunological approaches

Bats had been demonstrated to possess great abilities in controlling intracellular pathogens, including viruses (Pereira *et al.*, 2023). This is achieved through the overexpression of *ANXA1* and *MRC1* genes, which regulates inflammation (Han *et al.*, 2020; Ibrahim *et al.*, 2020), and the basal expression of certain ISGs including *ISG15*, *IFIT1* and *OAS3* without induction by pro-inflammatory genes (Schountz *et al.*, 2017), a phenomenon not found in humans. Besides, the type I IFN loci of humans and bats differs. Zhou *et al.* (2016) discovered a severely contracted type I IFN locus in the genome of *P. alecto* with only 3 functional IFN- α genes in bats compared to 12 in humans (Zhou *et al.*, 2016; López de Padilla and Niewold, 2016), while an expansion is observed in *Rousettus aegyptiacus*, *Pteropus vampyrus*, and *Myotis lucifugus* (Kepler *et al.*, 2010; Pavlovich *et al.*, 2018). The contraction is found to be driven by IFN- α but not by other type I IFNs (Zhou *et al.*, 2016; Scheben *et al.*, 2023), while the expansion is mainly driven type I IFNs other than IFN- α (Al-Eitan *et al.*, 2023). For example, *R. aegyptiacus* contain 22 IFN- ω while humans only have 1 copy (Pavlovich *et al.*, 2018). Moreover, IFN- α 1 mRNAs were only found in the spleen, kidney and liver of humans, but they were found in all organs in bats (Zhou *et al.*, 2016). Furthermore, Zhou *et al.* (2016) observed a constitutive expression of IFN- α in *P. alecto* that is not observed in humans, and the high interferon levels, which are toxic to mammalian cells apart from bats (Smith and Wang, 2013), provides a high and permanent protection niveau to bats against viruses (El-Sayed and Kamel, 2021). Such differed IFN-I and other gene expression patterns suggests different mechanisms of viral control may be implemented in humans and bats.

Bat PKR adaptations

Protein kinase R (PKR) is a protein encoded by the

ISG *PKR* in both humans and bats, which acts as a stress sensor in cells that detects and arrests viral replication by phosphorylating the alpha subunit of the transcription factor eIF2 (Sadler and Williams, 2007). Jacquet *et al.* (2022) discovered *PKR* had undergone positive selection and multiple genomic duplications in bats, a phenomenon not observed in humans. Duplicated *PKR* in bats diversified genetically, allowing bats to escape from and enhance control to viruses (Jacquet *et al.*, 2022), which may explain the ability of bats to be an asymptomatic viral carrier, and can conduct viral spillover effectively by having multiple copies of *PKR* acting against a multitude of viruses.

Diversity and lineage-specific innate immune response in bats

Unlike humans, which are only made of one species (*Homo sapiens*), there are over 1400 bats species worldwide (Arnaout *et al.*, 2022). Although all bats shared a certain proportion of genes, a lot of them were different across the species. Jacquet *et al.* (2022) identified differences in the bat antiviral repertoire across different bat species in a lineage-specific manner, and this was brought about by gene diversification of *PKR*. Also, as mentioned above, many other ISGs (e.g. *MX* and *ISG15*) are different across species level in bats in terms of expression patterns and functions. This suggests there may be functional diversity in bat innate defence via IFNs and ISGs.

Bat physiological adaptations

Being the only mammal capable of flight (O'Shea *et al.*, 2014), bats have certain physiological adaptations to cope with the energy requirements through metabolism (Apoorva and Singh, 2024). One hypothesis known as the "flight-as-fever hypothesis" suggested that flying increases the metabolic rate, hence increasing the body temperature (O'Shea *et al.*, 2014), mimicking the effects of a fever during an infection, which may improve viral tolerance of bats (Eisenstein, 2018). Also, the increased metabolic rate in bats due to flight also increases the amount of reactive oxygen species, leading to increased oxidative damage towards self-DNA, leading to the activation of immune responses towards damaged DNA (O'Shea *et al.*, 2014). Since the robust immune response towards damaged self-DNA requires a lot of energy, bats are thought to adapt mechanisms to suppress inflammatory responses (Irving *et al.*, 2021). These physiological adaptations and immunological

suppression allows better defence against viruses for bats, and also allows them to be asymptomatic carriers of multiple viruses simultaneously.

Scientific gaps

Incomplete bat genomic annotation

The genomic annotation of bats is still incomplete, where only a limited selection of cell lines from a few bat species are available for research (Clayton and Munir, 2020). Although the Bat1K project had provided more genomic annotations for bats in recent years (Jebb *et al.*, 2020), only 83 bat species out of the 1400 are currently annotated (Bat1K, 2024). As a result, the full bat-virus relationship remains unclear due to limited number of bat colonies and reagents available for research, and the results generated from previous research may be biased towards certain bat species (Clayton and Munir, 2020). Without the full genomic annotation, it would be difficult to conclude on how the bat innate immune system identify and eradicate invading pathogens as it will be impossible to identify the ISG differences between species in the protein and genetic structural level, which may allow better understanding of the interactions of the bat innate immune system with viruses.

Limited understanding towards bat-virus relationship

There were little previous research on the bat-virus relationship, such as their co-evolution and how do bats become effective asymptomatic pathogen carriers. Also, while light has been shed on bat IFN production and signalling as part of their innate immune response (Clayton and Munir, 2020), the full picture of the bat immune system and how it reacts with viruses remains unclear.

Bias in studies leading to inaccurate conclusions of bat-virus relationships

Despite efforts within the scientific community to advance the understanding of the bat innate immune system, biases in these studies led to inaccurate conclusions to the relationship between bats and viruses (Weber *et al.*, 2023). There are many differences in the behaviour, characteristics and environments between wild bats and bats used in the experiments. For example, wild bats may be infected by or carrying a multitude of pathogens, but such heterogeneity is lost in the lab, which may cause the bat cells to be in a different immune state (Clayton and Munir, 2020). Moreover, some viruses

used in the labs are from human-borne isolates that had undergone propagations and mutations, which fails to represent the original bat viral isolate (Clayton and Munir, 2020). This may cause current results generated in the experiments incapable of reflecting the true picture of how the bat innate immune system works. Moreover, the viruses used in the laboratories for the studies may not fully represent the diversity or proportionality of the virus due to adaptations to the laboratory environment. Therefore, the results may not fully represent how bats and human cells act against viruses in the environment. In addition, the predominant use of a select subgroup of bat species in experiments, the preferred use of cave and cave-like environments as study sites, and intrinsic biases in viral genetic material detection in bats through PCR amplification of specific partial sequences and of viral RNA or DNA in bat cells or direct viral isolation, all contribute to biased findings (Weber *et al.*, 2023). As a result, the conclusions disproportionately represent certain species instead of encompassing the entire Chiroptera order (Clayton and Munir, 2020; Weber *et al.*, 2023). Moreover, the lack of ecological and life history data supplied in these studies hinders the understanding towards viral maintenance and infection dynamics (Weber *et al.*, 2023). To achieve a more thorough knowledge of how viruses persist in bats and whether bats act as reservoir hosts for viral spillovers, it is crucial to improve data collection methods. This can be done by studying a wider range of bat species, selecting other natural bat habitats as study sites, using viral genetic material detection techniques that indicates viral replication instead of mere presence which may be caused by exposure to the viruses, and including ecological and life history data of bats in the research.

Viral co-infections in bats

Co-infection refers to the simultaneous or successive infection of the same host by multiple infectious agents, such as viruses, bacteria and fungi (Du *et al.*, 2022). Co-infecting agents were found to have facilitating and competing dynamics with one another (Pantin-Jackwood *et al.*, 2015), and their interactions had effects on susceptibility and severity of infections, agent transmissibility, host-host contact rate, infectiousness duration and disease transmission (Vaumourin *et al.*, 2015; Jones *et al.*, 2023). Although efforts had been made in recent years to understand more particularly in viral co-infection in bats (Jones *et al.*, 2023), bias towards studying certain bats in the

suborder Yinpterochiroptera, which only represents around 30% of bat diversity (Simmons and Cirranello, 2024), and RNA viruses with zoonotic potential, as well as the low priority of studying the effect of co-infections in bat-virus research all led to the lack of understanding of the effect of viral co-infection in disease transmission and viral spillover (Jones *et al.*, 2023). By furthering the understanding towards viral co-infections in bats, the dynamics of virus-virus and bat-virus interactions can be clearer, and hence the ability of bats to remain asymptomatic whilst infected by multiple viruses can be understood.

Conclusions and Recommendations

Both humans and bats share IFN production and ISG induction and expression in their innate immune systems. However, despite discovering more ISGs in bats, challenges like incomplete bat genetic annotation, a lack of understanding of bat-virus interactions and viral co-infection, and biases in bat-virus relationship studies persist. To further understand bat-virus relationships and control of bat-borne viral infections, it is crucial to complete the genetic annotation, develop wild-like environments when studying the bat immune system, improving data collection methods and conducting further studies on bat immunity. This will greatly contribute to the prevention of pandemics in the future.

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Novelty Statement

This review paper provides a comprehensive overview of the immune system, as well as a comparison between innate immune responses in humans and bats, in particular on interferon-stimulated genes (ISGs). This review also provides an insight on possible scientific gaps in understanding bat antiviral immunity, as well as suggesting possible methods to improve the understanding towards the differences in human and bat immunity against viruses. While previous studies focused on individual components of bat immunity and its similarities and differences with humans, this

review integrates these components to provide a more holistic overview towards the current understandings and future perspectives of bat immunity, offering valuable possible directions of focus in improving studies related to bat antiviral innate immunity, which can contribute to understanding the dynamics of the emergence of bat-borne viruses, making this review paper a useful resource in response to an increase in interest of studying bat-virus interactions.

Conflict of interest

The author has declared no conflict of interest.

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