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# Immune Response to Viruses

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<b>Immune system</b>	<b>1</b>
<b>Innate immunity - First line of host defense</b>	<b>1</b>
The skin	1
Mucosal surfaces	2
<b>Innate immunity - viral recognition</b>	<b>3</b>
Pattern recognition receptors (PRRs)	3
Toll like receptors (TLRs)	3
C-type lectin receptors (CLRs)	4
Retinoic acid inducible gene-I (RIG-1) like receptors (RLRs)	4
Nucleotide-binding oligomerization domain-like receptors (NLRs)	4
Cytosolic DNA sensors	5
<b>Downstream signalling after PRR activation</b>	<b>5</b>
Interferon (IFN) pathway	6
NK- $\kappa$ B pathway	6
Mitogen-activated protein kinase (MAPK) pathway	6
<b>Innate immune cells in the antiviral response</b>	<b>6</b>
Natural killer (NK) cells	7
Neutrophils and neutrophil extracellular traps (NETs)	7
<b>Adaptive immune cells in the antiviral response</b>	<b>7</b>
B cells and antibody	7
Cytotoxic T lymphocytes (CD8+)	8
Cytotoxic T lymphocytes (CD4+)	8
Natural killer T cells (NKT)	9
<b>Viral avoidance of the immune response</b>	<b>9</b>
Interference of viral antigen presentation on MHC class I molecules	9
Antigenic variation (antibody escape)	9
Modulation of PRR signalling	10
Modulation of the IFN response	11
Hiding within immune cells	11
Viral latency	11
<b>References</b>	<b>11</b>

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## Immune system

The immune system is a tightly regulated, complex system of tissues and cellular components (immune cells, lymph nodes and mucosal tissues), and humoral components (antibody, antimicrobial proteins, and complement proteins), that have evolved to work in unison to protect us from infectious diseases. The immune system can also be broken down into innate immunity and adaptive immunity. The innate immune system is a rapid non specific response that helps the body prevent infection from pathogens never encountered before, prior to an antibody response being developed. The adaptive immune system is a slower more pathogen specific response (B cells/T cells). In this chapter we will discuss the above components of the immune system in relation to viral infections. Specifically, how we recognise and respond to viral infections, and ways in which viruses have evolved to try to avoid the host immune system.

## Innate immunity - First line of host defense

Before we progress to the key components of the immune system we will first look at the initial barriers that viruses must cross in order to initiate infection, and ways in which the body tries to counteract this. The main routes of pathogen entry into the body are via the mucosal surfaces and the skin.

## The skin

The skin, the largest organ of the body, is a very strong physical barrier, that many pathogens find impenetrable. Alongside the physical barrier, the skin is also inhospitable to many pathogens, containing antimicrobial peptides that can kill pathogens (Handfield et al., 2018). It is also covered in commensal skin flora that promote wound healing and restrict the growth of other microbes (Robinson and Pfeiffer, 2014).

Despite this many viruses utilise this as a route of entry into the host, discussed in detail in Bomsel and Alfsen (2003) and Lei et al. (2020). This includes as examples, Human papilloma viruses (HPV) and Herpes Simplex viruses (HSV). Although these infect via the skin an abrasion of some sort is required for viral entry into the body and for infection to occur. Other viruses bypass the skin barrier by transmitting via vectors, that again penetrate the skin barrier. Some examples of common vectors include Mosquitos, Ticks, Fleas, Sandflies. With mosquitos being a common vector aiding transmission of many human viruses, such as Zika virus, Dengue fever virus (DENV), Yellow Fever virus (YFV) and Chikungunya virus (Onyango et al., 2020).

## Mucosal surfaces

Other key entry points for viruses and other pathogens into the body include the mucosal surfaces (Bomsel and Alfsen, 2003). This includes the mouth, nose, eyes, respiratory tract, gastrointestinal tract, urinary tract and reproductive tract. With the respiratory and gastrointestinal tract being the main sites of viral entry. All these sites have an arsenal of antimicrobial agents, specialist cells types, mucosal antibody (mainly secretory IgA) and some have inhospitable conditions (low pH). Further they are resident to an array of immune cells that patrol these entry points to prevent pathogen invasion and infection. Some of which we will discuss briefly here in relation to viral infections and are reviewed in Sato and Kiyono (2012) and Holmgren and Czerkinsky (2005).

One clear example of how viruses are able to manipulate these mucosal sites to aid infection and transmission, is seen during infection of the respiratory epithelium by respiratory viruses. The respiratory tract is lined by specialised cell types, mainly the ciliated epithelial and goblet cells, both key for the proper functioning of the mucociliary escalator (Kilburn, 1968; Tam et al., 2011). Ciliated airway epithelial cells (AECs) line the vast majority of the respiratory epithelium and beat in a coordinated directional manner to remove mucus from the airways. This mucus, produced by goblet cells, lines the epithelium and traps pathogens and other inhaled particulates, which is then removed from the airways by ciliated AECs (Jeffery, 1983). Malfunctioning of these cells and the mucociliary escalator, like that seen in conditions such as cystic fibrosis and primary ciliary dyskinesia, results in chronic respiratory infections and lung damage (Wijers et al., 2017; Afzelius, 1976; Boucher, 2007).

The functioning of the mucociliary escalator can also be temporarily damaged due to infection (Pittet et al., 2010). Either through generalised damage to the respiratory epithelium as seen during Influenza virus infection (Plotkowski et al., 1986; Nugent and Pesanti, 1983; Short et al., 2014), or by targeted infection of the ciliated epithelial cells. The latter is a feature seen for many of the common respiratory viruses, such as Respiratory Syncytial Virus (RSV), Rhinovirus (RV) C and some of the Severe Acute Respiratory Syndrome associated Coronaviruses (SARS-CoV). RSV has been shown to specifically targets the ciliated AECs, causing ciliary loss (shedding) and ciliary dyskinesia (uncoordinated movement of the ciliated cells) (Zhang et al., 2002; Smith et al., 2014). The most recently discovered RV species, RVC, has also been shown to target the ciliated epithelium for viral entry and infection leads to shedding of the infected cells, reducing the number of ciliated cells present within the epithelium (Griggs et al., 2017). The receptor used for SARS-CoV infection, angiotensin-converting enzyme 2 (ACE2), has also been shown to be preferentially expressed on ciliated AECs, and targeted infection of these cells causes cell death and shedding into the airway (Li et al., 2003; Sims et al., 2005). Due to the fact SARS-CoV-2 also used ACE2 as its receptor, the viral cause of the 2019 global pandemic, this virus has also been shown to target ciliated cells for infection (Ahn et al., 2021; Zhu et al., 2020). Studies have similarly shown this leads to damage to the ciliated cells and cell shedding into the lower airways, and has been shown to perturb mucociliary clearance (Robinot et al., 2021). Some strains of Influenza A virus (IAV) also show a tropism for ciliated cells (Ibricevic et al., 2006).

Other routes of viral entry into the host and examples of viruses that utilise these routes are summarised in Table 1.

**Table 1** Examples of viral pathogens that utilize different entry routes into the host.

Entry route	Viruses
Mouth, Nose, Eyes	RV, Ebola virus (EBOV), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV)
Respiratory tract	IAV, SARS-CoV, SARS-CoV-2, RSV, RV
Gastrointestinal tract	Norovirus, Rotavirus
Urinary tract	Uncommon in immunocompetent hosts
Reproductive tract	Human immunodeficiency virus (HIV), Hepatitis C virus (HCV), EBOV, CMV
Skin	Abrasion – Human papilloma virus (HPV), Herpes Simplex virus (HSV), EBOV, HIV Vector - Zika virus, YFV, DENV

## Innate immunity - viral recognition

Once these barriers are breached pathogens are detected by epithelial cells, patrolling immune cells, or antibody, which initiate an immune response to aid pathogen clearance.

### Pattern recognition receptors (PRRs)

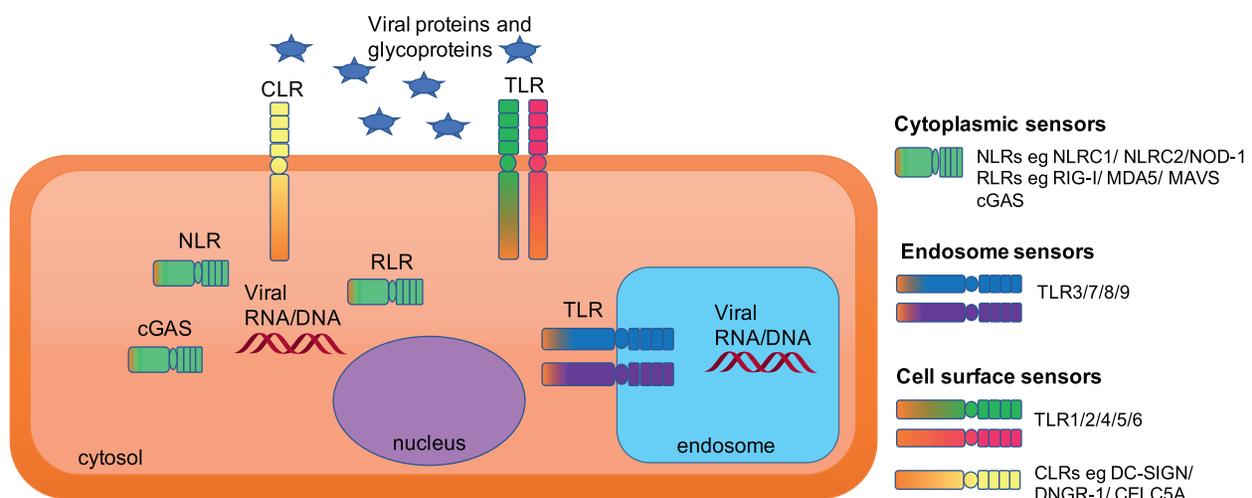
Key component of the innate immune system are pattern recognition receptors (PRRs). These are present on the cell surface of a number of different cell types (immune cells, epithelial cells, endothelial cells etc), and recognise components shared by many pathogens, which are not present in the host, distinguishing self from non self (Janeway, 1989, 2013; Takeuchi and Akira, 2010). These are known as Pathogen Associated Molecular Patterns (PAMPs). PAMPs include things such as lipopolysaccharide (LPS), flagellin, peptidoglycan, which are present on the surface of different bacterial pathogens. They also recognise the genetic material of some viruses (dsRNA/ssRNA), and other ubiquitous components shared by other microorganisms (fungi, parasites) (Takeuchi and Akira, 2010). The ability to recognise different pathogens depend on which PRRs cells have, and therefore dictate the ensuing immune response. Pathogens will often activate multiple PRRs allowing cross talk between receptors and a more robust immune response.

The location of PRRs also varies within the cell, some are present on the cell surface (plasma membrane) and recognise extracellular pathogens. These are mainly present on immune and epithelial cells. Other PRRs are present within the cells and recognise intracellular pathogens, such as viruses (endosome membrane/cytoplasm). Intracellular PRRs can also be membrane bound and present within the endosome membrane or free within the cytoplasm. These are often found in all cell types (Chan and Gack, 2016). PRR cellular localisation is summarised in Fig. 1.

There are four main groups of PRR. Toll Like receptors (TLRs) are the most widely studied, C-type lectin receptors (CLRs), Retinoic acid inducible gene-I (RIG-1) like receptors (RLRs) and Nucleotide-binding oligomerisation domain-like receptors (NLRs). Cytosolic DNA sensors are another group of recently discovered PRRs (Chan and Gack, 2016). We will discuss the above in more detail below in relation to their role in recognition of viral pathogens.

### Toll like receptors (TLRs)

In humans there are 10 functional TLRs (Medzhitov, 2001; Takeda and Akira, 2005). These are found as heterodimers or homodimers in the plasma membrane or endosome membrane (Lester and Li, 2014). TLR1, 2, 4, 5, 6, 10 are found in the plasma membrane, and TLR3, 7, 8, 9 in the endosome membrane (recognise intracellular pathogens). These signalling molecules consist of a extracellular domain that recognises PAMPs and an intracellular domain that has cell signalling capabilities, known as the Toll Interleukin Receptor (TIR) domain. TLRs present within the endosome have the signalling domain present within the cell cytoplasm and PAMP recognition domain present within the endosome. TLR3, 7 and 8 are the main TLRs that detect the presence of viral genetic material. TLR3 recognises dsRNA, and TLR7/8 ssRNA, which can either be the composition of the viral genome or it can be an intermediate produced during viral replication (Alexopoulou et al., 2001; Heil et al., 2004; Lund et al., 2004).



**Fig. 1** Cellular localisation of Pattern recognition receptors (PRRs). Schematic shows the cellular localisation of PRRs. TLRs are located in the plasma membrane and endosome membrane. Those present in the plasma membrane detect extracellular pathogens and those within the endosome intracellular pathogens. The pathogen recognition domain is present outside of the cell (plasma membrane TLRs) or within the endosome, with the c-terminal signalling domain being present within the cytosol for both. CLR PRRs are also present within the plasma membrane and recognise extracellular pathogens. NLRs, RLRs and cGAS PRRs are all present within the cell cytosol and recognise intracellular pathogens.

As well as recognising viral genetic material, viral proteins have also been shown to activate a number of the cell surface exposed TLRs. Some examples include the cell surface exposed F protein of RSV, which can directly activate TLR4 (Funchal et al., 2015). This is also the case for the non structural protein (NSP) 1 of DENV, and surface glycoprotein of EBOV, which both also directly activate TLR4 (Modhiran et al., 2015; Okumura et al., 2010). Examples of TLR2 being directly activated by viral proteins include that of the measles hemagglutinin protein and the NSP4 of rotavirus (Bieback et al., 2002; Ge et al., 2013).

Once activated the TLRs undergo a conformational change which leads to recruitment of adaptor proteins to the signalling domain, this includes proteins such as Myeloid differentiation factor 88 (MYD88) (TRL7/8) or TIR-domain-containing adapter-inducing interferon- $\beta$  (TRIF). This can also include Toll-interleukin-1 Receptor domain-containing adaptor protein (TIRAP) and TRIF-related adaptor molecules (TRAM)) (Takeuchi et al., 2000; Hayashi et al., 2001; Kawai et al., 1999). These activate a downstream signalling cascade which eventually leads to the translocation of transcription factors into the cell nucleus, which alters gene expression. This includes transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), Activator Protein 1s (AP1s) and Interferon Regulatory Factor (IRF) 3/IRF7, which are the end products of the NF- $\kappa$ B, Mitogen activated protein (MAP) kinase and Interferon (IFN) signalling pathways respectively, resulting in expression of key genes of the innate immune system (discussed below). Signalling through TLRs is discussed in more detail in (Kawasaki and Kawai (2014); Takeda and Akira (2005))

### ***C-type lectin receptors (CLRs)***

The function of C-type lectin receptors in antiviral immunity and downstream signalling is nicely summarised in Bermejo-Jambrina et al. (2018) and Geijtenbeek and Gringhuis (2009). C-type lectin receptors are present within the plasma membrane of the host cell and recognise extracellular pathogens. They are predominantly on immune cells, such as dendritic cells (DCs) and macrophages. These PRRs recognise carbohydrate structures (recognised through their carbohydrate recognition domain), present on the pathogen surface glycoproteins such as mannose, glucan and fucose. Mannose being the one most predominantly recognised on viral pathogens. Some examples of these receptors which recognise viral pathogens includes DC-SIGN, which recognises mannose on Human immunodeficiency virus (HIV) and IAV (Gringhuis et al., 2007; Yu et al., 2017), DNGR-1 is able to recognise the vaccinia virus (Iborra et al., 2012) and CELC5A has been shown to recognise Japanese encephalitis virus (JEV) glycoproteins (Chen et al., 2012).

Downstream signalling after activation of the CLR is complex and the pathways activated varies depending on the CLR activated. Signalling through CLRs is summarised nicely in Geijtenbeek and Gringhuis (2009). Some CLR signalling pathways also cross talk with TLR signalling pathways further complicating the downstream signalling (Meyer-Wentrup et al., 2009). Activation of the IFN and NF- $\kappa$ B signalling pathways, is similarly to TLRs, a key feature of activation of CLRs. However, as these receptors are predominantly on professional antigen presenting cells (APCs) the viral antigens are internalized and processed for presentation to T cells on major histocompatibility complex (MHC) molecules. Due to the antigen being from an extracellular source these are processed and expressed on MHC class II molecules and presented to CD4+ T helper cells (Engering et al., 2002; Gurer et al., 2008). DCs also possess a special ability to cross present exogenous antigen (extracellular) on MHC class I molecules (normally present intracellular antigens to T cells), allowing presentation of antigen to CD8+ cytotoxic T cells, which are key for the antiviral immune response (Schreibelt et al., 2012; Iborra et al., 2012; Zelenay et al., 2012).

Although activation of these PRRs is important in the induction of the antiviral immune response (Long et al., 2013; Chen et al., 2012). There are also multiple cases where viruses have adapted to avoid these receptors and can also use these receptors to aid infection and propagation, some examples include HIV, EBOV and Hepatitis C virus (HCV) (Hodges et al., 2007; Simmons et al., 2003; Ludwig et al., 2004).

### ***Retinoic acid inducible gene-1 (RIG-1) like receptors (RLRs)***

RIG-like-receptors are a trio of RNA helicases proteins with the RIG-1 being the most recognisable member of the RLR family. Followed by melanoma differentiation antigen 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2). All three have a key role in the cellular recognition of RNA viruses (Kell and Gale, 2015; Loo and Gale, 2011). During non-infectious periods, RLR proteins act as sentinels for viral PAMPs and are ubiquitously expressed at low levels in the cell. Both RIG-1 and MDA5 have a c-terminal caspase activation and recruitment domains (CARDs) which directly interacts with other downstream signalling molecules activating an immune response (Loo and Gale, 2011). Upon viral RNA recognition, these proteins change their structural conformation activating a downstream signalling cascade, eventually forming a complex with the mitochondrial antiviral signalling (MAVS) adaptor protein. Resulting in preferential expression of the type III IFNs and other interferon stimulated genes (ISGs) (Dixit et al., 2010; Chan and Gack, 2016).

These receptors have been shown to be key in recognising infection by a number of important viruses such as IAV, HCV, Hepatitis B virus (HBV), West Nile virus (WNV), picornaviruses etc. However, these viruses have evolved mechanisms to avoid detection via RLRs and some of these are summarised in Chan and Gack (2016).

### ***Nucleotide-binding oligomerization domain-like receptors (NLRs)***

Nucleotide-binding and oligomerisation domain NOD-like receptors (NLRs) are PRRs expressed in the cytosol. NLRs constantly assess the cytosolic environment for signs of infection, molecules that can affect the cellular equilibrium (such as toxins), or even imbalances in metabolic processes. There are 22 NLRs with nucleotide-binding oligomerization domain-containing protein (NOD) 1/NOD-2 and NOD-, LRR- and pyrin domain-containing 3 (NLRP3) being the most well characterised. These receptors detect

different stimulus including viral RNA and DNA. NLRs contain multiple domains, core NLR domains such as NLRC1 and NLRC2, have a pivotal role in the activation of the mitogen-activated protein kinase (MAPK) producing Type I IFNs (Anand et al., 2011). Whereas some receptors activate the inflammasome and caspase pathways. Activation of inflammasome is achieved through NLRP1, NLRP3, and NLRC4 (Malireddi et al., 2010; Masters et al., 2012; Thomas et al., 2009), resulting in the breakdown of pro-interleukin-1 $\beta$  (pro-IL-1 $\beta$ ) and pro-IL-18. This caspase 1-modulated breakdown initiates the mechanisms for pyroptosis, which is cellular death due to pro-IL-1 $\beta$  and pro-IL-18 (Malireddi et al., 2010).

RNA viruses can activate the NLRP3 inflammasome, as demonstrated in a study where murine macrophages exhibited caspase-1 activation due to influenza virus and rotavirus (Kanneganti et al., 2006). IL-1 $\beta$  secretion was NLRP3-dependent in an *in vitro* model where encephalomyocarditis virus (ECMV) and vesicular stomatitis virus (VSV), challenged DCs and macrophages (Rajan et al., 2011). The NLRP3 inflammasome in THP-1 cells can be activated by measles virus, leading to the expression of IL-1 $\beta$  (Komune et al., 2011) where in other instances the NLRP3 inflammasome can be activated by human RV and viroporin 2B protein (a pore-forming protein of HRV) (Triantafilou et al., 2013). This is achieved through the increase of Ca<sup>2+</sup> concentration in the cytosol (Shrivastava et al., 2013).

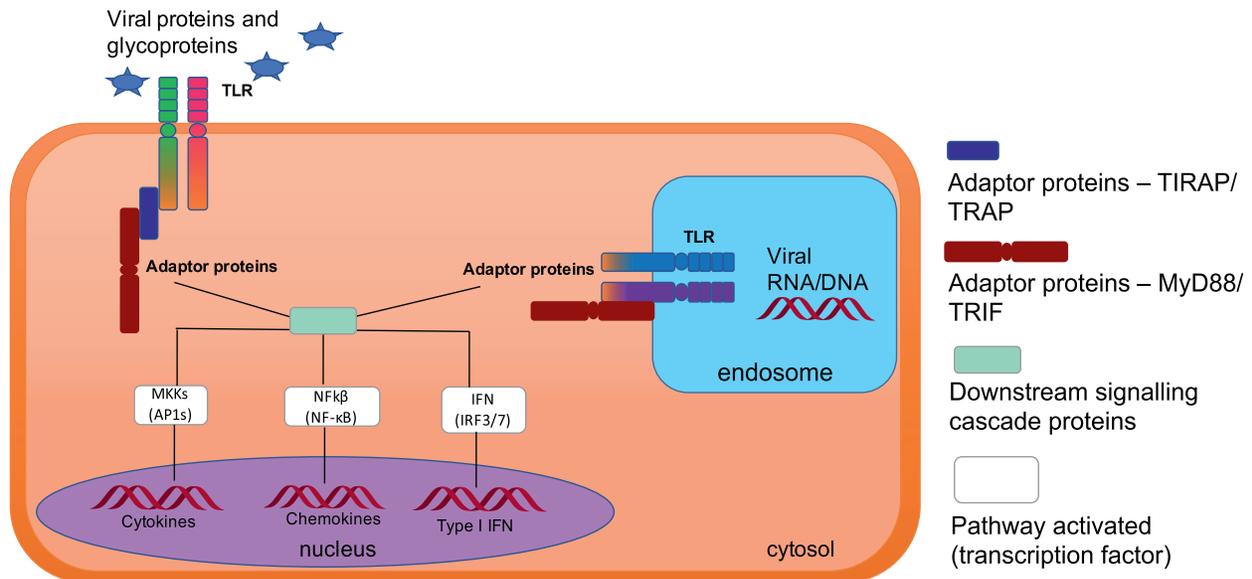
Similarly to the above PRRs these viruses have evolved mechanisms to avoid detection via NLRs and some of these mechanisms are summarised in Chan and Gack (2016).

### Cytosolic DNA sensors

Recognition of viral DNA is also important to identify infection by viruses with DNA genomes or RNA viruses that use DNA intermediates during viral replication (such as HIV). This is recognised by cytosolic DNA sensors such as cyclic GMP-AMP synthase (cGAS) which works in unison with the adaptor protein STING (Ishii et al., 2006; Ishikawa and Barber, 2008), and interferon- $\gamma$  (IFN $\gamma$ )-inducible protein 16 (IFI16) (Goubau et al., 2013). These are ubiquitously expressed in almost all cells. These sensors do not distinguish between host and pathogen derived DNA (White et al., 2014; Barber, 2015). However host DNA is localised in the cell nucleus so responses to self-DNA are avoided. Upon activation a downstream signalling cascade ensues resulting in activation of the IFN and NF- $\kappa$ B signalling pathways, similar to other PRRs (Ishikawa et al., 2009). A detailed understanding the role of these PRRs in viral infection is reviewed in Abe et al. (2019) and Chan and Gack (2016).

### Downstream signalling after PRR activation

Three main pathways are activated by PRRs, is summarised in Fig. 2. Focus in this chapter will be on the Interferon (IFN) pathway due to its critical importance in the immune response to, and clearance of viral infections.



**Fig. 2** Signalling through pattern recognition receptors (PRRs). Schematic shows signalling through PRRs, using TLRs as an example. Upon activation adaptor proteins bind to the c-terminal (TIR) signalling domain of the TLR. For TLRs this is TIRAP/TRIF/MyD88/TRIF. This activates a signalling cascade which activates further proteins in the cascade, eventually resulting in activation of transcription factors NF- $\kappa$ B, AP1s and IRF3/7. These transcription factors are subsequently translocated into the cell nucleus where they bind to the promoter regions of target genes, turning on transcription of these genes. This includes cytokines, chemokines and Interferons. All PRRs function similarly however the adaptor proteins and signalling cascade proteins differ. The pathways activated may also differ with some PRRs preferentially activating certain pathways.

### **Interferon (IFN) pathway**

Interferons (IFNs) are key members of the cytokine family that are vital components of the anti-viral innate immune response (Levy et al., 2011; Schulz and Mossman, 2016; Hoffmann et al., 2015). There are three types of IFN, type I, II and III. Type I IFNs, are made up of 17 cytokines, type II a single cytokine, and type III IFNs 4 cytokines. Type I (especially IFN- $\alpha$  and IFN- $\beta$ ) and Type III IFNs (IFN- $\lambda$ ) are the key families of cytokines that play essential roles in the anti-viral immune response. These families of cytokines are mainly produced in response to activation of PRRs that detect viral nucleic acids (such as TLR3, RIG-1, MDA5, TLR7). Activation and production of IFNs are able to restrict viral replication and spread through modulating cell survival, replication and protein translation, they also promote tissue repair, and induction of adaptive immunity. Eventually facilitating viral clearance.

Due to their wide ranging effects on the host their expression is tightly controlled. Partly due to the fact these small proteins can effect multiple host cells. Type I IFNs signal through IFNAR1 (interferon alpha and beta receptor subunit 1) and IFNAR2, which is present on most nucleated cells (Gibbert et al., 2013). Whereas Type III IFN signal through a IL-10R2 (most cells)/IFNLR1 (epithelial cells) heterodimeric receptor, whose effects are more restricted to epithelial cells (Sommerreyns et al., 2008).

Once expressed and secreted IFNs bind to IFN receptors on the host cell surface, these activate a downstream signalling cascade, through phosphorylation of Janus tyrosine kinase (JAK) proteins, the JAK1 and tyrosine kinase 2 (TYK2) (Schneider et al., 2014). This promotes recruitment of other signalling proteins, signal transducer and activator of transcription proteins (STAT1 and STAT2), which again are activated through phosphorylation. This is referred to as the JAK/STAT pathway. These STAT proteins then combine with Interferon regulatory protein (IRF) 9 to form a heterotrimeric transcription factor complex called IFN-stimulated gene factor (ISGF) 3. This complex translocates into the host cell nucleus, where it binds to the interferon stimulated response elements (ISREs) promoter, inducing the expression of numerous interferon stimulated genes (ISGs) (Schneider et al., 2014).

These genes have far reaching effects on the host and target all aspects of the viral life cycle (reviewed in Schoggins, 2019; and Yang and Li, 2020). Some examples include the family of Tripartite Motif Family (TRIM) proteins which have been shown to inhibit translation of numerous viral pathogens, this includes TRIM22 which has been shown to prevent transcription factor binding to the HIV-1 promoter region (Hattlmann et al., 2012). This protein is also upregulated during viral infection with HBV/HCV, Epstein Barr virus (EBV) and Rubella virus infection, suggesting it may also play a role here in viral infection control (Su et al., 2002; Wieland et al., 2004; Mo et al., 2007). TRIM32 ubiquitinates the IAV PB1 polymerase marking it for degradation (Fu et al., 2015). These are just a few examples and more are discussed in detail in reviews by Schoggins (2019) and Yang and Li (2020). However, because of their importance in the antiviral immune response, viruses have adapted ways to avoid this response, which is discussed later in this chapter.

### **NF- $\kappa$ B pathway**

NF- $\kappa$ B pathways is one of the three main pathways activated in response to pathogen recognition. The family of five structurally related transcription factors (NF- $\kappa$ B1, NF- $\kappa$ B2, RelA, RelB and c-Rel) are involved in the activation/expression of cytokine and chemokine genes and genes involved in the inflammasome (Oeckinghaus and Ghosh, 2009). The activity of these transcription factors are regulated by being coupled to inhibitory proteins (I $\kappa$ B family) in the cell cytoplasm, and are therefore inactive. Activation of the NF- $\kappa$ B pathway eventually results in the degradation of I $\kappa$ B and translocation of NF- $\kappa$ B transcription factors into the nucleus, and ultimately induction of NF- $\kappa$ B controlled genes. Signalling through the NF- $\kappa$ B pathway and its role in the ensuing immune response is covered in detail in Liu et al. (2017).

Numerous PRRs activate this signalling pathway, which results in production of pro-inflammatory cytokines, chemokines and inflammatory mediators that have far reaching effects on different innate immune cells. For instance these cytokines impact T cell differentiation and activation (Oh and Ghosh, 2013) and recruit neutrophil to the site of infection (Liu et al., 2017).

### **Mitogen-activated protein kinase (MAPK) pathway**

The final pathway activated by PRRs is the MAPK pathway. The MAPK pathway is comprised of highly conserved serine/threonine kinases that are activated in response to many stimuli, including viral components. Signalling through this pathway is propagated via phosphorylation of upstream MAP kinases. This pathway is responsible for regulating many cellular functions including cell differentiation, proliferation, and survival. The role of the MAPK pathway in viral recognition and removal is discussed in detail in DuShane and Maginnis (2019) and Kumar et al. (2018), but will not be discussed further here.

## **Innate immune cells in the antiviral response**

Although the immune system is all interlinked and many cell types contribute to the antiviral immune response, we will specifically focus on a few key cells/mechanisms of viral removal. Other cells of the innate immune response, such as the professional phagocytes, macrophages and DCs, are also important in the antiviral immune response. Especially dendritic cells, which bridge the innate and adaptive arm of the immune response. However, these will not be discussed further, and their functions in regards to viral infections are reviewed in Gracia-Hernandez et al. (2020); Sang et al. (2015); Soto et al. (2020), and Marongiu et al. (2021).

## Natural killer (NK) cells

Natural Killer (NK) cells have cytotoxic functions and can secrete cytokines when activated (Vivier et al., 2008). NK cells target host cells which are either infected, have genetic mutations, or have increased stress markers, removing cells that are no longer functional and restore homeostasis (Cichocki et al., 2014).

Once virally infected, host cells are a potential targets for NK cells, which recognise compromised cells by the activation of NK cell surface receptors. NK cells have two different types of cell surface receptor, activating and inhibitory receptors (Bartel et al., 2013; Biassoni and Malnati, 2018; Bryceson et al., 2006). Normal healthy host cells express MHC class I molecules on their surface, which are recognised by NK cell inhibitory receptors and promote self-tolerance (Paul and Lal, 2017; Abel et al., 2018). At the same time NK cell activating receptors bind to host cell surface motifs. Virus infected cells often (also tumor cells) lose surface MHC class I expression, preventing the NK cell inhibitory signal (renders them undetectable by CD8+ cytotoxic T cells), activating the NK cell.

NK cells once activated kill infected cells using similar mechanisms to cytotoxic CD8+ T cells, discussed in more detail below. Cell death occurs through release of cytotoxic granules (perforin/granzyme) onto infected cells, or via death receptor mediated apoptosis (Fas/FasL interaction). NK cells can also recognise and kill cells via antibody-dependent cellular cytotoxicity (ADCC) (Ochoa et al., 2017). Recognising antibody bound to the surface of infected cells. NK cells also produce a variety of cytokines, mainly IFN- $\gamma$  and TNF. These potent inflammatory cytokines activate other immune cells at the site of infection (Nutt and Huntington, 2019).

Studies indicate the importance of these cells during viral infection as they actively remove viral infected cells. This has been shown for a number of viruses such as IAV, where NK numbers correlated to reduced disease severity (Björkström et al., 2021; Jegaskanda et al., 2013). However, these cells can also exacerbate chronic viral infections, through elimination and manipulation of viral infected immune cells, rendering the immune system less functional, allowing the virus to propagate further (Waggoner et al., 2011; Lang et al., 2012). Interestingly some viruses can also directly infect these cells rendering them non functional (van Erp et al., 2019).

## Neutrophils and neutrophil extracellular traps (NETs)

Neutrophils are the most abundant circulating white blood cell in the body and are the first immune cells to move to the site of infection. Although predominantly associated with the anti-bacterial and anti-fungal immune response they have also been shown to play a role in the removal of viruses. The three main mechanism of pathogen removal are degranulation, phagocytosis and the most recently discovered mechanisms of Neutrophil Extracellular Trap (NET) formation. Their importance in viral infection is clear as in animal models where neutrophils numbers are depleted increased viral load and clinical symptoms are observed (Tate et al., 2011; Stacey et al., 2014; Haick et al., 2014).

Although phagocytosis is a key mechanisms for removal of bacterial pathogens by neutrophils, the role of this anti-microbial removal is controversial for viruses, as the presence of some viruses within neutrophils is not necessarily due to phagocytic uptake but could be due to viral infection of the neutrophil itself (Orenstein, 2000; Halfhide et al., 2011). In some instances active uptake of viruses has been confirmed and this has also been shown to be modulated through uptake of apoptotic viral infected cells, leading to virus removal (Grundy et al., 1998; Hashimoto et al., 2007).

NETs are the newest mechanism of neutrophil killing discovered in 2004 by Brinkmann and colleagues (Brinkmann et al., 2004). These are web like structures composed of the nuclear DNA of the neutrophil studded with the granular proteins, such as neutrophil elastase, myeloperoxidase and citrullinated histones. These have been shown to trap and kill pathogens including viruses, and also enable the neutrophil to increase its surface area to help prevent further spread of the pathogen. Again although mainly studied in the context of bacterial and fungal pathogens there are many examples where they have been shown to trap and neutralise viral pathogens, such as HIV, RSV and IAV (Saitoh et al., 2012; Cortjens et al., 2016; Hoeksema et al., 2015).

Viral induced NETs however have also been shown to cause damage to the host. This is the case for RSV Bronchiolitis in young infants. The virus itself seems to cause little damage to the host (Deng et al., 2018; Villenave et al., 2011; Herbert et al., 2020), but the level of neutrophils and neutrophil extracellular traps (NETs) found in the airways of young children during severe RSV bronchiolitis positively correlates to disease severity (Cortjens et al., 2016). This phenomenon has also been observed during IAV infection, RV infection in asthmatics and during SARS-CoV-2 infection (Cortjens et al., 2016; Zhu et al., 2018; Toussaint et al., 2017; Veras et al., 2020). These are just a few examples.

## Adaptive immune cells in the antiviral response

### B cells and antibody

The function of B cells, specifically those that produce antibodies (plasma B cells), have a well characterised role in the immune response to viruses (Radbruch et al., 2006). Production of antibody is the premise for all vaccines and these are effective against many viral pathogens (measles, rubella, smallpox, yellow fever, SARS-CoV-2, influenza etc) producing neutralising antibodies. In many cases these also produce long lived memory B cells, which recognise the same pathogen on future encounters, rapidly produce antibody (von Behring and Kitasato, (1890); Ahmed and Gray, 1996). Production of these two cell types in response to viral infection is summarised in Palm and Henry (2019) and Dörner and Radbruch (2007)). However, in some instances

production of antibody to viral infections are short lived such as that observed for SARS-CoV-2 and RSV, and this allows reinfection to occur (Antia et al., 2018; Lyski et al., 2021; Gaebler et al., 2021; Habibi et al., 2015; Siggins et al., 2021).

B cells also have antibody independent functions during viral infection. This includes primarily production of pro and anti-inflammatory (Bregs) cytokines which interact and modulate the immune response of other cells (Iwata et al., 2011; Shen and Fillatreau, 2015). They also present antigen to T cells on MHC class II molecules, which helps dictate the T cell response to viral antigens (Constant et al., 1995). Further information on these are summarised in Upasani et al. (2021) and Shen and Fillatreau (2015).

### Cytotoxic T lymphocytes (CD8+)

Cytotoxic T cells (CTLs) are a key component of the adaptive immune system and are key for destruction of viral infected cells (Nutt and Huntington, 2019). These T cells recognise antigen, via their T cell receptor, presented in MHC class I molecules. MHC class I molecules are present on the surface of all nucleated cells within the body. Peptides generated within these cells, that are loaded onto MHC class I molecules, are from endogenous (intracellular) peptides. This includes peptides generated from host cell proteins, but also from intracellular pathogens such as viruses. There are multiple MHC class I molecules on a single cell, which can have give a readout of up to 10,000 proteins on the cell surface, this array is interpreted by CTLs and NK cells. Processing of peptides for the MHC class I pathway is nicely reviewed in Neeffjes et al. (2011).

There are two main host cell killing mechanisms employed by CTLs to remove infected or tumour cells. Loss of function of these killing mechanisms by CTLs through genetic deficiencies such as, familial hemophagocytic lymphohistiocytosis (perforin dysfunction), shows increased susceptibility of these individuals to severe uncontrolled viral infections (Katano and Cohen, 2005).

One mechanism includes production and release of cytotoxic granules (similar to those produced by NK cells), which are mainly composed of perforin and granzyme (Voskoboinik et al., 2015). These are released from the CTLs in a directional manner towards the target cell to reduce bystander damage. This occurs as the T cell forms an immunological synapse between itself and the target cell, which is a highly organised structure made through the interaction with receptors and ligands on target cell and T cell surfaces. Perforin once released forms a pore in the host cell membrane, damaging it, but this also allows entry of the granzyme protein into the host cell. This protease once within the cell degrades cellular components such as protein or DNA, shutting down the production of viral proteins, and ultimately killing the infected host cell.

The second killing mechanism is through death receptor mediated apoptosis (Fas/FasL interaction) (Keckler, 2007). FasL expression is restricted to CTLs and NK cells, whereas Fas is expressed on the surface of many different cell types. The interaction of Fas, which has a death domain, with FasL on CTLs causes Fas to trimerise on the target cell surface, activating a downstream signalling cascade which ultimately leads to the activation of the apoptosis initiating caspase cascade, including caspase 8 and 10, which eventually results in the target cell undergoing apoptosis. This process is discussed in more detail in Yamada et al. (2017).

Finally CTL produce a number of pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$  and IL-2 which interact with other immune cells, promoting a T helper cell response and further CTL differentiation (Nutt and Huntington, 2019; Cox et al., 2013). One mechanism by which viruses are able to avoid these is through downregulating the expression of MHC class I molecules on the infected cells surface.

### Cytotoxic T lymphocytes (CD4+)

CD4<sup>+</sup> T cells are most commonly associated with T helper (Th) cell subsets, and recognise antigen presented in MHC class II molecules (on immune cells) with their TCR (Sant and McMichael, 2012). Naïve CD4<sup>+</sup> T cells, when stimulated, can differentiate into a number of different effector T cell populations. The type of T cell produced depends on the specific cytokines within the microenvironment, which ultimately coordinates the type of immune response. The cytokines IL-12 and IL-4 respectively, induce differentiation into Th1 and Th2 subsets, and these were the first to be described (Mosmann et al., 1986). Further and more recent studies elucidated other Th subsets, such as Th17 cells, regulatory T cells (Treg), Th22, Th9 and follicular helper T cells (Tfh) (Raphael et al., 2015). These cells functions mainly through production of cytokines which interact with other cells of the immune systems and dictate the ensuing immune response.

More recently an unexpected CD4<sup>+</sup> T cell subset was recognised, which have similar cytotoxic function as CD8<sup>+</sup> CTLs. Their function and role in antiviral immunity is nicely summarised in Muraro et al. (2017). CD4<sup>+</sup> CTLs, similar to CD8<sup>+</sup> T cells, can release cytotoxic granules containing granzyme B and perforin (Fleischer, 1984), which when in direct contact with the target cell can kill them (Brown et al., 2016). They also kill target cells using the Fas/FasL interaction, as noted above. These mostly rare cells increase significantly in their numbers during transient and chronic viral infection, and have been shown to have cytolytic activity against viral infected cells (Nemes et al., 2010; Brown et al., 2016). This has been shown during Cytomegalovirus (CMV), Epstein-Barr virus (EBV), HCV, HBV and HIV infections (Facchinetti et al., 2005; Aslan et al., 2006; Appay et al., 2002; Rosenberg et al., 1997; Musey et al., 1997; van Leeuwen et al., 2004). Such is the importance of CD4 CTLs, they can replace CD8<sup>+</sup> CTLs during chronic infections, as CD8<sup>+</sup> CTLs lose their functionality. Further studies are being undertaken on this cell population to elucidate further their role in antiviral immunity.

### Natural killer T cells (NKT)

Another cell type of potential importance during viral infections is the Natural Killer T cell (Gumperz et al., 2002; Gapin et al., 2001). These are innate like cells and can respond rapidly to antigen that has not been encountered previously. These cells contain an invariant TCR which recognise lipid antigens presented in a MHC class I like molecule (CD1d). They also have a number of cell surface molecules in common with NK cells, hence the name. Once activated these cells can produce a wide range of cytokines and chemokines which influence other cells of the immune system (similar to T helper cells) (Coquet et al., 2008; Paget et al., 2012), such as DC maturation (Fujii et al., 2003), B cell antibody production (King et al., 2011) and T cell polarisation (Godfrey and Kronenberg, 2004). These cells can also directly lyse infected cells using cytolytic proteins (granzyme/perforin), similarly to CTLs, however this is a CD1d-dependent mechanism (Kok et al., 2012).

Some evidence suggests these cells help protect against viral infection, but more research is still needed in this area. During influenza (H1N1) viral infection NKT cell numbers are reduced in patients with severe disease (Chen et al., 2010). However, when present these cells have been shown to selectively lyse influenza infected cells and reduce lung pathology (Kok et al., 2012; Paget et al., 2012). During chronic HBV infection, the frequency of circulating CD4<sup>+</sup> NKT cells is lower in asymptomatic carriers (Jiang et al., 2011), but numbers increase after treatment (Tripathy et al., 2011). NKT cell numbers are also reduced during HIV-1 infection, due to viral infection of the CD4<sup>+</sup> NKT cell subset, which occurs preferentially to conventional CD4<sup>+</sup> T cells, due to the expression of multiple co-receptors (CD4/CCR5, CXCR4, and CXCR6) involved in viral fusion and cell entry (Motsinger et al., 2002; Fernandez et al., 2014; van der Vliet et al., 2002; Sandberg et al., 2002; Fleuridor et al., 2003). NKT cell numbers recover following effective antiretroviral therapy (van der Vliet et al., 2006). More information on NKT cells and their role during viral infection is summarised in Slauenwhite and Johnston (2015) and Tupin et al. (2007).

### Viral avoidance of the immune response

Despite the arsenal of antiviral mechanisms in place to prevent viral infection and recognise and destroy viral infected cells, viruses have evolved ways to avoid detection by the immune system in a number of different ways. Some of these will be discussed in more detail below.

#### Interference of viral antigen presentation on MHC class I molecules

As discussed above CTLs can recognise and kill viral infected cells through recognition of viral peptides in MHC class I molecules (on all nucleated cells). A commonly used viral strategy to evade CTL killing mechanisms is to interfere with the presentation of antigen in MHC class I molecules. This can occur through multiple mechanisms, but mainly via interfering with antigen processing in the infected cell, or by reducing the number of MHC molecules on the target cell surface. Examples of this are discussed in the following reviews Schuren et al. (2016),; Loch and Tampé (2005), ; Horst et al. (2011).

Ways in which viruses have been able to interfere with antigen processing within the target cell, which ultimately leads to reduced presentation of viral peptides to CTLs, includes: producing proteins that are resistant to antigen digestion by the proteasome. Proteins must first be digested within the target cell by proteases to allow short peptides to be loaded onto MHC class I molecules, preventing this degradation prevents these viral peptides being presented to CTLs. This mechanism is used by the EBNA-1 (Epstein Barr Nuclear Antigen 1) protein of EBV (Levitskaya et al., 1995). Some viruses also interfere with the Transporter associated with Antigen Processing (TAP) protein, which transports peptide antigens into the endoplasmic reticulum for loading into MHC class I molecules. This is the case for Herpes Simplex virus (HSV) where ICP47 (infected cell protein 47) interferes with the binding of the peptides to the TAP protein (Ackerman et al., 2006). This is also a mechanism used by CMV through protein US6 (Unique short 6 glycoprotein) (Lehner et al., 1997).

Other viruses reduce viral antigen presentation through interfering with MHC I presentation on the cell surface. This can target multiple steps in the production and trafficking of MHC in the cell (van de Weijer et al., 2015). Adenovirus is able to do this using its E3 protein, which forms a complex with MHC class I molecules to prevent antigens from being processed (Fu et al., 2011). CMV achieves this through multiple mechanisms, proteins US2 and US11 promote the rapid degradation of newly synthesised MHC class I complexes (Gabor et al., 2020). CMV gpm152 protein causes retention of the MHC class I molecules in the Golgi compartment through which MHC class I loaded with peptide are trafficked. Varicella zoster virus open reading frame 66 protein also performs this immune evasion tactic (Purohit et al., 2021). Further some viral protein of the Kaposi Sacoma virus (Kaposi Sacoma Virus ubiquitin ligase) promote rapid endocytosis of surface expressed MHC Class I and their subsequent degradation (Coscoy and Ganem, 2000).

#### Antigenic variation (antibody escape)

Antigenic variation is a key mechanism by which many different viral pathogens are able to avoid the adaptive arm of the immune system (antibody recognition). This is most notably utilised by the respiratory RNA genome viruses, such as Influenza viruses, coronaviruses and RVs (Duffy, 2018). One key feature that allows this to occur more readily in RNA genome viruses is the fact the RNA polymerase enzyme required for replication of the viral genome has no proof reading functionality (not the case for

coronaviruses) (Smith and Denison, 2012). Meaning during genome replication mutations are constantly being introduced into the genome. If these are beneficial genetic changes they will be selected for and that strain will thrive. These mutations can provide many benefits, such as increased ability to bind to the host receptor, increased replication capabilities, increased transmission capabilities, but also an ability to evade antibody binding if the mutation is present within a key cell surface epitope (Harvey et al., 2021).

Key examples of this have frequently been seen during the SARS-CoV-2 pandemic (Harvey et al., 2021). Many novel strains have emerged, which have been shown to have genome changes that give that strain a selective advantage. Changes specifically in the viral cell surface spike protein, which binds to the host receptor ACE2, are common (Forni et al., 2020). The B.1.1.529 variant (given the name Omicron), is a highly mutated variant with a significant number of gene alterations, including 26-32 mutations in the spike protein, some of which are associated with immune escape and higher transmissibility (Kannan et al., 2021; Zhang et al., 2021). This is also the protein target for all vaccines to date.

RVs also use this mechanism to avoid immune system detection. These are some of the most genetically diverse group of viruses (Stobart et al., 2017). They are categorised into three distinct serotypes, RVA, RVB and RVC. Within these serotypes there are over 150 different types, which are antigenically distinct from one another (Lau et al., 2007). It has been shown that antibodies produced against RV infection are robust and protective, however, antibodies produced against one type are not cross protective against another, allowing different strains to circulate annually (Lee et al., 2016). This has hindered vaccine design.

Influenza viruses also use this mechanism to avoid the immune system. This is known as antigenic drift, where genetic changes accumulate in the regions targeted by antibodies (Shao et al., 2017). For influenza viruses this is normally within the genes that encode the cell surface proteins haemagglutinin and neuraminidase, which bind to the host cell receptor (sialic acid) and cleave sialic acid to release the virus, respectively (Byrd-Leotis et al., 2017). Antigenic drift where we see minor genetic changes results in influenza strains that circulate annually causing epidemics. These strains can reinfect the host with antibodies being less effective, but in general a level of protection still exists, limiting the severity of infection (Shao et al., 2017; Wang et al., 2017).

Another phenomenon occurs in influenza viruses known as antigenic shift (Shao et al., 2017). This occurs in IAV only, which can infect humans and other animals, most notably pigs and poultry. This process which leads to the genetic rearrangement of two viral strains, is facilitated through the fact influenza viruses have a segmented RNA genome (Krammer et al., 2018). This allows easier reassortment of the genes during infection (two distinct viruses infect the same cells), which produces novel strains from reassortment of the zoonotic strains that can jump species barrier into humans, or from reassortment of a human and zoonotic strain (Sun et al., 2020). These strains have never before been encountered by humans, therefore there is no immunity (antibody) to prevent infection and disease can often be very severe. This phenomenon generates pandemic influenza strains, and since 1918 (Spanish flu) has generated 4 pandemics, with varying severity (Saunders-Hastings and Krawski, 2016).

Although not technically avoidance of the immune system, RSV for reasons unknown does not produce long lasting immunity. This means that antibodies produced against one strain one year are no longer present the following year, meaning that strain can reinfect the same person. This allows this virus to cause seasonal epidemics. This also seems to be the case in relation to antibodies produced against SARS-CoV-2, with evidence showing antibodies only last for roughly 6 months (Antia et al., 2018; Lyski et al., 2021; Gaebler et al., 2021; Habibi et al., 2015; Siggins et al., 2021).

Other mechanisms used by respiratory RNA viruses to avoid the immune system are nicely summarised in Kikkert (2020).

## Modulation of PRR signalling

To avoid activation of the key signalling pathways many viruses have adapted to subvert the PRR signalling pathways, this is nicely reviewed in Bowie and Unterholzner (2008). This occurs either through preventing their activation or blocking the downstream signalling cascade. Vaccinia virus is able to subvert signalling via its protein A46R, which contains a TIR domain (Stack et al., 2005). This is able to sequester TIR domain binding adaptor proteins, preventing activation of the downstream signalling pathways (Stack et al., 2005). TRIF, a TLR signalling adaptor protein is cleaved by the NS3-4A viral protease of HCV. Cleavage of TRIF results in its inactivation rendering it unable to activate the downstream signalling pathways during HCV infection (Li et al., 2005). Viruses such as EBOV and IAV can also sequester their genetic material from the environment to prevent activation of the TLRs (Cárdenas et al., 2006; Hatada and Fukuda, 1992).

Avoidance of the RLR PRR is also a common adaptation of viruses. They modify the structure of their genetic material to avoid detection by these important PRRs. This can involve adding a cap structure to viral RNA making it mimic host mRNA. The ability to do this can be using viral encode capping enzymes or can involve stealing host encoded cap proteins, known as cap snatching (e.g. IAV) (Plotch et al., 1981). Alternatively viruses can protect their genetic material via adding a protein to protect it (e.g. VPg protein of picornaviruses) (Flanagan et al., 1977). Genetic material can also be sequestered to prevent detection by PRRs. Many viruses encode RNA binding proteins, that shield the dsRNA species from recognition by PRRs. Examples include Vaccinia virus E3L protein, EBOV viral protein (VP) 35 (Haasnoot et al., 2007) and HIV Tat protein (Weeks et al., 1990). Other viruses produce proteins that directly interact with signalling molecules involved in the RLR pathways, such as the V proteins of many paramyxoviruses (Andrejeva et al., 2004) and NS1 protein of IAV (Mibayashi et al., 2007).

Viral avoidance of cytoplasmic DNA sensors using similar strategies is summarised in review Abe et al. (2019).

## Modulation of the IFN response

IFN, especially type I and type III IFN are key players in the antiviral immune response, as discussed above. Therefore many viruses have evolved ways in which to avoid this key immune response. Some key examples of this will be discussed below.

EBOV has multiple mechanisms that allow it to avoid the host IFN response. Two key viral proteins involved in this include the VP24 and VP35, which inhibits the activation of the IFN-stimulated genes through preventing STAT1 translocation into the host nucleus, and inhibits IFN production through preventing phosphorylation of IRF-3, respectively (Messaoudi et al., 2015; Fanunza et al., 2019). *In vitro* and *in vivo* (murine infection model) studies, where mutations have been introduced into these proteins, show reduced viral replication, increased host IFN response and severe attenuation compared to infection with strains containing the wild type proteins (Hartman et al., 2008a,b, 2006; Lubaki et al., 2016).

Deficiencies in the IFN response to SARS-CoV-2 infection have also been identified as a hallmark of disease, aiding viral replication and disease pathology. It is suggested to use multiple mechanisms to prevent the IFN response, including: inhibiting IFN induction by evading host PRR sensing or disrupting IFN signalling cascades, interfering with host protein production which included IFNs, and suppressing IFN action (reviewed in (Min et al., 2021)). Some examples of how this is achieved is via methylating the 5'-end of viral mRNA by NSP16/NSP10, which then mimics host mRNA (Viswanathan et al., 2020). This makes the viral genome undetectable by host PRRs. Multiple other viral proteins have the ability to interfere with the IFN signalling cascade, including SARS-CoV-2 PLpro (papain like protease) which can directly cleave IRF3, NSP6 inhibits IRF3 activation, NSP1 can suppress STAT1 transcription factor phosphorylation and its nuclear translocation, all which suppress IFN production (Xia et al., 2020; Moustaqil et al., 2020).

Some viruses also inhibit the initial binding of IFNs to their cognate receptors (IFNAR) on host cells. This includes IAV haemagglutinin protein, which tags the IFNAR1 protein for degradation (Xia et al., 2015). The NS5 protein of WNV can inhibit IFNAR1 intracellular trafficking and glycosylation and therefore surface expression of this receptor (Lubick et al., 2015).

## Hiding within immune cells

Some viruses are also able to modulate the immune system through the infection of, destruction of and modulation of immune cells function. The most notable example of this is HIV, which infects CD4+ T cells, NKT cells, macrophages and DCs (Kruize and Kootstra, 2019; Harman et al., 2011). This phenomenon may be due to the virus having a broad cell tropism, as the host receptor is expressed on many different cell types, or this may be a more immune cell targeted infection. In some instances it can also be hard to prove whether the virus is able to actively infect and replicate within immune cells, or whether this is an artefact of viral phagocytosis by antigen presenting cells.

EBOV has a broad cell tropism and can infect many different cell types, this however includes some antigen presenting cells such as macrophages and dendritic cells, for which EBOV seems to have a preference for. This is also the case for other filoviruses and is reviewed in Olejnik et al. (2011). Evidence suggests that active replication of EBOV occurs within these cells (Geisbert et al., 2003; Ryabchikova et al., 1999; Johnson et al., 1995). Both of which play a key role in the ensuing immune response, especially dendritic cells, which bridge the adaptive and innate immune response. Although work is still ongoing as to the effect of infection of immune cells in EBOV infection, current studies suggest this induces a pro-inflammatory state (Bray and Geisbert, 2005). This over exuberant immune response and apoptosis of lymphocytes is associated with poor disease outcomes (Baize et al., 1999).

RSV has been found inside neutrophils (Halfhide et al., 2011). These are important cells in RSV disease as their number in the lungs, as mentioned above, directly correlate with disease severity (McNamara et al., 2003). The presence of RSV within neutrophils is controversial and it is still unclear if this is due to infection of these immune cells or if this is due to phagocytosis of the virus (Halfhide et al., 2011). Whether this virus can infect and manipulate these cells for their own benefit is yet to be elucidated.

## Viral latency

Another way viruses can avoid the immune system is to reside within the host in a latent form. This is a common feature of herpesviruses where after initial infection they become transcriptionally inactive. For herpes simplex virus the viral genetic material is retained within infected cells as circular episomes (not integrated into host DNA), however some herpesviruses can integrate their DNA into the host chromosome, such as EBV. Establishment of latency allows these viruses to infect their host for life. Viral latency is discussed further in Sorel and Dewals (2018); Brar et al. (2020) and Bennett et al. (2005), in regards to how these viruses avoid and manipulate the host immune response.

This chapter summarizes how viruses are detected during infection, the key cells involved in the antiviral immune response and ways in which viruses have evolved to avoid the host immune system. More in depth discussion on each topic can be found in the cited reviews.

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