Chapter 3
Antiviral Host Defence Peptides

**Filipa Henderson Sousa, Victor Casanova, Craig Stevens
and Peter G. Barlow**

Abstract The ongoing global mortality and morbidity associated with viral pathogens highlights the need for the continued development of effective, novel antiviral molecules. The antiviral activity of cationic host defence peptides is of significant interest as novel therapeutics for treating viral infection and predominantly due to their broad spectrum antiviral activity. These peptides also display powerful immunomodulatory activity and are key mediators of inflammation. Therefore, they offer a significant opportunity to inform the development of novel therapeutics for treating viral infections by either directly targeting the pathogen or by enhancing the innate immune response. In this chapter, we review the antiviral activity of cathelicidins and defensins, and examine the potential for these peptides to be used as novel antiviral agents.

3.1 Introduction

The ongoing mortality and disease associated with circulating viral infections of humans and animals, together with the ongoing threat of emerging viral strains underscores the requirement for the development of novel antiviral molecules. While vaccination against common viral pathogens is effective and desirable, direct antiviral therapeutics play a key role in treating diseases caused by viral pathogens that have no vaccine, that lack a global vaccination programme, or those with vaccines of limited efficacy. In addition, as the resistance of viral pathogens to common antiviral drugs increases, new classes of antiviral molecules could provide a strategy for treatment of both existing and emerging infections for decades to come.

The antiviral activity of Cationic Host Defence Peptides (CHDP; also known as antimicrobial peptides) is of increasing interest for informing the development of novel antiviral therapeutics. Due to their broad spectrum activity, CHDP play a key

F.H. Sousa · V. Casanova · C. Stevens · P.G. Barlow (✉)
School of Life, Sport and Social Sciences, Edinburgh Napier University,
Edinburgh EH11 4BN UK
e-mail: p.barlow@napier.ac.uk

role in the innate immune response to both bacterial and viral pathogens. In addition, CHDP have substantial immunomodulatory activities that can contribute to the rapid clearance of infections. Therefore, a better understanding of the antiviral and immunomodulatory activities of CHDP in the context of viral infection will be of great importance in the race to develop new treatments that are broadly effective against viral pathogens.

CHDP are small, evolutionarily conserved peptides with a positive charge that have broad spectrum activity against a range of pathogens, both in vitro and in vivo. In humans, there are two major families of CHDP; the cathelicidins and the defensins, however, more families exist in mammals, birds, fish, reptiles, arthropods and plants, each showing antimicrobial potential. While the antiviral activity of many peptides has been established in a significant number of studies, a comprehensive understanding of the mechanism(s) of action involved remains elusive. Of particular interest are the immunomodulatory and inflammomodulatory activities of CHDP, from gaining a more fundamental understanding of innate responses to infection in addition to informing development of novel therapeutics. CHDP have been shown to have the capacity to modulate cell death pathways in infected cells, assist in the recruitment of immune cells to sites of infection, promote angiogenesis, alter immune cell differentiation and to mediate production of pro- and anti-inflammatory cytokines.

In this chapter, we review the antiviral activities of both cathelicidins and defensins, and also highlight key CHDP from other species that demonstrate antiviral potential, either through direct antiviral activity or by modulation of the immune response to the infection.

3.2   The Antiviral Activity of Cathelicidins

Cathelicidins range from 12–88 amino acids in length and are characterised by the presence of an N-terminal signal sequence which directs the newly synthesised protein towards the secretory pathway, a conserved cathelin-like domain which has a high sequence homology with the porcine cysteine protease inhibitor, cathelin and a variable C-terminal antimicrobial domain which becomes the mature functional peptide upon proteolytic cleavage.

Cathelicidins were first identified in bovine neutrophils and are widely distributed in mammals including humans, rhesus monkeys, rats, mice, guinea pigs, rabbits, sheep, cows, horses and dogs and also in non-mammalian species including chicken, rainbow trout and hagfish (Zanetti et al. 1993). In humans, only one cathelicidin has been described—the cationic antimicrobial peptide of 18kDa (hCAP18), which can be found at high concentrations in the specific granules of neutrophils and can be expressed by epithelial cells of skin and mucosa of the respiratory, urogenital and gastrointestinal tracts (De et al. 2000). hCAP18 is cleaved extracellularly by proteinase-3 to generate its active form LL-37, a linear 37 aminoacids peptide with two leucine residues at the N-terminal and an amphipathic

α-helical structure (Sorensen et al. 2001). The peptide is known to be expressed by macrophages, eosinophils, lymphocytes, mast cells and NK, T- and B-cells (Agerberth et al. 2000).

Mice express the cathelicidin mCRAMP (murine cathelin-related antimicrobial peptide), which has high sequence identity with hCAP18 and the porcine cathelicidin PR-39. mCRAMP shows similar expression and function patterns to its human ortholog (Gallo et al. 1997) that is stored in neutrophil granules and is expressed by epithelial cells and leukocytes. mCRAMP knock-out mice have a high susceptibility to infections when compared to wild type mice (Huang et al. 2007; Iimura et al. 2005; Kovach et al. 2012).

In contrast to humans and mice, which only express one cathelicidin, pigs express a variety of cathelicidins which differ in activity and structure. The porcine cathelicidins include five different protegrins (PGs), three α-helical peptides (PMAP-23, -36, -37), two prophenins (PF-1, -2) and the PR-39 peptide (Zhang et al. 2000). PGs are produced and stored by porcine neutrophils as inactive propeptides but are proteolytically cleaved into their active forms by neutrophil elastase in the extracellular environment. Their expression is enhanced by bacterial LPS, IL-6, retinoic acid and salmonella infections (Wu et al. 2000) and PG-1 has been shown to have the broadest antimicrobial activity spectrum (Yasin et al. 1996a, b). Cathelicidins have also been characterized in many other species, such as sheep, monkeys, horses and cows. In sheep, eight cathelin-associated peptides have been identified and SMAP-29 (sheep myeloid antimicrobial peptide 29) is one of the most potent cationic host defence peptide known in terms of antimicrobial activity, having a wide spectrum of activity against bacteria, fungi and virus (Tomasinsig and Zanetti 2005).

Cathelicidins play key roles in host defence via direct antimicrobial activity (Putsep et al. 2002), by acting as critical immunomodulatory molecules and in the control of inflammation. Recently, a number of studies conducted in humans, mice and other in vitro models have highlighted the potent antiviral activity of cathelicidins. Viruses that are most susceptible to cathelicidins include enveloped DNA and RNA viruses, and while all of the antiviral mechanisms remain to be elucidated, there does appear to be a direct effect on the viral envelope. However, non-enveloped viruses such as adenovirus can also be inactivated by cathelicidins (Gordon et al. 2005; Barlow et al. 2014). Therefore, the antiviral activity of these peptides likely comprises complex array of mechanisms that cannot all be explained by a direct effect on the virus particles.

3.3   RNA Viruses

3.3.1   *Influenza Virus (IAV)*

Influenza virus (IAV) is an enveloped virus from the *Orthomyxoviridae* family. Viral influenza has caused the death of more people in short periods of time than any other infectious disease (Taubenberger and Morens 2006). There is a well-established

global vaccination programme in place for preventing influenza infection on an annual basis, but this is limited to protecting against the prevalent circulating strains, and therefore emerging new strains can potentially lead to a global pandemic outbreak. Antiviral treatments are available, although the emerging resistance of circulating strains to neurominidase inhibitors, one of the current front-line treatment, is of serious concern (Nitsch-Osuch and Brydak 2014; Hurt 2014).

Studies have demonstrated the antiviral potential of several cathelicidins against influenza virus. A study by Barlow et al. 2011 demonstrated the antiviral properties of human and murine cathelicidins in vivo and in vitro (Barlow et al. 2011). mCRAMP and LL-37, but not porcine cathelicidin PG-1, showed antiviral properties when pre-incubated with IAV in vitro. Tripathi et al. (2013) further demonstrated that pre-incubation of LL-37 peptide with IAV is necessary for optimal inhibition of IAV, although a host cell pre-treatment or a delayed treatment with exogenous LL-37 also inhibits IAV replication to an extent (Tripathi et al. 2013). This reveals that LL-37 peptide has the ability to interact with epithelial cells although the most potent activity of the peptide involves direct interactions with the virus particles.

In in vivo studies, murine models receiving LL-37 or mCRAMP treatment showed a significant increase in survival compared to saline treated mice. Mice treated with PG-1 showed no significant alterations compared to the control group (Barlow et al. 2011). This demonstrates that antiviral activities of cathelicidins are species-specific, and it was proposed that LL-37 protects against IAV infection through modulation of inflammatory response in the lungs. Mice infected with IAV exhibited a pronounced up-regulation of numerous pro-inflammatory cytokines, although this was attenuated in LL-37-treated mice, suggesting that LL-37 modulates the inflammatory response by inhibiting excessive inflammation (Barlow et al. 2011).

In order to determine the effects of LL-37 on the cellular uptake and replication of IAV, qPCR was used to quantify viral infection and replication. The results showed that LL-37 did not reduce the number of virus particles associated with cells after 45 min of infection, although at 24 h post-infection, LL-37 caused a significant reduction in the amount of virus present in cells and in the cell culture supernatant (Tripathi et al. 2013). Electron microscope images revealed that LL-37 had induced disruption of viral membranes, which may be one possible mechanism of antiviral activity.

Interestingly, pandemic IAV strains have shown to be more resistant to innate inhibitors of seasonal IAV strains, such as human and murine cathelicidins. A recent study compared the antiviral activities of LL-37 and derived fragments from LL-37 against seasonal and pandemic strains of influenza virus and revealed that the central fragment of LL-37 showed greater activity against the pandemic IAV strain than LL-37 in vitro (Tripathi et al. 2015). This finding suggests the possibility that synthetic derivatives of LL-37 with more potent antiviral activity could be used as a potential therapeutic for this infection.

3.3.1.1 Human Immunodeficiency Virus (HIV)

HIV is an enveloped *lentivirus* of family *Retroviridae* that causes HIV infection and acquired immune deficiency syndrome (AIDS). An estimate of 34.2 million people worldwide live with HIV and around 2.5 million new infections and 1.7 million deaths were detected in 2011 only (Piot and Quinn 2013). The hallmark of this infection is the gradual loss of $CD4^+$ T-cells which leads to an acquired immune deficiency syndrome or AIDS (Simon et al. 2006). The production of up to 10^{10} viral particles per day together with low fidelity of reverse transcription and recombination generate viral quasi-species in chronically infected subjects makes lifelong treatment with a combination of highly active antiretroviral drugs (HAART) the only option capable of keeping the infection controlled.

Indolicidin, a cathelicidin isolated from large granules of bovine neutrophils, was the first to show anti-HIV activity (Robinson et al. 1998). It is thought that the potent antimicrobial properties of indolicidin are related to their ability to disrupt pathogen membranes. Experimentally, indolicidin directly inactivated the HIV-1 virus particles, an observation that was attributed to a membrane-mediated antiviral mechanism.

A in vitro study by Bergman et al. (2007) showed that LL-37 could inhibit HIV-1 replication in peripheral blood mononuclear cells (PBMC), including primary $CD4^+$ T-cells. This was shown to be independent of formyl peptide receptor-like-1 (FPRL-1) signalling, a receptor which is thought to be partially responsible for mediating some of the chemotactic and immunomodulatory effects of LL-37 (Bergman et al. 2007; Barlow et al. 2006). Another study examined the anti-HIV effects of LL-37 and its derived fragments, together with BMAP-18, a fragment derived from bovine cathelicidin BMAP-27, in vitro (Wang et al. 2008). The peptide sequence order, aromatic residues and helical structures were examined and were shown to play an important role in HIV inhibition. Again, a central fragment of LL-37 (known as GI-20), and BMAP-18, were the most active against HIV-1 compared to LL-37 and BMAP-27. This study essentially provides new antimicrobial templates that could be used to develop novel anti-HIV therapies.

A more recent study examined the effects of LL-37 and its derived fragments on HIV-1 reverse transcriptase, HIV-1 integrase and HIV-1 protease (Wong et al. 2011). It was shown that all peptides tested lacked the ability to inhibit translocation of HIV-1 integrase, an enzyme essential for HIV replication. The most potent inhibitory effects of the peptides were seen on HIV-1 reverse transcriptase, and the central peptide, LL13-37, was revealed to have the strongest inhibitory activity.

hCAP-18 has been shown to be strongly expressed in the epithelium of the epididymis, which suggests an important role of hCAP-18 in the antimicrobial protection of the reproductive male system (Malm et al. 2000). It has also been shown that vaginal fluid of healthy women has intrinsic anti-HIV-1 properties and these were conferred by cationic polypeptides. A depletion of cationic polypeptides caused a reduction of the intrinsic anti-HIV-1 activity (Venkataraman et al. 2005) and, in addition to this, cervicovaginal secretions (CVS) of Kenyan women in HIV-serodiscordant relationships contained HIV neutralizing activity and CVS

which revealed no intrinsic anti-HIV activity could be enhanced by the addition of recombinant LL-37 (Levinson et al. 2012). Further studies have revealed that high concentrations of LL-37 were found in cervicovaginal secretions (CVS) collected from Kenyan sex workers with bacterial transmitted infections, which are associated with increased HIV acquisition (Levinson et al. 2009). This finding does not seem to correlate with previous studies, where CVS contain HIV neutralizing activity conferred by cationic polypeptides. Therefore, there is a pressing need to determine the in vivo significance of LL-37 peptide in HIV infections.

3.3.1.2 Junin Virus (JV)

Junin virus (JV) is an enveloped virus of the *Arenaviridae* family, which causes Argentine haemorrhagic fever (AHF). A study by Albiol Matanic and Castilla (2004) assessed the antiviral effects of indolicidin against junin virus, although it was determined that this cathelicidin was not able to induce substantial rates of viral inactivation (Albiol Matanic and Castilla 2004). However, the relatively low virucidal action of indolicidin against junin virus that was observed was thought to be due to direct inactivation of the virus particles, similar to the antiviral mechanisms proposed for the action of cathelicidins against HIV-1 (Robinson et al. 1998).

3.3.1.3 Dengue Virus (DENV)

Dengue virus (DENV) is an enveloped member of the *Flaviviridae* family which causes dengue fever—a mosquito-borne tropical disease. An important target for antiviral therapies against dengue virus is NS2B/NS3 serine protease, as disruption of NS2B/NS3 serine protease functions inhibit virus replication. A study by Tambunan and Alamudi (2010) demonstrated that cationic cyclic peptides have a high potential to inhibit NS2B/NS3 serine protease activities of dengue virus (Tambunan and Alamudi 2010). A more recent study proposed that protegrin-1 (PG-1), a cationic cyclic peptide which was originally isolated from porcine blood cells, is able to inhibit NS2B/NS3 serine protease activity, thus translating to reduced viral replication in vitro (Rothan et al. 2012).

3.3.1.4 Human Respiratory Syncytial Virus (RSV)

RSV is an enveloped virus and a member of the *Paramyxoviridae* family, and has been shown to be responsible for significant numbers of respiratory tract infections. It is the major cause of viral bronchiolitis in young children (Nair et al. 2010). A recent study demonstrated that human cathelicidin displays concentration-dependent antiviral activity against RSV in vitro at physiologically relevant concentrations of 25 µg/ml (Currie et al. 2013). LL-37 inhibited RSV replication and decreased the spread of infection, and these effects were highest when the peptide

was pre-incubated with RSV or added to cells simultaneously. This study demonstrated that LL-37 mediates direct effects against the virus particles, similar to the action of LL-37 against influenza A virus (Tripathi et al. 2013). It was also demonstrated that a delayed LL-37 exposure, taking place 2 h after infection, resulted in the loss of antiviral effects which revealed the inability of the peptide to rescue infected cells. However, pre-treating cells with LL-37 prior to infection resulted in a reduction of infectivity, suggesting that the peptide is retained by the epithelial cells exerting a protective antiviral state. These results indicate that LL-37 can protect epithelial cells from viral infection through a mechanism distinct from direct antiviral activity. In addition, LL-37 was also shown to actively protect RSV-infected epithelial cells from cell death.

3.3.2 DNA Viruses

3.3.2.1 Vaccinia Virus (VV)

Vaccinia virus (VV) is an enveloped poxvirus, of the family *Poxviridae*, which is the active constituent of the vaccine that eradicated smallpox. It has been demonstrated that individuals with atopic dermatitis (AD) have a predisposition to develop eczema *vaccinatum* in response to the vaccine, and that, in these individuals, the expression of hCAP18 is reduced (Howell et al. 2006). It has been shown that in normal skin biopsies, the expression of LL-37 was induced by vaccinia virus, but this was not observed in not in AD skin. Furthermore, a study by Howell et al. (2004) demonstrated that both LL-37 and the murine cathelicidin, mCRAMP, have antiviral activity against vaccinia virus, and the antiviral mechanism by which LL-37 exerts its effect involves the removal of the outer membrane of vaccinia virus, thus causing envelope damage (Howell et al. 2004; Dean et al. 2010).

3.3.2.2 Herpes Simplex Virus (HSV)

Herpes simplex virus 1 and 2 (HSV-1 and -2) are enveloped viruses of the family *Herpesviridae*, that are widely found in humans and are particularly infectious. While they can be suppressed by some antiviral drugs, they are not normally susceptible to complete eradication from a host. A study by Yasin et al. (2000) screened 20 host defence peptides to test their antiviral activity against HSV type 1 and 2 (Yasin et al. 2000). LL-37 was shown to have very little capacity to induce viral inactivation. However, the bovine cathelicidin, indolicidin, displayed potent antiviral activity against both HSV types.

Other peptides which were investigated for anti-HSV activity include BMAP-27 and -28 (acronym of "bovine myeloid antimicrobial peptides"), which are cathelicidins found in bovine neutrophils. BMAP-27 and -28, and their synthetic 1–18 fragments, were analysed for their in vitro antiviral activity against HSV-1. Only

BMAP-28 was shown to provide some protection in vitro against HSV-1 whereas all other peptides were ineffective at non-cytotoxic concentrations (Benincasa et al. 2003). Another study examined the underlying mechanism for the potent antiviral activity of indocilidin observed against HSV type -1 and -2 in vitro, and suggested that the mechanism underlining the antiviral activity was related to the ability of the peptide to disrupt the viral envelope, thus inactivating the virus particles (Albiol Matanic and Castilla 2004). However, contrary to previous reports, Gordon et al. 2005 reported a potent antiviral activity of LL-37 against HSV-1 in vitro (Gordon et al. 2005).

It is known that a subgroup of patients with atopic dermatitis (AD) will develop eczema herpeticum (ADEH) due to a disseminated infection with HSV (Wollenberg et al. 2003). Patients with AD have decreased expression of host defence peptides, and it has been suggested that a deficiency of LL-37 may cause patients with AD to be more susceptible to ADEH (Ong et al. 2002). A study by Howell et al. (2006) showed that LL-37 exhibited direct antiviral activity against HSV-2 in vitro. In addition, a particularly physiologically relevant model was employed whereby human keratinocytes cells were pre-incubated with HSV for a period of 6 h before treatment with LL-37 for 18 h to assess whether intracellular viral replication could be inhibited with physiologic concentrations of LL-37 (Howell et al. 2006). This study showed that the peptide was able to significantly reduce the levels of HSV gene expression in infected keratinocytes. In vivo studies using mice deficient in mCRAMP revealed higher rates of HSV replication compared to the wild type mice, indicating an important role for host defence peptides in controlling HSV in skin infection.

Interestingly, a recent study tested and compared two different approaches to fight HSV-1 corneal infection. A sustained release of LL-37 delivered through nanoparticles incorporated within corneal implants was compared with a cell-based delivery of LL-37 cDNA transfected into HCECs (human corneal epithelial cells). LL-37 released from implants showed an ability to inhibit HSV-1 activity, but did not clear HSV-1 from infected cells. HCEC producing LL-37 also showed direct anti-HSV-1 activity, although none of these approaches were able to completely eliminate the virus infection (Lee et al. 2014).

3.3.2.3 Adenovirus (Ad)

Adenovirus is non-enveloped virus that is part of the *Adenoviridae* family. Adenoviruses are a major cause of conjunctivitis and keratoconjunctivitis, but can also cause upper and lower respiratory and gut infections. Although usually self-limiting, human adenovirus (HAdV) infections are quite contagious and put immunocompromised individuals at serious risk of severe and recurrent pulmonary infections, with mortality rates that reach up to 55 % (Lion 2014). Treatment for an infection is largely supportive therapy rather than direct antiviral therapeutics.

A study by Gordon et al. (2005) investigated the antiviral activity of LL-37 against different adenovirus serotypes (Ad19, Ad8, Ad5 and Ad3) (Gordon et al. 2005). LL-37 demonstrated a significant reduction of Ad19 titer in vitro (2 log

Table 3.1 Antiviral activities of cathelicidins

Cathelicidin	Structure	Source	Virus	Genome	Mechanism	References
LL-37	α-helix	Human	IAV	RNA	Viral envelope damage; cellular target; modulation of inflammatory response in vivo;	Tripathi et al. (2013), Barlow et al. (2011)
			HIV	RNA	Inhibition of HIV-1 reverse transcriptase	Wong et al. (2011)
			RSV	RNA	Direct effects on virus particles; cellular target;	Currie et al. (2013)
			VV	DNA	Viral envelope damage	Dean et al. (2010)
			HSV	DNA	Viral envelope damage; virus inactivation;	Howell et al. (2006)
			Ad	DNA	Unknown	Gordon et al. (2005)
mCRAMP	α-helix	Mouse	IAV	DNA	Virus inactivation; modulation of inflammatory response in vivo;	Barlow et al. (2011)
			VV	DNA	Unknown	Howell et al. (2004)
			HSV	DNA	Unknown	Howell et al. (2006)
Indocilidin	Extended	Bovine	HIV	RNA	Viral envelope damage	Robinson et al. (1998)
			JV	RNA	Viral inactivation	Albiol Matanic and Castilla (2004)
			HSV	DNA	Viral envelope damage	Albiol Matanic and Castilla (2004)
BMAP-18 (fragment derived from BMAP-27)	α-helix	Bovine	HIV	RNA	Viral inhibition	Wang et al. (2008)
BMAP-28	α-helix	Bovine	HSV	DNA	Viral inhibition	Benincasa et al. (2003)
Protegrin-1	β-sheet	Porcine	DENV	RNA	Inhibit NS2B/NS3 serine protease activity; viral inhibition	Rothan et al. (2012a, b)

reduction over 4 h). This study also provided some insight on a potential antiviral mechanism of cathelicidins, based on the comparison of HSV and Ad19 time-kill assays. The data demonstrated a rapid killing of HSV-1 which suggested a disruption of the viral lipid membrane as a possible mechanism. Several other studies have also proposed similar mechanisms for other cathelicidins (Robinson et al. 1998; Albiol Matanic and Castilla 2004; Dean et al. 2010). Interestingly, for the Ad19 strain, LL-37 produced a much slower progressive reduction in virus titers. As adenovirus lacks a viral envelope, this suggests that the direct antiviral mechanism of cathelicidins does not involve membrane disruption. Alternative mechanisms have been proposed such as disruption of the adenovirus particles (detergent-effect) and/or blockage of viral entry into the cell.

3.3.3   Summary—The Antiviral Activity of Cathelicidins

In summary, a review of the current literature shows that cathelicidins have antiviral properties against a broad spectrum of viruses; the underlying mechanisms likely involve a direct effect on viral particles as well as the capacity to modulate host immune responses that may contribute in the clearance of infection. A better understanding of how cathelicidins interact with virus particles directly, in addition to their effects on infected host cells, remains to be established. However, it is clear that cathelicidins are ideal targetable components of the innate immune system that can be used to inform the development of novel therapeutics with broad activity targeting a number of viruses (Table 3.1).

3.4   The Antiviral Activity of Defensins

Defensins are small, cysteine-rich cationic peptides that act as important effectors of the innate immune system (Ding et al. 2009; Ganz 2003). Human defensins are classified according to their structure, α and β-defensins differing in their disulphide bond pairing, and θ-defensins, being present in Old World monkeys, displaying a circular structure (Lehrer 2004). Of note, despite RNA transcripts for θ-defensins are found in human bone marrow cells, a premature stop codon prevents protein translation (Nguyen et al. 2010).

Neutrophil α-defensins (HNPs 1–4) are mainly synthesized as prepropeptides in promyelocytes in the bone marrow, and the mature peptide is stored in the granules of neutrophils. These peptides are found in lower concentrations in NK-cells, B-cells, γδ T-cells, monocytes, macrophages and immature dendritic cells (Rehaume and Hancock 2008). In contrast, human alpha defensins 5 and 6 (HD5 and HD6) are constitutively expressed and secreted as a propeptide in Paneth cells, salivary glands and also in genital mucosa (Ouellette 2006). Human β defensins (HBDs) 1-3 are mainly expressed in epithelial cells, but can also be found in

immune cells, mainly monocyte/macrophages and dendritic cells, whereas 3 θ-defensins (RTD1-3) have been found in rhesus macaque leukocytes (Ganz 2003; Tang et al. 1999). Retrocyclin, an artificial peptide based on the human θ defensins pseudogene has been also shown to possess antimicrobial capacity (Tran et al. 2008; Yasin et al. 2004).

Defensins have broad antimicrobial activities, including the capacity to inhibit viral infections. Despite structural and physical similarities, such as overall size and positive charge, each defensin has variable antiviral activity. The differences in activity are likely due to the mechanism of action exhibited by each peptide towards a particular DNA or RNA virus.

3.4.1   DNA Viruses

3.4.1.1   Herpes Simplex Virus

One of the first viruses which was shown to be inhibited by α-defensins was HSV-1, which was inactivated after incubation with HNP-1, -2 and -3, an effect that was abrogated by serum addition (Daher et al. 1986). Further work has shown that one β defensin (hBD3) and all six α-defensins inhibited HSV-2 infection (Hazrati et al. 2006). Interestingly, while HNP1-3 and HD5 interacted with the viral glycoprotein Gb2 present on the viral envelope, HNP-4 and HD6 bound to heparan sulfate and heparin, cellular receptors used for HSV-2 to gain entry to cells. All of these interactions have been shown to result in diminished viral entry. In contrast, the same study demonstrated that β-defensin 1 and 2 (hBD1 and hBD2) which lack anti-HSV-2 effects, do not bind to neither Gb2 nor heparan sulfate.

Similar antiviral effects against HSV are displayed by θ defensins, as both rhesus θ defensins 3 (RTD3) and retrocyclins 1 and 2 (RC1 and RC2) have been demonstrated to inhibit HSV viral entry to cells (Yasin et al. 2004). Of these peptides, retrocyclin 2 was shown to interact with the viral glycoprotein Gb2, thus interfering with viral entry without causing significant cytotoxicity to target cells. Defensins often display an antiviral activity that spans different steps on the target virus cycle. In this regard, HNP-1 and HD5 are able to block HSV viral gene expression even when added after the virus infection, indicating that defensins are also able to block post-entry events in the HSV cycle.

3.4.1.2   Human Papilloma Virus (HPV)

HNP-1-3 and HD5 but not hBD1, hBD2 or HD6 have been shown to exhibit antiviral activity against HPV, which is the primary cause of cervical cancer in sexually transmitted infections (Buck et al. 2006). HNP-1-3 and HD5 block HPV infection by impairing virion escape from endocytic vesicles. A recent study also suggested that HD5 blocks viral entry by interacting with viral particles and

blocking L2 cleavage, a necessary step for successful viral entry and post-entry events (Wiens and Smith 2015). Detailed studies on HD5 and HPV interactions suggest that hydrophobic residues, in particular, Arg-28, are very important for the antiviral activity of HD5 against HPV and other non-enveloped viruses (Gounder et al. 2012; Tenge et al. 2014).

3.4.1.3 Vaccinia Virus (VV)

Several defensins have been shown to have varying potential to neutralize VV infection. Incubating VV for 24 h with hBD3 was shown to reduce the number of viral plaques formed on BSC-1 green monkey kidney cells. In addition, hBD3 reduced the expression of viral DNA-dependent RNA polymerase (Howell et al. 2007) during viral infection. However, HNP-1, hBD1 and hBD2 showed no activity against this enveloped virus (Howell et al. 2004).

3.4.1.4 JC Polyomavirus (JCPyV) and BK Virus

JC polyomavirus (also known as John Cunningham virus) is a member of the family *polyoviridae*, and chronically infects between 70–90 % of the human population. This pathogen only tends to cause clinical symptoms in immunocompromised individuals, where infection spreads to the central nervous system (Shackelton et al. 2006; Wollebo et al. 2015). In experimental studies, a panel of α and β-defensins were tested for their capacity to neutralize JCPyV infection, resulting in HD5 and hBD3 being able to block the infection when incubated at 100 μg/ml with the virus for 1 h before infecting SVG-A human foetal glial cells (Zins et al. 2014). Interestingly, hBD3 showed significant cytotoxicity on cells at this concentration, whereas HD5 neutralized JCPyV in a dose-dependent manner (Zins et al. 2014; Dugan et al. 2008). Of note, HNP1-3 and hBD1, 2 and 4 showed no anti JCPyV activity. Further experiments also showed that HD5 was able to interact with JCPyVvirions, stabilizing the viral capsid and thus preventing the viral genome release (Zins et al. 2014), a novel mechanism of action for a peptide that is generally thought to employ detergent-like modes of antiviral activity.

BK virus shares 75 % of its genome with JCPyV, and was first isolated from the urine of a renal transplant individual (Gardner et al. 1971). Around 80 % of healthy individuals in England have been shown to display antibodies against the virus, generally in the absence of symptoms (Gardner 1973). If symptoms are noted, these can consist of fever and nonspecific upper respiratory infection which might lead to kidney manifestations such as cystitis or nephritis in immunocompromised individuals or those receiving transplants (Reploeg et al. 2001).

HNP1 and HD5 were shown to reduce viral V-protein expression in VERO cells when incubated directly with the virus at 20 or 50 μg/ml for 1 h, while hBD2 only was effective at 50 μg/ml. In contrast, hBD1 showed no inhibitory effect (Dugan et al. 2008). When the direct antiviral effect of defensins was studied further, HD5

was shown to interact directly with BK virus particles, inducing aggregation, and thus reducing viral attachment to cell membranes. Of note, similar antiviral effects of HD5 were also observed against other related polyomaviruses such as simian virus-40 (SV40). It was also shown that both HNP-1 and HD5 were also able to block adenovirus escape from endosomes.

3.4.1.5   Adenovirus (Ad)

It has been shown that hBD-1 and HD-5, when expressed on eukaryotic cell lines, showed potential to protect those cells against adenoviral infection, in particular from Av1CF2 (Gropp et al. 1999). Different HAdV species show variable susceptibility to defensin actions. In this regard, HNP-1 inhibited HAdV A, B and C infection, while increased HAdV D, E and F infectivity (Smith et al. 2010). HD5 showed similar actions, blocking HAdV A, B, C and E while increasing D and F infectivity. Interestingly, and similar to other non-enveloped viruses, HD5 interacts with adenoviral capsids preventing viral uncoating and avoiding its release from endocytic vesicles (Nguyen et al. 2010; Smith et al. 2010; Smith and Nemerow 2008). Further studies confirmed that Arg-28 residues of HD5 are critical for the antiviral effects seen against adenovirus (Gounder et al. 2012). Much less is known about other defensins effects on adenovirus. However, HNP-1 was shown to be effective at a concentration of 50 μg/ml in blocking adenovirus-type 5 infection of 293 cells, whereas hBD-2 showed a reduced effect (Bastian and Schäfer 2001).

3.4.1.6   Cytomegalovirus (CMV)

CMV is an enveloped virus that belongs to the *Herpesviridae* family, and is the most common congenital infection, affecting up to 0.2–2.2 % of all live births (Huygens et al. 2014). Foetal or perinatal infections can have devastating neurological consequences for the baby. However, post-natal CMV infections are usually asymptomatic, establishing lifelong infections without severe consequences on immune competent individuals.

In the context of CHDP activity against this virus, super physiological concentrations (100 and 200 μg/ml) of HNP-1 peptide were shown to directly inhibit CMV viral particles reducing the PFU/ml by 0.29 and 0.81 $\log_{10}$, respectively (Daher et al. 1986). However, this virus notably showed less susceptibility to HNP-1 compared to HSV-1, which was also assessed in the same study.

3.4.1.7   Baculovirus

Baculovirus naturally infects insect larvae hosts, usually *Lepidoptera* (Butterflies and moths), with no known diseases caused by this virus in organisms others than arthropods (Airenne et al. 2013). Due to its efficient reproduction cycle and ability

to carry large DNA inserts, baculovirus are extensively used as tools for gene delivery and recombinant production of proteins in insect cells. Baculovirus gp64 protein allows viral fusion in an acidified endosome, an event seen upon infection of *Spodoptera frugiperda* insect cells, resulting in gp64 expression and the formation of cell syncytia (Leikina et al. 2005). However, it has been shown that RC-2 peptide is capable of blocking baculovirus fusion with host cells, inhibiting the virus-mediated syncytium formation.

3.4.2 RNA Viruses

3.4.2.1 Human Immunodeficiency Virus (HIV)

It has been shown that a variety of defensin peptides can have an impact on HIV infection. HNP-1 is clearly deleterious for viral dissemination, having a direct effect against a low multiplicity of infection (MOI) of viral particles in the absence of serum, whereas in the presence of serum HNP-1 acts on host cells (Chang et al. 2005). One of the suggested mechanisms for such cellular effects is the HNP-1 mediated inhibition of the PKC signalling pathway, which is required for viral uncoating (Fields et al. 1988). Importantly, this HNP-1 effect did not affect the expression of viral receptors CD4, CXCR4 or CCR5 (Chang et al. 2003). Interestingly, as a part of its direct effects on HIV viral particles, HNP1-3 peptides were shown to interact with gp120, a viral glycoprotein, thus impairing viral attachment to cell membranes. This effect was further potentiated by HNP-1-3 interactions with cellular CD4. Both antiviral effects were reduced, but not completely abolished by the presence of serum (Demirkhanyan et al. 2012; Furci et al. 2006; Wang et al. 2004). A closely related peptide, HNP-4 was also able to bind gp120 and CD4 (Wu et al. 2005). A more indirect but also effective anti-HIV effect of HNP-1-3 peptides is their capacity to increase the secretion of the C-C chemokines MIP-1α, MIP-1β and RANTES, which can bind to CCR5 to act as antagonists for viral R5 strains that use CCR5 as a co-receptor (Guo et al. 2004).

In stark contrast to HNP1-3, HD5 and HD6 seem to increase viral infectivity without any blockage of post-entry viral events (Klotman et al. 2008). Further assessment of this unexpected effect suggested that HD5 and HD6 actually enhance viral attachment to the cells (Rapista et al. 2011). Another study, however, showed HD5 to inhibit HIV infection by blocking gp120–CD4 interaction (Furci et al. 2012). Further work is needed to clarify HD5 effects on the HIV infection process, particularly when considering sexually transmitted infections may increase HD5 and HD6 secretions in the genital mucosa prior to a possible HIV infection (Klotman et al. 2008).

Given the importance of HIV interaction with mucosal surfaces, β-defensin impact on HIV infection has also been investigated. HIV was shown to upregulate hBD2 and hBD3 release by human oral epithelial cells, and incubation of viral particles with these peptides protected cells from infection (Quiñones-Mateu et al.

2003). Interestingly, hBD1 was neither upregulated nor protective in this context. However, hBD2 and hBD3 did appear to act both directly on viral particles, and also on the host cell, by downregulating CXCR4 expression. Accordingly, these peptides were found to be more effective against X4 viral isolates. A later study found a similar anti-HIV activity of hBD2 and hBD3 to both X4 and R5 strains, indicating that defensin treatment inhibited early products of reverse transcription (Sun et al. 2005).

Given the interest in the broad antiviral effects of defensins, rhesus macaque θ-defensins (RTD) and synthetic retrocyclins (RC) have been also tested for their anti-HIV activity. RC-1 and RC-2 were shown to bind glycosylated gp120 and CD4, thus explaining the previously observed protective activity (Cole et al. 2002; Wang et al. 2003). Interestingly, RTD peptides also showed anti-HIV activity (Wang et al. 2004). Further work demonstrated that RC-1 was able to block HIV-1 fusion with target cells (Gallo et al. 2006). Finally, rhesus macaque α-defensins 4 (RMAD 4) also showed anti-HIV activity at 150 μg/ml by blocking viral entry (Tanabe et al. 2004). Interestingly, the same study showed that cryptidin-3 (a mouse derived α-defensin) actually increased HIV-1 replication. In this regard, guinea pig, rabbit and rat α-defensins have also been tested for anti-HIV activity, demonstrating an ability to inhibit infection of T-cell lines (Nakashima et al. 1993).

3.4.2.2   Hepatitis C (HCV)

Hepatitis C infection primarily affects the liver, being a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Maheshwari et al. 2008). HCV infection is estimated to affect 170 million people worldwide, is frequently asymptomatic, and spontaneous clearance is seen in a third of infected individuals. Chronic infection (with viral replication detected for more than 6 months) leads to hepatic complications. Little is known about the capacity of defensins to impact viral hepatitis. However, it has been shown that HCV core protein have been shown to activate the transcription of alpha-defensin genes, indicating that they may play a role in the innate immune response to the virus (Aceti et al. 2006).

3.4.2.3   Influenza A Virus (IAV)

Early studies have reported HNP-1-3 activity against the A/WSN (H1N1) strain of IAV (Daher et al. 1986). More detailed work has shown that HNP-1 affects influenza replication by blocking the PKC signalling pathway on host cells, needed for viral endosomal trafficking (Salvatore et al. 2007). It was shown that HNP-1 did not have a direct impact on viral particles, but did increase viral clearance by neutrophils (Tecle et al. 2007). A similar effect was also observed with HNP-2, HD5 and to a lesser extent with hBD2 but not with HNP-3 or hBD1. Another β-defensin, hBD3, was also shown to block IAV infection by blocking hemagglutinin-mediated fusion and immobilizing membrane proteins (Leikina et al.

2005). Interestingly, RC2 also showed similar effects to hBD3. Of note, murine β-defensin 2 and 3 (mBD2 and mBD3) protected mice from infection with the A/PR/8 (H1N1) IAV strain, and in similarity to their human analogues, their activity was attributed to impaired viral entry (Gong et al. 2010; Jiang et al. 2012).

3.4.2.4 Respiratory Syncytial Virus (RSV)

Defensins are expressed at high concentrations in the inflamed lung, and are usually upregulated during viral infections of the airway epithelia. In this context, it has been demonstrated that RSV infection increased hBD2 secretion by alveolar A549 cells, which was subsequently able to block further viral entry by directly disrupting the viral envelope (Kota et al. 2008). Interestingly RSV did not induce the expression of hBD1, as this is constitutive, but hBD1 lacked direct anti-RSV activity. Although alveolar macrophages are permissive to RSV infection, they do not tend to influence the later development of disease (Pribul et al. 2008). However, this interaction can result in increased secretion of pro-inflammatory cytokines that can impact on β-defensin expression in the lungs (Becker et al. 1950).

3.4.2.5 Rhinovirus (HRV)

Rhinovirus is a major cause of common cold and it is associated with asthma exacerbations (Jartti and Korppi 2011). It has been demonstrated that RV16 infection of primary bronchial epithelial cells results in the induction of hBD2 and hBD3 mRNA, whereas hBD1 remains unaltered (Duits et al. 2003). It was also demonstrated that the same serotype also upregulated hBD2 mRNA and protein in A549 alveolar epithelial cells. Interestingly this effect was conserved in other major group serotype HRV-14 or in 2 minor group serotypes such as HRV-2 and HRV-1A.

Further work has investigated the inoculation of human subjects divided into non-smokers, smokers and COPD groups with RV-16 (Proud et al. 1950). Interestingly, a larger proportion of smokers (78.6 %) were successfully inoculated with the virus, compared to those with COPD (66.7 %) or non-smokers (58 %). RV16 was shown to increase α-defensin secretion in the sputum 9 days post-infection compared to baseline, but this was only observed in the COPD group (Mallia et al. 2012). RV-16 infection also resulted in increased neutrophil elastase, which may subsequently degrade secreted host defence peptides.

3.4.2.6 Echovirus and Reovirus

The Enteric Cytopathic Human Orphan (ECHO) virus, belongs to the *Picornaviridae* family. Enteroviruses are mainly found in the gastrointestinal tract, and can cause opportunistic infections mainly in children by indirect faecal–oral

transmission, causing febrile illness (Sherris Medical Microbiology 2004). HNP-1 peptide was tested for its antiviral activity against this non-enveloped RNA virus without showing any direct antiviral effect at concentrations of peptide known to inhibit HSV-1 (Daher et al. 1986).

In similarity to Echovirus, HNP-1 showed no direct activity against this dsRNA, non-enveloped virus, which generally causes a mild and limited upper respiratory and gastrointestinal tract infection which can spread across individuals, and also across species (Daher et al. 1986). Interestingly, the use of reovirus is being contemplated in cancer therapy due to its oncolytic activity in melanoma lines and xenografts (Galanis et al. 2012).

3.4.2.7 Vesicular Stomatitis Indiana Virus (VSIV)

VSIV belongs to the *Rhabdoviridae* family and is an arthropod-borne virus primarily affecting rodents, cattle, swine and horses. Infected livestock or sand flies can be a source of infection for humans, which develops as mild flu-like symptoms (Kuzmin et al. 2009). This enveloped RNA virus showed an intermediate susceptibility to direct inactivation by HNP-1 peptide, reducing its PFU/ml by 0.74 and 0.84 $\log_{10}$ with 50 or 100 μg/ml of peptide, respectively (Daher et al. 1986).

3.4.2.8 SARS Coronavirus (SARS-CoV)

Severe acute respiratory syndrome (SARS) affected over 8000 individuals in 2002–2003, causing almost 800 deaths, underscoring the importance of testing antiviral agents (Peiris et al. 2003). It has been shown that intranasal injections of ~ 125 μg RTD-1 peptide prior to virus inoculation protected BALB/c mice against a mouse-adapted strain of SARS-CoV (Wohlford-Lenane et al. 2009). Of note, untreated animals exhibited around 75 % mortality rate, whereas treated ones showed a 100 % survival. RTD-1 treatment altered lung cytokine responses to the virus, suggesting immunomodulatory effects where at least in part, behind the protective action of RTD-1. Interestingly *DEFA-3* AND *DEFA-4* genes (coding for HNP-3 and -4) were upregulated in blood samples of patients suffering acute SARS coronavirus infection (Lee et al. 2005).

3.4.2.9 Dengue Virus (DENV)

Recombinant RC-1 peptide has shown to reduce DENV-2 viral replication in VERO cells when incubated directly with the viral particles, but also showed a moderate effect when pre-treating or treating cells post-viral entry (Rothan et al. 2012). This study suggested that RC-1 impacts DENV-2 replication by inhibiting the activity of viral NS2B-NS3 serine protease. Interestingly further studies showed

that human skin fibroblasts release HD5 and hBD2 upon infection with DENV-2 (Bustos-Arriaga et al. 2011).

3.4.2.10   Sindbis Virus (SINV)

SINV, a member of the *Togaviridae* family, is transmitted by a mosquito vector, and causes sindbis fever which results in arthralgia, malaise and rash. It has been shown that both RC2 and hBD3 peptide were able to block the virus fusion with target cells (Leikina et al. 2005) (Table 3.2).

3.5   Other CHDP with Antiviral Activity

In addition to the well-characterized activity of cathelicidins and defensins against a wide variety of viral pathogens, a number of CHDP from other non-human organisms have been the focus of a number of studies attempting to understand whether these peptides, or synthetic derivatives, could be used to inform the design of novel therapeutics against viral infections specific to humans.

A substantial diversity in CHDP exists across a number of other species that possess activity against human pathogens. The Antimicrobial Peptide Database (http://aps.unmc.edu/AP) now contains in excess of 2,500 peptides with demonstrable antimicrobial activity isolated from six kingdoms, and includes peptides from bacteria, fungi, plant, amphibians, fish, reptiles and birds. Interestingly, approximately 170 of these peptides (which include cathelicidins and defensins) demonstrate antiviral activity against a broad range of viral pathogens.

3.5.1   Cecropin

A family of CHDP with particularly potent activity against human viral pathogens is the cecropins. These peptides, identified initially in the Cecropia moth (*Hyalophoracecropia*) form part of the immune response to infection in a number of insect orders including Diptera and Lepidoptera, and are typically 30–39 amino acids in size (Boman 1991). Cecropin and cecropin-like peptides are a highly conserved, predominantly alpha helical group of peptides that have broad spectrum antibacterial and antifungal activity (Bulet and Stocklin 2005).

A recent study revealed that the mature form of an induced cecropin-like peptide found in the salivary glands of the female mosquito, *Aedesaegypti*, had substantial antiviral activity against Dengue virus (Luplertlop et al. 2011). The virus utilizes *A.aegypti* as a vector for transmission to humans and induces an innate immune response, characterized by the expression of a cecropin-like peptide, produced by up-regulation of the AAEL000598 gene. The peptide is subsequently cleaved from

Table 3.2 Antiviral activities of defensins

Defensin	Structure	Source	Virus	Genome	Antiviral mechanism	REF
HNP-1-3 (including HNP-1)	α-defensin	Human	HSV-2	dsDNA	Interacts with viral gb2; prevents binding to target cell; also blocks post-entry events	Yasin et al. (2004), Hazrati et al. (2006)
			HPV	dsDNA	Blocks virus escape from endocytic vesicles	Buck et al. (2006)
			VV	dsDNA	No antiviral effect	Howell et al. (2004)
			JCPyV	dsDNA	No antiviral effect	Zins et al. (2014)
			BK virus	dsDNA	Inhibits infection; mechanism unknown	Dugan et al. (2008)
			HAdV A, B1,B2,C	dsDNA	Inhibits infection; direct interaction with viral particles preventing uncoating	Smith et al. (2010), Bastian and Schäfer (2001)
			CMV	dsDNA	Modest direct antiviral effect	(Daher et al. 1986)
			HIV-1	ssRNA	Direct effect on virion; blocks viral gp120–cellular CD4 interaction; blocks host PKC signalling, affecting reverser transcription and integration; increased secretion of C–C chemokines	Chang et al. (2003), Demirkhanyan et al. (2012), Furci (2006), Wang et al. (2004), Guo (2004)
			VSIV	(−)ssRNA	Direct effect on virus, inhibits infection. mechanism unknown	Daher et al. (1986)
			HCV	(+)ssRNA	HCV core protein activates HNP transcription (antiviral activity untested)	Aceti et al. (2006)
			Echovirus	(+)ssRNA	Lack of direct effect on virion	Daher et al. (1986)
			Reovirus (type 3)	dsRNA	Lack of direct effect on virion	Daher et al. (1986)
			IAV	(−)ssRNA	Inhibition of PKC pathway in host cells; blocks viral replication and protein synthesis; increased uptake and clearance by neutrophils	Salvatore et al. (2007), Tecle et al. (2007)

Table 3.2 (continued)

Defensin	Structure	Source	Virus	Genome	Antiviral mechanism	REF
HNP-4	α-defensin	Human	HSV-2	dsDNA	Interacts with heparan sulfate on host cells; prevents viral entry	Hazrati et al. (2006)
			JCPyV	dsDNA	No antiviral effect	Zins et al. (2014)
			HIV-1	ssRNA	Lectin independent antiviral effect; weak interaction with gp120 and CD4	Wu et al. (2005)
RMAD3	Rhesus Macaque α-defensin 3	Rhesus	HIV-1	ssRNA	Moderate direct antiviral effect	Tanabe et al. (2004)
RMAD4	Rhesus Macaque α-defensin 4	Rhesus	HIV-1	ssRNA	Blocks viral entry	Tanabe et al. (2004)
HD5	α-defensin	Human	HSV-2	dsDNA	Interacts with viral gb2; prevents binding to target cell; blocks post-entry events	Hazrati et al. (2006)
			HPV	dsDNA	Blocks virus escape from endocytic vesicles; blocks virus unfolding (host mediated capsid L2 cleavage)	Yasin et al. (2004), Hazrati et al. (2006), Buck et al. (2006), Gounder et al. (2012)
			JCPyV	dsDNA	Binds to viral particles inhibiting genome release	Zins et al. (2014), Dugan et al. (2008)
			BK virus	dsDNA	Causes aggregation of viral particles, reducing viral attachment to cells	Zins et al. (2014), Dugan et al. (2008)
			HAdV A,B1,B2,C, E	dsDNA	Inhibits infection by direct interaction with viral particles preventing uncoating	Gounder et al. (2012), Smith et al. (2010)
			HIV-1	ssRNA	Enhances HIV-1 infection by increasing viral attachment; effects independent on CD4 or viral co-receptors in target cells	Klotman et al. (2008), Rapista et al. (2011)

Table 3.2 (continued)

Defensin	Structure	Source	Virus	Genome	Antiviral mechanism	REF
			IAV	(−)ssRNA	Increased neutrophil uptake and viral clearance	Tecle et al. (2007)
HD6	α-defensin	Human	HSV-2	dsDNA	Interacts with heparansulfate on host cells; prevents viral entry	Hazrati et al. (2006)
			HPV	dsDNA	No antiviral effect	Buck et al. (2006)
			HIV-1	ssRNA	Enhances HIV-1 infection by increasing viral attachment; effects independent on CD4 or viral co-receptors In target cells	Klotman et al. (2008), Rapista et al. (2011)
NP-1	α-defensin	Rabbit	HSV-1	dsDNA	Direct effect on viral particles; prevents viral entry and VP16 translocation to the nucleus	Sinha et al. (2003)
			HSV-2	dsDNA	Direct effect on viral particles; prevents viral entry and VP16 translocation to the nucleus	Sinha et al. (2003)
			HIV-1	ssRNA	Inhibits HIV infection in transformed cell lines	Nakashima et al. (1993)
α-defensins	α-defensin	Rat	HIV-1	ssRNA	Inhibits HIV infection in transformed cell lines	Nakashima et al. (1993)
α-defensins	α-defensin	Guinea pig	HIV-1	ssRNA	Inhibits HIV infection in transformed cell lines	Nakashima et al. (1993)
Crp 3	α-defensin	Mouse	HIV-1	ssRNA	Moderate increase in HIV infectivity	Tanabe et al. (2004)
Crp 4	α-defensin	Mouse	HIV-1	ssRNA	Moderate antiviral activity	Tanabe et al. (2004)
hBD1	β-defensin	Human	HSV-2	dsDNA	No antiviral effect	Hazrati et al. (2006)
			HPV	dsDNA	No antiviral effect	Buck et al. (2006)
			VV	dsDNA	No antiviral effect	Howell et al. (2004)

Table 3.2 (continued)

Defensin	Structure	Source	Virus	Genome	Antiviral mechanism	REF
			JCPyV	dsDNA	No antiviral effect	Zins et al. (2014)
			BK virus	dsDNA	No antiviral effect	Dugan et al. (2008)
			HAdV (Av1CF2)	dsDNA	Inhibits infection; mechanism unknown	Gropp et al. (1999)
			HIV-1	ssRNA	No antiviral effect; not upregulated by virus	Quiñones-Mateu (2003)
			IAV	(−)ssRNA	Increased virus uptake by neutrophils	Tecle et al. (2007)
			RSV	(−)ssRNA	No antiviral effect	Kota et al. (2008)
			HRV	(+)ssRNA	Not induced by virus	Duits et al. (2003)
hBD2	β-defensin	Human	HSV-2	dsDNA	No antiviral effect	Hazrati et al. (2006)
			HPV	dsDNA	No antiviral effect	Buck et al. (2006)
			VV	dsDNA	No antiviral effect	Howell et al. (2004)
			JCPyV	dsDNA	No antiviral effect	Zins et al. (2014)
			BK virus	dsDNA	Moderate inhibitory effect; mechanism unknown	Dugan et al. (2008)
			HAdV (5)	dsDNA	Moderate inhibitory effect; mechanism unknown	Bastian and Schäfer (2001)
			HIV-1	ssRNA	Inhibits both X4 and R5 infection; downregulates CXC4; inhibits early products of reverse transcription	Quiñones-Mateu et al. (2003), Sun et al. (2005)
			IAV	(−)ssRNA	Increased uptake by neutrophils	Tecle et al. (2007)
			RSV	(−)ssRNA	Increased secretion; direct effect on viral particles; disruption of the viral envelope	Kota et al. (2008)
			HRV	(+)ssRNA	Induction of expression by virus	Duits et al. (2003)

Table 3.2 (continued)

Defensin	Structure	Source	Virus	Genome	Antiviral mechanism	REF
mBD2	β-defensin	Mouse	IAV (PR8)	(−)ssRNA	Blocks viral entry to target cells	Gong et al. (2010)
			DENV-2	(+)ssRNA	Induction of expression	Bustos-Arriaga et al. (2011)
hBD3	β-defensin	Human	HSV-2	dsDNA	Interacts with heparansulfate on host cells and also viral gb2; prevents viral binding	Hazrati et al. (2006)
			VV	dsDNA	Reduced viral DNA-dependent RNA pol expression and plaque formation	Howell et al. (2004)
			JCPyV	dsDNA	Inhibits infection; cytotoxicity towards host cells	Zins et al. (2014)
			HIV-1	ssRNA	Inhibits both X4 and R5 infection; downregulates CXC4; inhibits early products of reverse transcription	Quiñones-Mateu (2003), Sun et al. (2005)
			IAV	(−)ssRNA	Blocks hemagglutinin-mediated viral fusion to host cells	Leikina et al. (2005)
			SINV	(+)ssRNA	Blocks viral fusion with target cells	Leikina et al. (2005)
mBD3	β-defensin	Mouse	IAV (PR8)	(−)ssRNA	Blocks viral entry to target cells	Jiang et al. (2012)
RC1	Inferred from human θ defensin genes	Human	HSV-2	dsDNA	Blocks viral attachment; reduced nuclear translocation of VP16	Yasin et al. (2004)
		Human	HSV-1	dsDNA	Direct effect on viral particles; mechanism unknown	Yasin et al. (2004)
		Human	HIV-1	ssRNA	Blocks viral fusion; binds to viral gp41 and glycosylated gp120 and cellular CD4	Cole et al. (2002), Gallo et al. (2006), Wang et al. (2004)
		Human	HIV-2	ssRNA	Modest inhibition of viral fusion	Gallo et al. (2006)

(continued)

Table 3.2 (continued)

Defensin	Structure	Source	Virus	Genome	Antiviral mechanism	REF
		Human	SIV	ssRNA	Modest inhibition of viral fusion	Gallo et al. (2006)
		Human	DENV-2	(+)ssRNA	Reduces replication by inhibiting viral NS2B-NS3 serine protease	Rothan et al. (2012)
RC2	Inferred from human θ defensin genes	Human	HSV-2	dsDNA	Blocks viral attachment; reduced nuclear translocation of VP16	Yasin et al. (2004)
			HSV-1	dsDNA	Direct effect on viral particles; mechanism unknown	Yasin et al. (2004)
			Baculovirus	dsDNA	Blocks viral fusion with target cells, avoids syncytium formation	Leikina et al. (2005)
			HIV-1	ssRNA	Blocks viral fusion; binds to viral glycosylated gp120 and cellular CD4	Wang et al. (2004), Cole et al. (2002)
			IAV	(−)ssRNA	Prevents hemagglutinin-mediated viral fusion with target cells	Leikina et al. (2005)
			SINV	(+)ssRNA	Prevents viral fusion with target cells	Leikina et al. (2005)
RTD1	Rhesus θ defensin	Rhesus	HSV-2	dsDNA	No antiviral effect	Yasin et al. (2004)
			HSV-1	dsDNA	No antiviral effect	Yasin et al. (2004)
			HIV-1 (various isolates)	ssRNA	Moderate direct antiviral effect; mechanism unknown	Wang et al. (2004)
			SARScoV	(+)ssRNA	Immunomodulatory effect; reduction in lung cytokine secretion	Wohlford-Lenane et al. (2009)

Table 3.2 (continued)

Defensin	Structure	Source	Virus	Genome	Antiviral mechanism	REF
RTD2	Rhesus θ defensin	Rhesus	HSV-2	dsDNA	Moderate antiviral effect; mechanism unknown	Yasin et al. (2004)
			HSV-1	dsDNA	No antiviral effect	Yasin et al. (2004)
			HIV-1 (various isolates)	ssRNA	Moderate direct antiviral effect; mechanism unknown	Wang et al. (2004)
RTD3	Rhesus θ defensin	Rhesus	HSV-2	dsDNA	Direct effect on viral particles; cytotoxicity towards host cell	Yasin et al. (2004)
			HSV-1	dsDNA	Direct effect on viral particles; mechanism unknown	Yasin et al. (2004)
			HIV-1 (various isolates)	ssRNA	Moderate direct antiviral effect; mechanism unknown	Wang et al. (2004)

an immature form into a mature active form. Interestingly the immature (MK) form of the cecropin-like peptide was more active against all four strains of Dengue virus tested (Dengue-1, -2, -3 and -4) than the mature (GK) cleaved form. The authors also established that both the GK and MK forms of the peptide were active against Chikungunya virus, a pathogen also transmitted by the *A. aegypti* mosquito that can cause fever and severe long lasting joint pain. Another study revealed that scorpine, a hybrid peptide with structural similarities to cecropins and defensins derived from the venom of the scorpion *Pandinus imperator*, also exhibited antiviral activity against dengue virus by inhibiting the replication of Dengue-2 virus (Carballar-Lejarazu et al. 2008).

Cecropin A is reported to inhibit HIV production by infected T-cells and fibroblasts in a dose-dependent manner (Wachinger et al. 1998). The mechanism responsible for this inhibition was found to be reduced viral gene expression and synthesis of viral products, indicating that Cecropin has an antiviral role beyond that of direct interaction with the HIV virion.

Cecropins have also been shown to have antiviral activity at early and late points in the viral infection and replication cycle. For example, both cecropin P1 and cecropin D have been shown to have antiviral activity at several stages in infection with porcine reproductive and respiratory syndrome virus (PRRSV), an infection which can have substantial financial impact in the pig industry. Cecropin P1 is a peptide initially thought to be produced in the porcine intestine (Lee et al. 1989), but was later revealed to have been produced by the nematode, *Ascarissuum*, which survives in the porcine gut (Andersson et al. 2003). This peptide was shown to block attachment and replication of the virus in kidney and alveolar macrophage cell lines, and also reduced the number of infectious viral particles produced after infection in vitro (Guo et al. 2014). The peptide was also shown to have immunomodulatory properties by preventing the onset of PRRSV-induced apoptosis. Similarly, cecropin D was recently shown to inhibit PRRSV attachment and replication, and also attenuated apoptosis induced by the virus (Liu et al. 2015).

The broad spectrum antiviral activity of cecropins is further evidenced by a study demonstrating that cecropin A could inhibit replication of Junin virus, the cause of Argentine hemorrhagic fever (Albiol Matanic and Castilla 2004). The peptide inhibited Junin virus-related protein production in host cells, but the authors suggested that the antiviral effects were predominantly limited to later stages in the virus replication cycle, since the peptide did not appear to alter viral infectivity. Interestingly, the same study also demonstrated that cecropin A did not exhibit any inhibitory activity against herpes simplex virus types 1 and 2, suggesting that any antiviral activity exhibited by these peptides is pathogen specific. It should be noted that all HSV-1 and HSV-2 contain a DNA genome, in contrast to HIV-1, Junin, PRRSV and Dengue, which are RNA viruses, and thus the activity of cecropins against other DNA viruses remains to be understood.

3.5.2 Dermaseptin

There have been a substantial number ($\sim$1000) Host Defence Peptides identified from amphibian skin, of which Dermaseptins are a superfamily. These host defence peptides have a cationic charge due to an abundance of lysine residues, and tend to be between 27–34 amino acids in size (Amiche et al. 1994). They have been found in several species of frogs, including the Hylidae (tree frogs) and the Ranidae (true frogs) (Nicolas and El Amri 2009). Dermaseptins have been demonstrated to have antimicrobial activity against a wide range of bacterial pathogens involved in human diseases including *Pseudomonas*, *Salmonella*, *Staphylococcus*, *Escherichia* and *Enterobacter* species. Interestingly, the peptide Dermaseptin S1, a 34-residue peptide isolated from the frog genus *Phyllomedusa*, was shown to have immunomodulatory activity via an ability to stimulate the production of reactive oxygen species and myeloperoxidase by primary human neutrophils (Ammar et al. 1998). Dermaseptin S2 has also been touted as a potential therapeutic molecule in the treatment of cancer in a recent study demonstrating antitumor and angiostatic activity in a range of tumour cell types, likely due to the induction of necrosis (van Zoggel et al. 2012).

In terms of their antiviral activity, dermaseptins have been shown to be highly effective against a broad range of viral pathogens, with activity that affects several steps in the infection and replication process. Dermaseptin-1 was initially identified to have antiviral activity against two viruses that are known to infect ectothermic animals; Frog virus 3 from the family *Iridoviridae*, and Channel catfish virus, a member of the *Herpesviridae* family (Chinchar et al. 2004). This study provided indication that dermaseptin peptides possessed antiviral activity and subsequent studies were extended to examine the activity against human viral pathogens.

Dermaseptins S1-S5 shown to have direct and varying antiviral activity against Herpes Simplex Virus-1 in vitro (Belaid et al. 2002). This study identified Dermaseptin S4 as having the most potent antiviral activity, but only at very early stages in the viral infection process as experiments suggested that it exerted an effect when exposed to the virus prior to infection or during viral attachment. A later study further evaluated the activity of Dermaseptin S1 and derivatives against Herpes Simplex Virus, demonstrating that the antiviral activity of the parent peptide could be increased by alteration of the original sequence (Savoia et al. 2010). Interestingly, the same study also showed that some of the derivatives also exhibited activity against Papillomavirus Psv-16 in vitro, but with very low cytotoxicity towards the host cells. A recent study by Bergaoui et al. also demonstrated that Dermaseptin S4 and synthetic derivatives exhibited activity against Herpes Simplex Virus-2 with reduced cytotoxicity, although in vivo efficacy remains to be determined (Bergaoui et al. 2013).

Other studies have revealed a possible role for Dermaseptins in the treatment of HIV-1 infection. Dermaseptins have been shown to partially inhibit HIV virus infection of T-cells although cytotoxicity was observed at higher concentrations (VanCompernolle et al. 2005). Another study by Lorin et al. identified Dermaseptin

S4 as having potential inhibitory activity against HIV-1 by inhibiting viral infection of human primary T-lymphocytes (Lorin et al. 2005). The authors attributed this activity to a direct disruption of the virion and, while the parent peptide elicited cytotoxicity at higher concentrations, were able to reduce host cell cytotoxicity by reducing the positive charge of the native peptide through amino acid deletion or substitution. Notably, the modified peptides were also able to reduce HIV-1 binding to endometrial cells together with inhibition of capture and transmission of virus from dendritic cells to CD4^{+} T-cells. Dermaseptin S9 was also identified as having weak activity against HIV-1, but a mutant S9 peptide, where three lysine residues were replaced with arginines, exhibited potent inhibitory activity against HIV-1 although the mechanism underlying this observation remains unclear (Wang et al. 2010).

3.5.3 Magainin

Magainins are cationic host defence peptides that were originally identified in the skin and granular secretions of *Xenopuslaevis* (the African clawed frog) (Zasloff 1987; Giovannini et al. 1987), but have also been identified as inducible peptides in other species in the *Xenopus* genus; *X. borealis, X. clivii, X. muelleri, X. petersii, X. amieti* and *X. andrei* (Conlon et al. 2012). These peptides are 23–34 amino acids in length and the native peptides, together with synthetic derivatives, have been demonstrated to have broad antimicrobial activity against a range of bacterial pathogens (Zairi et al. 2009; Chen et al. 1988). There is, however, a limited amount of information on the activity of magainins against viral pathogens. One study has assessed the activity of a number of synthetic magainin derivatives against Herpes Simplex-1 virus, establishing that several peptide derivatives have the capacity to reduce viral plaque formation in in vitro assays (Egal et al. 1999). Further evidence of antiviral activity of magainins was also revealed in a study by Chinchar et al. (2004) which showed magainin II, but not magainin I, was able to reduce the infectivity of channel catfish virus (CCV) (Chinchar et al. 2004). However, both magainins exhibited less activity against frog virus 3, indicating that the activity was likely virus specific.

3.5.4 Melittin

Melittin is an alpha helical peptide that is 26 amino acids in length and was initially identified in bee venom (Habermann and Jentsch 1967) and later characterized as an amphipathic peptide with broad ranging antimicrobial activity (Terwilliger and Eisenberg 1982; Wade et al. 1992). The native melittin peptide and synthetic analogues have been investigated in a number of studies as potential novel antimicrobial therapeutics, but their well-characterized antiviral activity against a number of pathogens is of particular interest.

One of the first studies to assess the antiviral activity of melittin was published Wachinger et al. (1992) which identified that melittin and six derivatives reduced HIV-1 replication in host cells (Wachinger et al. 1992). A subsequent study revealed that the mechanism underlying this inhibition was that melittin was capable of specifically reducing HIV-associated gene expression in the host cell while not affecting the overall gene expression profile (Wachinger et al. 1998). This suggests an important immunomodulatory role for this peptide, rather than direct antiviral activity, as potentially contributing to the treatment of HIV infection.

Several studies have also characterized the influence of melittin, and synthetic derivatives upon the establishment and progression of Herpes Simplex Virus infection. Baghian et al. (1997) synthesized a number of derivatives based upon the original melittin structure to assess their antiviral activity against HSV-1 virus. One such peptide was called Hecate, which has an altered amino sequence that changes the distribution of charged residues within the peptide without altering the overall amphipathic α-helical structure (Baghian et al. 1997). The authors determined that Hecate prevented HSV-1 plaque formation and prevented virus spread in in vitro models while some synthetic melittin analogues were unable to do so, suggesting that sequence played an important role in the antiviral activity of the peptide. A later study screened a number of known CHDP against HSV-1 and HSV-2 and established that many of the α-helical peptides screened (including magainins, cecropins and cathelicidin) did not display activity against the viruses (Yasin et al. 2000). However, melittin did have substantial activity against both HSV-1 and HSV-2, although the mechanism underlying this observation was not fully described.

More recently, it has been demonstrated that the native melittin peptide showed antiviral activity towards Junin virus (Albiol Matanic and Castilla 2004), and that synthetic melittin analogues showed activity towards Tobacco Mosaic Virus (Marcos et al. 1995). Interestingly, a recent study by Falco et al. (2013) used melittin-loaded liposomes to specifically target fish viral hemorrhagic septicemia rhabdovirus (VHSV) (Falco et al. 2013). The authors coated the immunoliposomes with antibodies targeting the surface G glycoprotein of VHSV, and showed a reduction in infectivity of greater than 95 %. This approach provides an exciting avenue for the targeted delivery of antiviral host defence peptides whilst minimizing cytotoxic damage to host cells.

3.5.5   Tachyplesin and Polyphemusin

Tachyplesin is a 17 amino acid cationic β-sheet peptide that was originally identified in the hemocytes of *Tachypleustridentatus* (Horseshoe crab) and was demonstrated to have broad spectrum antimicrobial activity (Nakamura et al. 1988). Polyphemusin I is a 18 amino acid peptide identified in the hemocytes of the American horseshoe crab, *Limulus polyphemus*. Both peptides are thought to play a key role in the innate immune system of the crab, and have been shown to have potent LPS binding and neutralization activity (Nakamura et al. 1988; Powers et al. 2006).

The antiviral activity of Tachyplesin against HIV was investigated by Morimoto et al. (1991) who showed that the peptide could reduce virus-mediated cytopathic effects by more than 70 % in in vitro models (Morimoto et al. 1991). The peptide also reduced the infectivity of the virus, an effect that was shown to be independent on the reverse transcriptase activity of HIV. Interestingly, subsequent studies by Nakashima et al. (1992), Murakami et al. (1997) and Xu et al. (1999) characterized the activities of the isopeptideT22 (Tyr^{5,12}, Lys^{7}-polyphemusin II), and synthetic analogues against HIV, and determined that the antiviral activity was due to ability of the peptide to bind to CXCR4 (Xu et al. 1999; Murakami et al. 1997; Nakashima et al. 1992). CXCR4 is a chemokine receptor used by T-cell tropic strains of HIV to infect host cells. Thus, the host cell mediated mechanism of action of these peptides against HIV contrasts to the direct antiviral activity exhibited by other CHDP.

Tachplesin peptides have also been demonstrated to have activity against other viruses that affect humans. It was shown that Tachyplesin peptides were able to inactivate Vesicular stomatitis virus (VSV; also known as vesicular stomatitis Indiana virus), a zoonotic member of the family *Rhabdoviridae* that can infect cattle and cause disease in humans (Murakami et al. 1991). The same study also identified that Influenza A (H1N1) was also moderately susceptible, although HSV-1 and -2, adenovirus-1, reovirus-2 and poliovirus-1 were not susceptible to the antiviral activities of the peptide. However, a subsequent study, which examined the antiviral activity of tachyplesin against HSV-1 and HSV-2 using an in vitro cyto-toxicity model, did suggest that the peptide offered a moderate degree of protection against both virus strains (Yasin et al. 2000).

3.6 Conclusion

Collectively, the experimental studies presented here highlight the crucial role that CHDP play in the innate immune response across a wide variety of cell types and species. These peptides possess powerful antiviral activity, and can modulate the cellular immune response to provide a key defence mechanism infection and pathology associated with a myriad of viruses.

While we are beginning to understand some of the underlying mechanisms through which cathelicidins, defensins and other CHDP mediate their antiviral effects; research into the activities of these peptides is still in relative infancy. It is clear, however, that CHDP have huge therapeutic potential as exogenous peptides, and for the development of powerful synthetic analogues that can be directed towards specific viral pathogens.

References

Aceti A, Mangoni ML, Pasquazzi C, Fiocco D, Marangi M, Miele R et al (2006) Alpha-defensin increase in peripheral blood mononuclear cells from patients with hepatitis C virus chronic infection. J Viral Hepatitis 13:821–827

Agerberth B, Charo J, Werr J, Olsson B, Idali F, Lindbom L et al (2000) The human antimicrobial and chemotactic peptides LL-37 and alpha-defensins are expressed by specific lymphocyte and monocyte populations. Blood 96(9):3086–3093

Airenne KJ, Hu Y-C, Kost TA, Smith RH, Kotin RM, Ono C et al (2013) Baculovirus: an insect-derived vector for diverse gene transfer applications. Mol Ther: J Am Soc Gene Ther 21:739–749

Albiol Matanic VC, Castilla V (2004) Antiviral activity of antimicrobial cationic peptides against Junin virus and herpes simplex virus. Int J Antimicrob Agents 23(4):382–389

Amiche M, Ducancel F, Mor A, Boulain JC, Menez A, Nicolas P (1994) Precursors of vertebrate peptide antibiotics dermaseptin b and adenoregulin have extensive sequence identities with precursors of opioid peptides dermorphin, dermenkephalin, and deltorphins. J Biol Chem 269 (27):17847–17852

Ammar B, Perianin A, Mor A, Sarfati G, Tissot M, Nicolas P et al (1998) Dermaseptin, a peptide antibiotic, stimulates microbicidal activities of polymorphonuclear leukocytes. Biochem Biophys Res Commun 247(3):870–875

Andersson M, Boman A, Boman HG (2003) Ascaris nematodes from pig and human make three antibacterial peptides: isolation of cecropin P1 and two ASABF peptides. Cellular and molecular life sciences: CMLS 60(3):599–606

Baghian A, Jaynes J, Enright F, Kousoulas KG (1997) An amphipathic alpha-helical synthetic peptide analogue of melittin inhibits herpes simplex virus-1 (HSV-1)-induced cell fusion and virus spread. Peptides 18(2):177–183

Barlow PG, Li Y, Wilkinson TS, Bowdish DM, Lau YE, Cosseau C et al (2006) The human cationic host defense peptide LL-37 mediates contrasting effects on apoptotic pathways in different primary cells of the innate immune system. J Leukoc Biol 80(3):509–520

Barlow PG, Svoboda P, Mackellar A, Nash AA, York IA, Pohl J et al (2011) Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PLoS One 6(10):e25333

Barlow PG, Findlay EG, Currie SM, Davidson DJ (2014) Antiviral potential of cathelicidins. Future Microbiol 9(1):55–73

Bastian A, Schäfer H (2001) Human α-defensin 1 (HNP-1) inhibits adenoviral infection in vitro. Regul Pept 101:157–161

Becker S, Quay J, Soukup J (1991) Cytokine (tumor necrosis factor, IL-6, and IL-8) production by respiratory syncytial virus-infected human alveolar macrophages. Journal of Immunology 147:4307–4312 (Baltimore, Md: 1950)

Belaid A, Aouni M, Khelifa R, Trabelsi A, Jemmali M, Hani K (2002) In vitro antiviral activity of dermaseptins against herpes simplex virus type 1. J Med Virol 66(2):229–234

Benincasa M, Skerlavaj B, Gennaro R, Pellegrini A, Zanetti M (2003) In vitro and in vivo antimicrobial activity of two alpha-helical cathelicidin peptides and of their synthetic analogs. Peptides 24(11):1723–1731

Bergaoui I, Zairi A, Tangy F, Aouni M, Selmi B, Hani K (2013) In vitro antiviral activity of dermaseptin S(4) and derivatives from amphibian skin against herpes simplex virus type 2. J Med Virol 85(2):272–281

Bergman P, Walter-Jallow L, Broliden K, Agerberth B, Soderlund J (2007) The antimicrobial peptide LL-37 inhibits HIV-1 replication. Curr HIV Res 5(4):410–415

Boman HG (1991) Antibacterial peptides: key components needed in immunity. Cell 65(2):205–207

Buck CB, Day PM, Thompson CD, Lubkowski J, Lu W, Lowy DR et al (2006) Human-defensins block papillomavirus infection. Proc Natl Acad Sci 103:1516–1521

Bulet P, Stocklin R (2005) Insect antimicrobial peptides: structures, properties and gene regulation. Protein Pept Lett 12(1):3–11

Bustos-Arriaga J, García-Machorro J, León-Juárez M, García-Cordero J, Santos-Argumedo L, Flores-Romo L et al (2011) Activation of the innate immune response against DENV in normal non-transformed human fibroblasts. PLoS Negl Trop Dis 5:e1420

Carballar-Lejarazu R, Rodriguez MH, de la Cruz Hernandez-Hernandez F, Ramos-Castaneda J, Possani LD, Zurita-Ortega M et al (2008) Recombinant scorpine: a multifunctional antimicrobial peptide with activity against different pathogens. Cellular and molecular life sciences: CMLS 65(19):3081–3092

Chang TL-Y, Francois F, Mosoian A, Klotman ME (2003) CAF-mediated human immunode-ficiency virus (HIV) type 1 transcriptional inhibition is distinct from -defensin-1 HIV inhibition. J virol 77:6777–6784

Chang TL, Vargas J, DelPortillo A, Klotman ME (2005) Dual role of α-defensin-1 in anti–HIV-1 innate immunity. J Clin Invest 115:765–773

Chen HC, Brown JH, Morell JL, Huang CM (1988) Synthetic magainin analogues with improved antimicrobial activity. FEBS Lett 236(2):462–466

Chinchar VG, Bryan L, Silphadaung U, Noga E, Wade D, Rollins-Smith L (2004) Inactivation of viruses infecting ectothermic animals by amphibian and piscine antimicrobial peptides. Virology 323(2):268–275

Cole AM, Hong T, Boo LM, Nguyen T, Zhao C, Bristol G et al (2002) Retrocyclin: a primate peptide that protects cells from infection by T- and M-tropic strains of HIV-1. Proc Natl Acad Sci USA 99:1813–1818

Conlon JM, Mechkarska M, King JD (2012) Host-defense peptides in skin secretions of African clawed frogs (Xenopodinae, Pipidae). Gen Comp Endocrinol 176(3):513–518

Currie SM, Findlay EG, McHugh BJ, Mackellar A, Man T, Macmillan D et al (2013) The human cathelicidin LL-37 has antiviral activity against respiratory syncytial virus. PLoS One 8(8): e73659

Daher KA, Selsted ME, Lehrer RI (1986) Direct inactivation of viruses by human granulocyte defensins. J Virol 60(3):1068–1074

De Y, Chen Q, Schmidt AP, Anderson GM, Wang JM, Wooters J et al (2000) LL-37, the neutrophil granule- and epithelial cell-derived cathelicidin, utilizes formyl peptide receptor-like 1 (FPRL1) as a receptor to chemoattract human peripheral blood neutrophils, monocytes, and T cells. J Exp Med 192(7):1069–1074

Dean RE, O'Brien LM, Thwaite JE, Fox MA, Atkins H, Ulaeto DO (2010) A carpet-based mechanism for direct antimicrobial peptide activity against vaccinia virus membranes. Peptides 31(11):1966–1972

Demirkhanyan LH, Marin M, Padilla-Parra S, Zhan C, Miyauchi K, Jean-Baptiste M et al (2012) Multifaceted mechanisms of HIV-1 entry inhibition by human α-defensin. J Biol Chem 287:28821–28838

Ding J, Chou Y-Y, Chang TL (2009) Defensins in viral infections. J Innate Immun 1:413–420

Dugan AS, Maginnis MS, Jordan JA, Gasparovic ML, Manley K, Page R et al (2008) Human -defensins inhibit BK virus infection by aggregating virions and blocking binding to host cells. J Biol Chem 283:31125–31132

Duits LA, Nibbering PH, van Strijen E, Vos JB, Mannesse-Lazeroms SPG, van Sterkenburg MAJA et al (2003) Rhinovirus increases human beta-defensin-2 and -3 mRNA expression in cultured bronchial epithelial cells. FEMS Immunol Med Microbiol 38:59–64

Egal M, Conrad M, MacDonald DL, Maloy WL, Motley M, Genco CA (1999) Antiviral effects of synthetic membrane-active peptides on herpes simplex virus, type 1. Int J Antimicrob Agents 13(1):57–60

Falco A, Barrajon-Catalan E, Menendez-Gutierrez MP, Coll J, Micol V, Estepa A (2013) Melittin-loaded immunoliposomes against viral surface proteins, a new approach to antiviral therapy. Antiviral Res 97(2):218–221

Fields AP, Bednarik DP, Hess A, Stratford May W (1988) Human immunodeficiency virus induces phosphorylation of its cell surface receptor. Nature 333:278–280

Furci L, Sironi F, Tolazzi M, Vassena L, Lusso P (2006) -defensins block the early steps of HIV-1 infection: interference with the binding of gp120 to CD4. Blood

Furci L, Tolazzi M, Sironi F, Vassena L, Lusso P (2012) Inhibition of HIV-1 infection by human α-defensin-5, a natural antimicrobial peptide expressed in the genital and intestinal mucosae. PLoS One 7:e45208

Galanis E, Markovic SN, Suman VJ, Nuovo GJ, Vile RG, Kottke TJ et al (2012) Phase II trial of intravenous administration of reolysin® (reovirus serotype-3-dearing strain) in patients with metastatic melanoma. Mol Ther 20:1998–2003

Gallo RL, Kim KJ, Bernfield M, Kozak CA, Zanetti M, Merluzzi L et al (1997) Identification of CRAMP, a cathelin-related antimicrobial peptide expressed in the embryonic and adult mouse. J Biol Chem 272(20):13088–13093

Gallo SA, Wang W, Rawat SS, Jung G, Waring AJ, Cole AM et al (2006) Theta-defensins prevent HIV-1 Env-mediated fusion by binding gp41 and blocking 6-helix bundle formation. J Biol Chem 281:18787–18792

Ganz T (2003) Defensins: antimicrobial peptides of innate immunity. Nat Rev Immunol 3:710–720

Gardner SD (1973) Prevalence in England of antibody to human polyomavirus (B.K.). BMJ 1:77–78

Gardner SD, Field AM, Coleman DV, Hulme B (1971) New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet (London, England) 1:1253–7

Giovannini MG, Poulter L, Gibson BW, Williams DH (1987) Biosynthesis and degradation of peptides derived from Xenopus laevis prohormones. Biochem J 243(1):113–120

Gong T, Jiang Y, Wang Y, Yang D, Li W, Zhang Q et al (2010) Recombinant mouse beta-defensin 2 inhibits infection by influenza A virus by blocking its entry. Arch Virol 155:491–498

Gordon YJ, Huang LC, Romanowski EG, Yates KA, Proske RJ, McDermott AM (2005) Human cathelicidin (LL-37), a multifunctional peptide, is expressed by ocular surface epithelia and has potent antibacterial and antiviral activity. Curr Eye Res 30(5):385–394

Gounder AP, Wiens ME, Wilson SS, Lu W, Smith JG (2012) Critical determinants of human -defensin 5 activity against non-enveloped viruses. J Biol Chem 287:24554–24562

Gropp R, Frye M, Wagner TOF, Bargon J (1999) Epithelial defensins impair adenoviral infection: implication for adenovirus-mediated gene therapy. Hum Gene Ther 10:957–964

Guo C-J, Tan N, Song L, Douglas SD, Ho W-Z (2004) Alpha-defensins inhibit HIV infection of macrophages through upregulation of CC-chemokines. AIDS (London, England) 18:1217–1218

Guo C, Huang Y, Cong P, Liu X, Chen Y, He Z (2014) Cecropin P1 inhibits porcine reproductive and respiratory syndrome virus by blocking attachment. BMC Microbiol 14:273

Habermann E, Jentsch J (1967) Sequence analysis of melittin from tryptic and peptic degradation products. Hoppe Seylers Z Physiol Chem 348(1):37–50

Hazrati E, Galen B, Lu W, Wang W, Ouyang Y, Keller MJ et al (2006) Human - and -defensins block multiple steps in herpes simplex virus infection. J Immunol 177:8658–8666

Howell MD, Jones JF, Kisich KO, Streib JE, Gallo RL, Leung DY (2004) Selective killing of vaccinia virus by LL-37: implications for eczema vaccinatum. J Immunol 172(3):1763–1767

Howell MD, Gallo RL, Boguniewicz M, Jones JF, Wong C, Streib JE et al (2006) Cytokine milieu of atopic dermatitis skin subverts the innate immune response to vaccinia virus. Immunity 24 (3):341–348

Howell MD, Streib JE, Leung DYM (2007) Antiviral activity of human β-defensin 3 against vaccinia virus. J Allergy Clin Immunol 119:1022–1025

Huang LC, Reins RY, Gallo RL, McDermott AM (2007) Cathelicidin-deficient (Cnlp -/-) mice show increased susceptibility to Pseudomonas aeruginosa keratitis. Invest Ophthalmol Vis Sci 48(10):4498–4508

Hurt AC (2014) The epidemiology and spread of drug resistant human influenza viruses. Curr Opin Virol 8:22–29

Huygens A, Dauby N, Vermijlen D, Marchant A (2014) Immunity to cytomegalovirus in early life. Front Immunol 5:552

Iimura M, Gallo RL, Hase K, Miyamoto Y, Eckmann L, Kagnoff MF (2005) Cathelicidin mediates innate intestinal defense against colonization with epithelial adherent bacterial pathogens. J Immunol 174(8):4901–4907

Jartti T, Korppi M (2011) Rhinovirus-induced bronchiolitis and asthma development. Pediatr Allergy Immunol: Eur Soc Pediatr Allergy Immunol 22(4):350–355

Jiang Y, Yang D, Li W, Wang B, Jiang Z, Li M (2012) Antiviral activity of recombinant mouse β-defensin 3 against influenza A virus in vitro and in vivo. Antiviral Chem Chemother 22:255–262

Klotman ME, Rapista A, Teleshova N, Micsenyi A, Jarvis GA, Lu W et al (2008) Neisseria gonorrhoeae-induced human defensins 5 and 6 increase HIV infectivity: role in enhanced transmission. J Immunol 180(9):6176–6185

Kota S, Sabbah A, Chang TH, Harnack R, Xiang Y, Meng X et al (2008) Role of human beta-defensin-2 during tumor necrosis factor-alpha/NF-kappaB-mediated innate antiviral response against human respiratory syncytial virus. J Biol Chem 283:22417–22429

Kovach MA, Ballinger MN, Newstead MW, Zeng X, Bhan U, Yu FS et al (2012) Cathelicidin-related antimicrobial peptide is required for effective lung mucosal immunity in gram-negative bacterial pneumonia. J Immunol 189(1):304–311

Kuzmin IV, Novella IS, Dietzgen RG, Padhi A, Rupprecht CE (2009) The rhabdoviruses: biodiversity, phylogenetics, and evolution. Infect Genet Evol 9:541–553

Lee JY, Boman A, Sun CX, Andersson M, Jornvall H, Mutt V et al (1989) Antibacterial peptides from pig intestine: isolation of a mammalian cecropin. Proc Natl Acad Sci USA 86 (23):9159–9162

Lee Y-S, Chen C-H, Chao A, Chen E-S, Wei M-L, Chen L-K et al (2005) Molecular signature of clinical severity in recovering patients with severe acute respiratory syndrome coronavirus (SARS-CoV). BMC Genom 6:132

Lee CJ, Buznyk O, Kuffova L, Rajendran V, Forrester JV, Phopase J et al (2014) Cathelicidin LL-37 and HSV-1 corneal infection: peptide versus gene therapy. Transl Vis Sci Technol 3 (3):4

Lehrer RI (2004) Primate defensins. Nat Rev Microbiol 2(9):727–738

Leikina E, Delanoe-Ayari H, Melikov K, Cho M-S, Chen A, Waring AJ et al (2005) Carbohydrate-binding molecules inhibit viral fusion and entry by crosslinking membrane glycoproteins. Nat Immunol 6:995–1001

Levinson P, Kaul R, Kimani J, Ngugi E, Moses S, MacDonald KS et al (2009) Levels of innate immune factors in genital fluids: association of alpha defensins and LL-37 with genital infections and increased HIV acquisition. AIDS 23(3):309–317

Levinson P, Choi RY, Cole AL, Hirbod T, Rhedin S, Payne B et al (2012) HIV-neutralizing activity of cationic polypeptides in cervicovaginal secretions of women in HIV-serodiscordant relationships. PLoS One 7(2):e31996

Lion T (2014) Adenovirus infections in immunocompetent and immunocompromised patients. Clin Microbiol Rev 27:441–462

Liu X, Guo C, Huang Y, Zhang X, Chen Y (2015) Inhibition of porcine reproductive and respiratory syndrome virus by Cecropin D in vitro. Infect Genet Evol. 34:7–16

Lorin C, Saidi H, Belaid A, Zairi A, Baleux F, Hocini H et al (2005) The antimicrobial peptide dermaseptin S4 inhibits HIV-1 infectivity in vitro. Virology 334(2):264–275

Luplertlop N, Surasombatpattana P, Patramool S, Dumas E, Wasinpiyamongkol L, Saune L et al (2011) Induction of a peptide with activity against a broad spectrum of pathogens in the Aedes aegypti salivary gland, following Infection with Dengue Virus. PLoS Pathog 7(1):e1001252

Maheshwari A, Ray S, Thuluvath PJ (2008) Acute hepatitis C. The Lancet 372:321–332

Mallia P, Footitt J, Sotero R, Jepson A, Contoli M, Trujillo-Torralbo M-B et al (2012) Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 186:1117–1124

Malm J, Sorensen O, Persson T, Frohm-Nilsson M, Johansson B, Bjartell A et al (2000) The human cationic antimicrobial protein (hCAP-18) is expressed in the epithelium of human epididymis, is present in seminal plasma at high concentrations, and is attached to spermatozoa. Infect Immun 68(7):4297–4302

Marcos JF, Beachy RN, Houghten RA, Blondelle SE, Perez-Paya E (1995) Inhibition of a plant virus infection by analogs of melittin. Proc Natl Acad Sci USA 92(26):12466–12469

Morimoto M, Mori H, Otake T, Ueba N, Kunita N, Niwa M et al (1991) Inhibitory effect of tachyplesin I on the proliferation of human immunodeficiency virus in vitro. Chemotherapy 37(3):206–211

Murakami T, Niwa M, Tokunaga F, Miyata T, Iwanaga S (1991) Direct virus inactivation of tachyplesin I and its isopeptides from horseshoe crab hemocytes. Chemotherapy 37(5):327–334

Murakami T, Nakajima T, Koyanagi Y, Tachibana K, Fujii N, Tamamura H et al (1997) A small molecule CXCR4 inhibitor that blocks T cell line-tropic HIV-1 infection. J Exp Med 186 (8):1389–1393

Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ et al (2010) Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 375(9725):1545–1555

Nakamura T, Furunaka H, Miyata T, Tokunaga F, Muta T, Iwanaga S et al (1988) Tachyplesin, a class of antimicrobial peptide from the hemocytes of the horseshoe crab (Tachypleus tridentatus). Isolation and chemical structure. J Biol Chem 263(32):16709–16713

Nakashima H, Masuda M, Murakami T, Koyanagi Y, Matsumoto A, Fujii N et al (1992) Anti-human immunodeficiency virus activity of a novel synthetic peptide, T22 ([Tyr-5,12, Lys-7]polyphemusin II): a possible inhibitor of virus-cell fusion. Antimicrob Agents Chemother 36(6):1249–1255

Nakashima H, Yamamoto N, Masuda M, Fujii N (1993) Defensins inhibit HIV replication in vitro. AIDS (London, England) 7:1129

Nguyen EK, Nemerow GR, Smith JG (2010) Direct evidence from single-cell analysis that human -defensins block adenovirus uncoating to neutralize infection. J Virol 84:4041–4049

Nicolas P, El Amri C (2009) The dermaseptin superfamily: a gene-based combinatorial library of antimicrobial peptides. Biochim Biophys Acta 1788(8):1537–1550

Nitsch-Osuch A, Brydak LB (2014) Influenza viruses resistant to neuraminidase inhibitors. Acta Biochim Pol 61(3):505–508

Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T et al (2002) Endogenous antimicrobial peptides and skin infections in atopic dermatitis. N Engl J Med 347 (15):1151–1160

Ouellette AJ (2006) Paneth cell alpha-defensin synthesis and function. Curr Top Microbiol Immunol 306:1–25

Peiris JSM, Yuen KY, Osterhaus ADME, Stöhr K (2003) The severe acute respiratory syndrome. N Engl J Med 349:2431–2441

Piot P, Quinn TC (2013) Response to the AIDS pandemic—a global health model. N Engl J Med 368:2210–2218

Powers JP, Martin MM, Goosney DL, Hancock RE (2006) The antimicrobial peptide polyphemusin localizes to the cytoplasm of Escherichia coli following treatment. Antimicrob Agents Chemother 50(4):1522–1524

Pribul PK, Harker J, Wang B, Wang H, Tregoning JS, Schwarze J et al (2008) Alveolar macrophages are a major determinant of early responses to viral lung infection but do not influence subsequent disease development. J Virol 82(9):4441–4448

Proud D, Sanders SP, Wiehler S (2004) Human rhinovirus infection induces airway epithelial cell production of human beta-defensin 2 both in vitro and in vivo. J Immunol 172:4637–4645 (Baltimore, Md: 1950)

Putsep K, Carlsson G, Boman HG, Andersson M (2002) Deficiency of antibacterial peptides in patients with morbus Kostmann: an observation study. Lancet 360(9340):1144–1149

Quiñones-Mateu ME, Lederman MM, Feng Z, Chakraborty B, Weber J, Rangel HR et al (2003) Human epithelial beta-defensins 2 and 3 inhibit HIV-1 replication. AIDS (London, England) 17:F39–48

Rapista A, Ding J, Benito B, Lo Y-T, Neiditch MB, Lu W et al (2011) Human defensins 5 and 6 enhance HIV-1 infectivity through promoting HIV attachment. Retrovirology 8:45

Rehaume LM, Hancock RE (2008) Neutrophil-derived defensins as modulators of innate immune function. Crit Rev Immunol 28(3):185–200

Reploeg MD, Storch Gregory A, Clifford David B (2001) BK virus: a clinical review. Clin Infect Dis 33:191–202

Robinson WE Jr, McDougall B, Tran D, Selsted ME (1998) Anti-HIV-1 activity of indolicidin, an antimicrobial peptide from neutrophils. J Leukoc Biol 63(1):94–100

Rothan HA, Abdulrahman AY, Sasikumer PG, Othman S, Rahman NA, Yusof R (2012a) Protegrin-1 inhibits dengue NS2B-NS3 serine protease and viral replication in MK2 cells. J Biomed Biotechnol 2012:251482

Rothan HA, Han HC, Ramasamy TS, Othman S, Rahman NA, Yusof R (2012b) Inhibition of dengue NS2B-NS3 protease and viral replication in Vero cells by recombinant retrocyclin-1. BMC Infect Dis 12:314

Salvatore M, García-Sastre A, Ruchala P, Lehrer Robert I, Chang T, Klotman Mary E (2007) α-Defensin inhibits influenza virus replication by cell-mediated mechanism(s). J Infect Dis 196:835–843

Savoia D, Donalisio M, Civra A, Salvadori S, Guerrini R (2010) In vitro activity of dermaseptin S1 derivatives against genital pathogens. APMIS. 118(9):674–680

Shackelton LA, Rambaut A, Pybus OG, Holmes EC (2006) JC virus evolution and its association with human populations. J Virol 80:9928–9933

Sherris medical microbiology (2004) An introduction to infectious diseases. 4th ed edn. McGraw-Hill, New York, 979 p

Simon V, Ho DD, Abdool Karim Q (2006) HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. The Lancet 368:489–504

Sinha S, Cheshenko N, Lehrer RI, Herold BC (2003) NP-1, a rabbit alpha-defensin, prevents the entry and intercellular spread of herpes simplex virus type 2. Antimicrob Agents Chemother 47 (2):494–500

Smith JG, Nemerow GR (2008) Mechanism of adenovirus neutralization by Human alpha-defensins. Cell Host Microbe 3:11–19

Smith JG, Silvestry M, Lindert S, Lu W, Nemerow GR, Stewart PL (2010) Insight into the mechanisms of adenovirus capsid disassembly from studies of defensin neutralization. PLoS Pathog 6:e1000959

Sorensen OE, Follin P, Johnsen AH, Calafat J, Tjabringa GS, Hiemstra PS et al (2001) Human cathelicidin, hCAP-18, is processed to the antimicrobial peptide LL-37 by extracellular cleavage with proteinase 3. Blood 97(12):3951–3959

Sun L, Finnegan CM, Kish-Catalone T, Blumenthal R, Garzino-Demo P, La Terra Maggiore GM et al (2005) Human beta-defensins suppress human immunodeficiency virus infection: potential role in mucosal protection. J Virol 79:14318–14329

Tambunan US, Alamudi S (2010) Designing cyclic peptide inhibitor of dengue virus NS3-NS2B protease by using molecular docking approach. Bioinformation 5(6):250–254

Tanabe H, Ouellette AJ, Cocco MJ, Robinson WE (2004) Differential effects on human immunodeficiency virus type 1 replication by -defensins with comparable bactericidal activities. J Virol 78:11622–11631

Tang YQ, Yuan J, Osapay G, Osapay K, Tran D, Miller CJ et al (1999) A cyclic antimicrobial peptide produced in primate leukocytes by the ligation of two truncated alpha-defensins. Science 286(5439):498–502

Taubenberger JK, Morens DM (2006) 1918 Influenza: the mother of all pandemics. Emerg Infect Dis 12(1):15–22

Tecle T, White MR, Gantz D, Crouch EC, Hartshorn KL (2007) Human neutrophil defensins increase neutrophil uptake of influenza a virus and bacteria and modify virus-induced respiratory burst responses. J Immunol 178:8046–8052

Tenge VR, Gounder AP, Wiens ME, Lu W, Smith JG (2014) Delineation of interfaces on human alpha-defensins critical for human adenovirus and human papillomavirus inhibition. PLoS Pathog 10:e1004360

Terwilliger TC, Eisenberg D (1982) The structure of melittin. II. Interpretation of the structure. J Biol Chem 257(11):6016–6022

Tomasinsig L, Zanetti M (2005) The cathelicidins–structure, function and evolution. Curr Protein Pept Sci 6(1):23–34

Tran D, Tran P, Roberts K, Osapay G, Schaal J, Ouellette A et al (2008) Microbicidal properties and cytocidal selectivity of rhesus macaque theta defensins. Antimicrob Agents Chemother 52:944–953

Tripathi S, Tecle T, Verma A, Crouch E, White M, Hartshorn KL (2013) The human cathelicidin LL-37 inhibits influenza A viruses through a mechanism distinct from that of surfactant protein D or defensins. J Gen Virol 94(Pt 1):40–49

Tripathi S, Wang G, White M, Qi L, Taubenberger J, Hartshorn KL (2015) Antiviral activity of the human cathelicidin, LL-37, and derived peptides on seasonal and pandemic influenza A viruses. PLoS One 10(4):e0124706

van Zoggel H, Carpentier G, Dos Santos C, Hamma-Kourbali Y, Courty J, Amiche M et al (2012) Antitumor and angiostatic activities of the antimicrobial peptide dermaseptin B2. PLoS One 7(9):e44351

VanCompernolle SE, Taylor RJ, Oswald-Richter K, Jiang J, Youree BE, Bowie JH et al (2005) Antimicrobial peptides from amphibian skin potently inhibit human immunodeficiency virus infection and transfer of virus from dendritic cells to T cells. J Virol 79(18):11598–11606

Venkataraman N, Cole AL, Svoboda P, Pohl J, Cole AM (2005) Cationic polypeptides are required for anti-HIV-1 activity of human vaginal fluid. J Immunol 175(11):7560–7567

Wachinger M, Saermark T, Erfle V (1992) Influence of amphipathic peptides on the HIV-1 production in persistently infected T lymphoma cells. FEBS Lett 309(3):235–241

Wachinger M, Kleinschmidt A, Winder D, von Pechmann N, Ludvigsen A, Neumann M et al (1998) Antimicrobial peptides melittin and cecropin inhibit replication of human immunodeficiency virus 1 by suppressing viral gene expression. J Gen Virol 79(Pt 4):731–740

Wade D, Andreu D, Mitchell SA, Silveira AM, Boman A, Boman HG et al (1992) Antibacterial peptides designed as analogs or hybrids of cecropins and melittin. Int J Pept Protein Res 40(5):429–436

Wang W, Cole AM, Hong T, Waring AJ, Lehrer RI (2003) Retrocyclin, an antiretroviral -defensin, Is a lectin. J Immunol 170:4708–4716

Wang W, Owen SM, Rudolph DL, Cole AM, Hong T, Waring AJ et al (2004a) Activity of - and -defensins against Primary Isolates of HIV-1. J Immunol 173:515–520

Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J et al (2004b) Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 173(5):2909–2912

Wang G, Watson KM, Buckheit RW Jr (2008) Anti-human immunodeficiency virus type 1 activities of antimicrobial peptides derived from human and bovine cathelicidins. Antimicrob Agents Chemother 52(9):3438–3440

Wang G, Watson KM, Peterkofsky A, Buckheit RW Jr (2010) Identification of novel human immunodeficiency virus type 1-inhibitory peptides based on the antimicrobial peptide database. Antimicrob Agents Chemother 54(3):1343–1346

Wiens ME, Smith JG (2015) Alpha-defensin HD5 inhibits furin cleavage of human papillomavirus 16 L2 to block infection. J Virol 89:2866–2874

Wohlford-Lane CL, Meyerholz DK, Perlman S, Zhou H, Tran D, Selsted ME et al (2009) Rhesus theta-defensin prevents death in a mouse model of severe acute respiratory syndrome coronavirus pulmonary disease. J Virol 83:11385–11390

Wollebo HS, White MK, Gordon J, Berger JR, Khalili K (2015) Persistence and pathogenesis of the neurotropic polyomavirus JC. Ann Neurol 77:560–570

Wollenberg A, Wetzel S, Burgdorf WH, Haas J (2003) Viral infections in atopic dermatitis: pathogenic aspects and clinical management. J Allergy Clin Immunol 112(4):667–674

Wong JH, Legowska A, Rolka K, Ng TB, Hui M, Cho CH et al (2011) Effects of cathelicidin and its fragments on three key enzymes of HIV-1. Peptides 32(6):1117–1122

Wu H, Zhang G, Minton JE, Ross CR, Blecha F (2000) Regulation of cathelicidin gene expression: induction by lipopolysaccharide, interleukin-6, retinoic acid, and Salmonella enterica serovar typhimurium infection. Infect Immun 68(10):5552–5558

Wu Z, Cocchi F, Gentles D, Ericksen B, Lubkowski J, DeVico A et al (2005) Human neutrophil α-defensin 4 inhibits HIV-1 infection in vitro. FEBS Lett 579:162–166

Xu Y, Tamamura H, Arakaki R, Nakashima H, Zhang X, Fujii N et al (1999) Marked increase in anti-HIV activity, as well as inhibitory activity against HIV entry mediated by CXCR4, linked to enhancement of the binding ability of tachyplesin analogs to CXCR4. AIDS Res Hum Retroviruses 15(5):419–427

Yasin B, Harwig SS, Lehrer RI, Wagar EA (1996a) Susceptibility of chlamydia trachomatis to protegrins and defensins. Infect Immun 64(3):709–713

Yasin B, Lehrer RI, Harwig SS, Wagar EA (1996b) Protegrins: structural requirements for inactivating elementary bodies of Chlamydia trachomatis. Infect Immun 64(11):4863–4866

Yasin B, Pang M, Turner JS, Cho Y, Dinh NN, Waring AJ et al (2000) Evaluation of the inactivation of infectious Herpes simplex virus by host-defense peptides. Eur J Clin Microbiol Infect Dis 19(3):187–194

Yasin B, Wang W, Pang M, Cheshenko N, Hong T, Waring AJ et al (2004) Defensins protect cells from infection by herpes simplex virus by inhibiting viral adhesion and entry. J Virol 78:5147–5156

Zairi A, Tangy F, Bouassida K, Hani K (2009) Dermaseptins and magainins: antimicrobial peptides from frogs' skin-new sources for a promising spermicides microbicides-a mini review. J Biomed Biotechnol 2009:452567

Zanetti M, Del Sal G, Storici P, Schneider C, Romeo D (1993) The cDNA of the neutrophil antibiotic Bac5 predicts a pro-sequence homologous to a cysteine proteinase inhibitor that is common to other neutrophil antibiotics. J Biol Chem 268(1):522–526

Zasloff M (1987) Magainins, a class of antimicrobial peptides from Xenopus skin: isolation, characterization of two active forms, and partial cDNA sequence of a precursor. Proc Natl Acad Sci USA 84(15):5449–5453

Zhang G, Ross CR, Blecha F (2000) Porcine antimicrobial peptides: new prospects for ancient molecules of host defense. Vet Res 31(3):277–296

Zins SR, Nelson CDS, Maginnis MS, Banerjee R, O'Hara BA, Atwood WJ (2014) The Human Alpha Defensin HD5 Neutralizes JC Polyomavirus Infection by Reducing Endoplasmic Reticulum Traffic and Stabilizing the Viral Capsid. J Virol 88:948–960