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REVIEW ARTICLE

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Interleukin-17—A multifaceted cytokine in viral infections

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Abstract

Viral infections are a major threat to the human population due to the lack of selective therapeutic measures. The morbidity and mortality reported worldwide are very alarming against viral pathogens. The proinflammatory environment is required for viral inhibition by initiating the host immune response. The host immune response fights these pathogens by secreting different cytokines. Interleukin-17 (IL-17) a proinflammatory cytokine mainly produced by T helper type 17 cells, plays a vital role in the regulation of host immune response against various pathogens, including viruses. However, dysregulated production of IL-17 induces chronic inflammation, autoimmune disorders, and may lead to cancer. Recent studies suggest that IL-17 is not only involved in the antiviral immune response but also promotes virus-mediated illnesses. In this review, we discuss the protective and pathogenic role of IL-17 against various viral infections. A detailed understanding of IL-17 during viral infections could contribute to improve therapeutic measures and enable the development of an efficient and safe IL-17 based immunotherapy.

KEYWORDS
Anti-viral immune response, IL-17, Inflammation, Pathogenesis, Viral Infections

1 | INTRODUCTION

Viral infections can cause acute and chronic pathological responses, which lead to high rates of mortality and morbidity. Their pathology is dependent on the type and nature of the virus as well as the infected organ of the human body (Figure 1). Different human viruses have unique pathologies and modes of infection. For instance, respiratory syncytial virus (RSV) and influenza viruses primarily infect the respiratory system and may cause respiratory failure. Coronaviruses (CoVs), such as severe acute respiratory syndrome virus (SARS), Middle East respiratory syndrome virus (MERS), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are associated with lung pathology and acute respiratory distress syndrome (ARDS) (Pal et al., 2020). Hepatitis B virus (HBV) and hepatitis C virus (HCV) attack hepatic cells, where persistent infection along with chronic liver inflammation can lead to complications such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) (Bray et al., 2018). Human papillomavirus (HPV) targets the epithelial layer of the genital tract creating lesions and may lead to cervical cancer (Blaskewicz et al., 2011). Severe dengue virus (DENV) infection affects kidneys, lungs and liver (Póvoa et al., 2014). Human immunodeficiency virus (HIV) mainly targets the host T-lymphocytes. The current prophylactic and therapeutic strategies are very limited against viral infections. In case of HPV, so far we could be able to develop only three vaccines that are currently being used (https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/human-papillomavirus-vaccines-(HPV). Similarly there are different vaccines under clinical trials against SARS-CoV-2 (Rawat et al., 2021) while on the therapeutic point of view, different antiviral drugs against HBV (de Clercq et al., 2010), HCV (Feeney & Chung, 2014; Pol et al., 2013), RSV (Empey et al., 2010), herpes simplex virus (HSV) (Hook & Friedman, 2007) and influenza (Allen et al., 2006) are being given to patients. However, there are several viral infections like HIV/Simian immunodeficiency virus (SIV), dengue, Zika virus (ZIKV), and coxsackievirus B3 (CVB3) with no effective antivirals.

The development of viral infection needs to win over both innate and adaptive immune responses (Braciale et al., 2012). Upon viral infection, the viral elements including nucleic acids and other

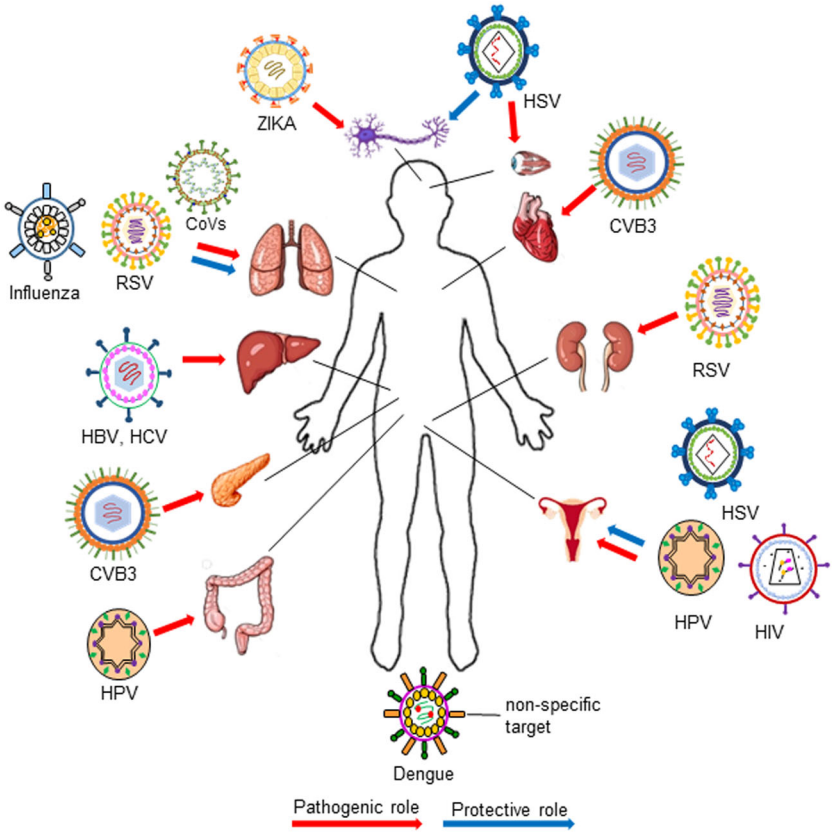

FIGURE 1 Association of interleukin-17 (IL-17) with various viruses and their target organs in the human body

pathogen associated molecular patterns are recognized by different pathogen recognition receptors such as toll like receptors, NOD like receptors, and RIG like receptors. This initiates a cascade of downstream signaling triggering the innate immune response. Entry of virus into the host activates innate immune cells such as macrophage cells, dendritic and granulocytes within a few hours at the site of infection which subsequently activates highly specific adaptive immune response mediated by lymphocytes (B & T cells) (Koyama et al., 2008). Development of specific adaptive immune response against various infections requires 1–2 weeks. A strong inflammatory response is required for viral clearance and control; however, the severity of inflammation has to be tightly regulated to avoid tissue damage and adverse pathogenesis.

IL-17 is a principal proinflammatory cytokine that plays an important role in producing a protective immune response along with other inflammatory cytokines. IL-17 also known as cytotoxic T-lymphocyte-associated protein 8 (CTLA-8), was discovered by Rouvier et al. (1993). Recently, it has emerged as a crucial factor in the host immune response and is produced by multiple cell types, including T helper type 17 (Th17) (Park et al., 2005), gamma delta T (γδT) (G. Kim et al., 2018), Type 17 $CD8^+$ T (Tc17) (Huber et al., 2013), and natural killer (NK) cells (Passos et al., 2010). The differentiation of mouse Th17 cells requires IL-1β, IL-6, IL-23, and transforming growth factor beta (TGF-β). However, the human Th17 cell differentiation is independent of TGF-β (Miossec & Kolls, 2012). The lineage-specific transcription factor retinoic acid receptor-related orphan receptor-γt (ROR-γt) and signal transducer and activator of transcription 3 (STAT3) are important players for Th17 cell differentiation (Miossec & Kolls, 2012). The IL-17 family has 6 members including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. Among them, IL-17A is the most explored member of the family and is also known as IL-17 (Brevi et al., 2020; McGeachy et al., 2019).

The IL-17 receptor family consists of five members: IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE which are single-pass transmembrane receptors with conserved domains (Brevi et al., 2020). IL-17 targets different cells such as endothelial cells, epithelial cells, macrophages and dendritic cells (S. Xu & Cao, 2010). After binding of IL-17 with its receptor IL-17RA, an adapter protein ACT1 recruits to the similar expression to fibroblast growth factor genes (SEF) and IL-17R (SEFIR) cytoplasmic domain of the receptor followed by TGF-β-activated kinase 1 (TAK1) and tumor necrosis factor (TNF)-receptor associated factor 6 (TRAF6) ubiquitin ligase. Recruitment and ubiquitination of TRAF6 activate transcription factor Nuclear factor kappa B (NF-κB) pathway (Brevi et al., 2020; Qian et al., 2007). IL-17 induces secretion of granulocyte colony-stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as various chemokine ligands such as, chemokine (C-X-C motif) ligand 1 (CXCL1), chemokine (C-X-C motif) ligand 2 (CXCL2) and chemokine (C-X-C motif) ligand 8 (CXCL8). The inflammatory response produced by IL-17 triggers the migration and accumulation of neutrophils at the site of infection (Gaffen, 2009). IL-17 plays a crucial role to protect from microbial infections (Veldhoen, 2017). In viral infections, it shows both protective and pathogenic roles in infected cells (Figure 2).

Host single nucleotide polymorphisms (SNPs) in various genes also modulate viral diseases in humans. SNP is a substitution of a single

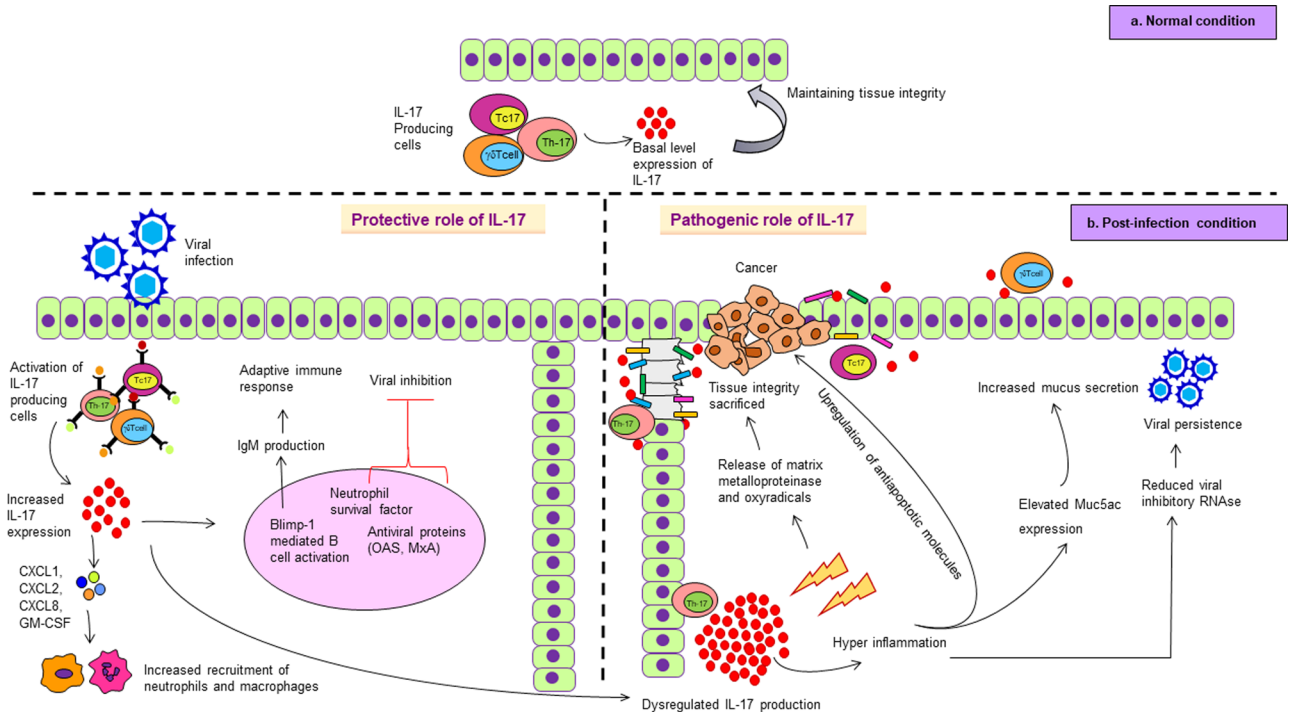

FIGURE 2 Protective and pathogenic role of interleukin-17 (IL-17). (a) Normal condition: The different subsets of IL-17 producing cells secrete basal level of IL-17 that is crucial for maintaining tissue integrity. (b) Postinfection condition: (i) Protective role—The IL-17 producing cells get differentiated/activated after viral infection and start secreting IL-17 that triggers the recruitment of neutrophils and macrophages by secreting different chemokinesand activates the adaptive immune response for viral clearance. (ii) Pathogenic role—Upon viral infection, the dysregulated IL-17 production leads to hyperinflammation causing elevated Muc5ac expression which leads to increased mucus secretion, it also reduces the expression of viral inhibitory RNAse which favors the viral persistence. Hyperinflammation induced by IL-17 also cause the release of matrix metalloproteinase and oxyradicals which leads to disruption of tissue integrity, further it upregulates the antiapoptotic molecules and finally leads to cancer

nucleotide by another at a specific position in the genome. IL-17 gene has different SNPs, closely associated with many human diseases, autoimmune disorders and cancer (Blauvelt & Chiricozzi, 2018; Z. M. Dai et al., 2016; Keshavarz et al, 2019). SNPs −737C>T (rs8193036) and −197G>A (rs2275913) in the IL-17A promoter and the SNP 7488T>C (rs763780) in exon 3 of IL-17F (Ren et al., 2017) are associated with viral persistence and pathology; however, the mechanism remains unexplored. The proinflammatory properties of IL-17 make it a key mediator of inflammation and immunopathology (S. Chen et al., 2019). Here, we have extensively explored the multifaceted role of IL-17 and its involvement against major viral infections (Table 1), specifically focusing on the pathogenic and protective role of IL-17 producing cells, IL-17, and IL-17 gene polymorphism in several viral infections.

2 | ROLE OF IL-17 IN DIFFERENT VIRAL INFECTIONS

2.1 | DNA viruses

2.1.1 | Human papillomavirus

HPV is a nonenveloped circular double-stranded DNA (dsDNA) virus with about a 8 kb genome belonging to the *Papillomaviridae* family (van Doorslaer et al., 2018). It is mainly associated with female genital tract infections causing cervical lesions and cancer. HPV has evolved several mechanisms to evade host immune response and establish a local immunosuppressive environment by downregulating the cytokine production and facilitating persistent viral infection. The uterine cervix epithelium seems to be hyperresponsive towards HPV infection (Blaskewicz et al., 2011; Tran et al., 2015). Th17 cells and IL-17A mediate immune augmentation in the high-risk HPV infection, especially in the cervical microenvironment leading to disease progression (Park et al., 2005; Xue et al., 2018). The analysis of Th17 cell percentages of patients with different grade cervical interepithelial neoplasia (CIN) revealed a gradual increase in Th17 cells during the progression of cervical lesions (Xue et al., 2018). The host immune system deviating environment induced by HPV can be overcome by the use of 2,4-dinitrochlorobenzene (DNCB). In keratinocytes expressing HPV16 E7 oncogenic protein, the DNCB treatment stimulated a hyperinflammatory environment via IL-17A mediated arginase-1 production which is responsible for viral clearance. The blockage of IL-17A or arginase-1 inhibited hyperinflammatory response in DNCB treated cells. This suggests an active involvement of IL-17A in DNCB mediated hyperinflammatory response against HPV16 E7 expressing cells (Blaskewicz et al., 2011; Tran et al., 2015). T-cell-mediated immune responses against HPV are believed to play a significant role in cervical carcinogenesis (Blaskewicz et al., 2011).

TABLE 1 Pathogenic and protective involvement of IL-17 with SNPs in viral infections

Virus	Protective and pathogenic role	References
DNA viruses		
HSV	Protective role • Enhances Th-1 mediated antiviral response in the female genital tract • Secretion of Beta-defensin-3 in vaginal mucosal surface • Peripheral nerve growth and survival signals to neurons • Neutrophil survival factor • Immune activator in HCF Pathogenic role • Increases corneal opacity • Production of matrix metalloproteinase and oxyradicals like tissue-damaging factors	(Bagri et al., 2017; Maertzdorf et al., 2002; Peng et al., 2017; Rolinski & Hus, 2014; Stanfield et al., 2018; Suryawanshi et al., 2011)
HPV	Pathogenic role • Inflammation and immune enhancement • Progression of lesions in the cervical microenvironment • STAT3 mediated progression of CRC and breast cancer • Promote tumor formation along with Mcl-1 by inhibiting apoptosis • People with AA and GA genotypes of IL-17 −197G>A SNP have higher risk of cervical cancer as compared to people with GG genotype	(Y. H. Chang et al., 2010; Cong et al., 2015; Gosmann et al., 2014; Y. X. Li et al., 2015; Park et al., 2005; Vidal et al., 2015; Xue et al., 2018; N. Zhang et al., 2016)
RNA viruses		
CVB3	Pathogenic role • Involved in CVB3 induced AVMC pathology and pancreatitis • Upregulated mRNA and protein levels of IL-17 promotes viral replication • CVB3 induces Th17 cell differentiation • The reduced IL-17 levels after nicotine treatment reduced disease severity • The reduced expression of IL-17 after Fasudil treatment reduced myocardial lesions, viral replication and increased survival in CVB3 infected hearts in murine model	(K. Dai et al., 2018; Kong et al., 2013; Li-Sha et al., 2015; Long et al., 2016; F. Yan et al., 2019; Yang et al., 2011; Yuan et al., 2010)
CoVs	Pathogenic role • Causes ARDS by contributing in the cytokine storm • Lung tissue damage by secretion of matrix metalloproteinases	(Huang et al., 2020; Mahallawi et al., 2018; D. Wu & Yang, 2020)
DENV	Protective role • Induces the expression of TNF-α mediated proadhesive molecules and GRO-α leading to neutrophil recruitment Pathogenic role • Increased secretion of proinflamatory cytokine IL-1β • High IL-17 levels in children with severe dengue • Increased IL-17 level in respiratory distress and pleural effusion • Promoting the production of proinflammatory cytokines IL-6 and IL-8 which contribute to DHF pathogenesis	(Jain et al, 2013; Jovanovic et al., 1998; Moreno-Altamirano et al, 2004; Raghupathy et al., 1998; Restrepo et al., 2008; Witowski et al., 2000)
HCV	Protective role • Inhibition of Th-17 cells by immunosuppressive cytokines (IL-10 and TGF-β) secreted during HCV Infection Pathogenic role • Th-17 cells are positively correlated with the severity of liver injury in CHC • A positive correlation between IL-17 levels and viral load • The GG and GA genotypes of IL-17A −197G>A SNP are more prominent in HCV infected HCC and non HCC patients	(Abou El-Khier et al., 2018; ELBassuoni et al., 2015; Gutkowski & Hartleb, 2009; Hassan et al., 2014)
ZIKV	Pathogenic role • Onset of clinical symptoms like headache • Neural tissue damage via iNOS production	(Azevedo et al., 2018; Zuñiga et al., 2020)

(Continues)

TABLE 1 (Continued)

Virus	Protective and pathogenic role	References
Influenza viruses	Protective role • B cell-associated adaptive immune response by Blimp-1 mediated IgM production • CXCL13 mediated B-cell migration into the lungs • Disease severity in H7N9 infection due to reduced Th17 cells and IL-17 Pathogenic role • Pathogenesis and proinflammatory activities • Involved in post influenza superinfection • Neutralizing IL-17 reduced lung injury in H1N1 infection • Pathogenesis and immune regulation in H3N2 infection • GG, AA and GA genotypes of −197G>A SNP of IL-17A are significantly associated with influenza A and B infection in Iranian population. Also, the absence of A allele in −197G>A SNP increased the risk of H1N1 infection	(Antalis et al., 2019; Bermejo-Martin et al., 2009; Crowe et al., 2009; Er et al., 2019; Keshavarz et al., 2019; Kudva et al., 2011; X. Wang et al., 2011)
RSV	Protective role • Aids disease recovery in RSV induced bronchiolitis • Negatively regulate AR Pathogenic role • Increased neutrophil recruitment and pulmonary pathogenesis • RSV induced bronchiolitis and reduced asthma tolerance by CCR6-CCL20 signaling • Increased mucus production in the respiratory tract by Muc5ac expression and airway distress • Kidney damage • Promotes viral clearance during early phase of infection	(Faber et al., 2012; Habibi et al., 2020; Hashimoto et al., 2005; X. Hu et al., 2019; Mebratu & Tesfaigzi, 2018; Newcomb et al., 2013; Shi et al., 2017; Stoppelenburg et al., 2013)
Retro viruses		
HIV/SIV	Protective role • Preferential loss of Th17 cells during HIV infection • Inability of Tc17 cells to produce IL-17 during HIV infection • Reduced IL-17A production in HIV^+ Latent TB patients and HIV^+ active TB patients. • Preferential loss of Th17 cells in HIV infected TB patients Pathogenic role • Th17 cells expressing CCR5 and CD90 showed increased susceptibility to HIV infection • Expression of CD4, CXCR4, and α4β7 viral receptors on Th17 cells increasing virus and Th17 cell association • Lack HIV viral inhibitory RNase in Th17 cells • Associated with HIV induced OC	(Alvarez et al., 2013; Christensen-Quick et al., 2016; Dunay et al., 2016; Mousavi et al., 2016; Murray et al., 2018; Perdomo-Celis et al., 2018; Rodriguez-Garcia et al., 2014)
HBV	Protective role • IL-17A inhibits HBV replication, which correlated with overexpression of myxovirus resistance protein A (MxA) and oligoadenylate synthetase (OAS) mRNA Pathogenic role • Associated with liver damage liver cirrhosis • IL-17 increases the proliferation of hepatocytes by STAT3 phosphorylation via IL-6 induction in HCC patients • Loss of IL-17/IL-23 inhibitory mechanism causing disease progression • Methylation of IL-17 promoter positively correlated with CHB progression • The G allele of GG genotype of IL-17A −197G>A SNP and T allele of TT genotype at IL-17F 7488T>C SNP are associated with increased risk to HBV infection. In addition, the IL-17A −737C>T SNP is also associated with increased HBV persistence	(Z. Hu et al., 2017; Liang, 2009; N. Li et al., 2014; Q. Wang et al., 2011; B. Yang et al., 2013; Yu et al., 2014)

Abbreviations: ARDS, acute respiratory distress syndrome; AVMC, acute viral myocarditis; CHC, chronic hepatitis C; CoVs, coronaviruses; CVB3, coxsackievirus B3; DENV, dengue virus: DHF, dengue hemorrhagic fever; HBV, hepatitis B virus; HCF, human corneal fibroblasts; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HSV, herpes simplex virus; IL, interleukin; iNOS, inducible nitric oxide synthase; mRNA, messenger RNA: SIV, Simian immunodeficiency virus; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor; ZIKV, Zika virus.

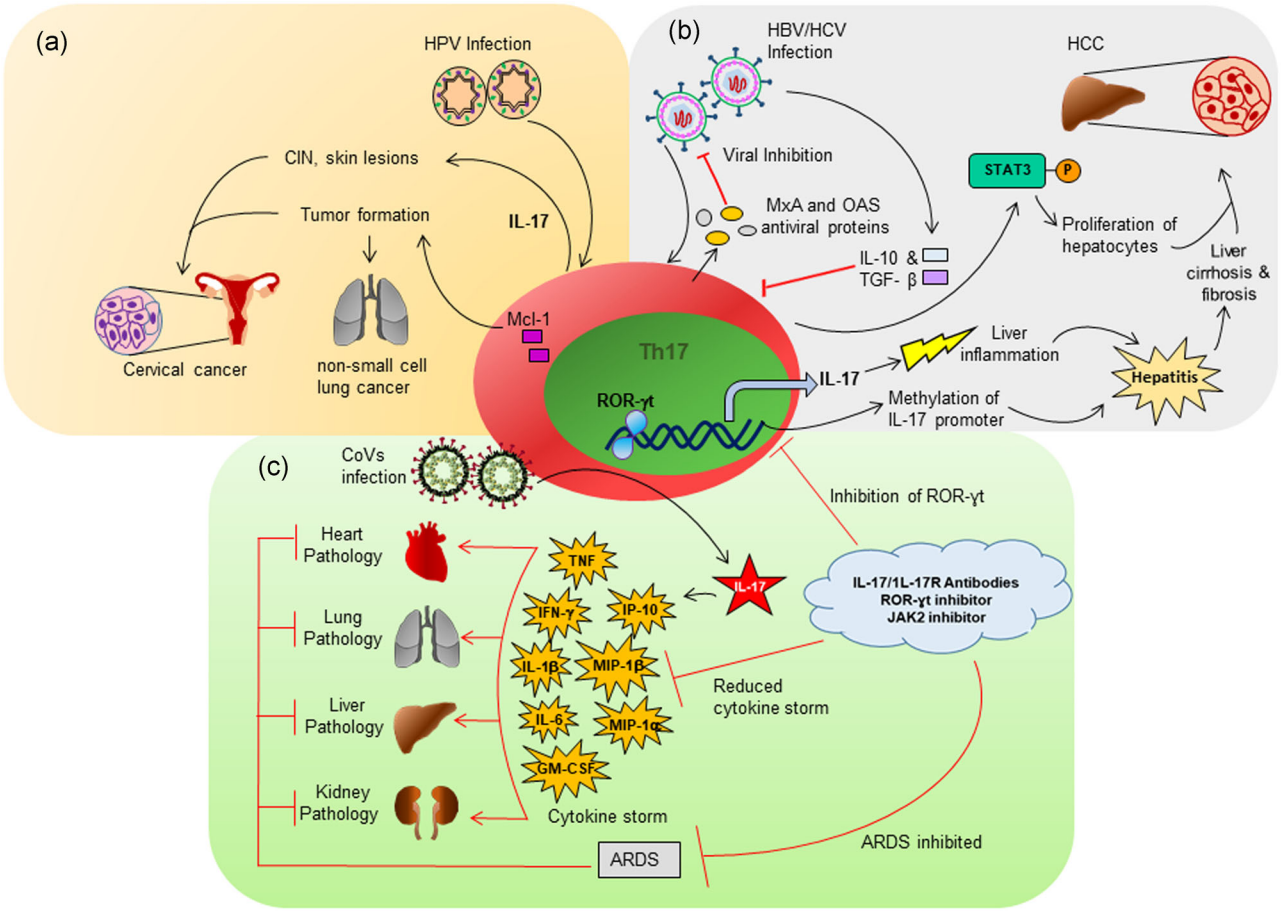

FIGURE 3 Pathogenic role of interleukin-17 (IL-17) in HPV, HBV/HCV, and CoVs infections. (a) HPV infection: After HPV infection the IL-17 producing cells secrete IL-17, causing hyper inflammation, CIN, skin lesions and finally cause cervical cancer. In addition, they also secrete Mcl-1 that leads to tumor formation in HPV induced nonsmall cell lung cancer. (b) HBV/HCV infection: (i) Pathogenic—The infection with hepatitis viruses is followed by the release of IL-17 and phosphorylation of STAT3, contributing to liver inflammation, hepatitis, proliferation of hepatocytes resulting in liver cirrhosis and fibrosis finally causing hepatocellular carcinoma. The methylation of IL-17 promoter during viral infection is associated with hepatitis. (ii) Protective—During viral infection, the Th17 cells are inhibited by immunosuppressive cytokines IL-10 and IL-1β secreted after viral infection. In addition, the Th17 cells secreted MxA and OAS antiviral proteins for viral inhibition. (c) CoVs infection: Infection with CoVs causes secretion of IL-17 that induces several factors associated with the "cytokine storm" causing several pathologies and ARDS. It is suggested that different antibodies and inhibitors targeting IL-17 and its signaling components can be effective in controlling the cytokine storm during CoV infection. ARDS, acute respiratory distress syndrome; CIN, cervical interepithelial neoplasia; CoVs, coronaviruses; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus

IL-17 can be recognised as an important determinant in HPV-associated, epithelial hyperplasia (Gosmann et al., 2014). Blocking of IL-17 could prevent the progression of premalignant lesions to cancer. The increased production of IL-17 in hyperplastic premalignant lesions is confirmed in cervical secretion of HPV infected women. This concludes the association between Th17 cells and IL-17A in cervical cancer, and their precursor lesions (Gosmann et al., 2014) (Figure 3a). High expression levels of IL-17A are associated with poor uterine cervical cancer prognosis, but the role of this response in tumor progression is still ambiguous (Punt et al., 2015) (Figure 3a). A tri-lateral relation between HPV infection, IL-17A level, and STAT3 activity was proposed by Li et al. that may induce a proinflammatory microenvironment in the colon and rectum, leading to colorectal cancer (CRC) in humans (Y. X. Li et al., 2015). A similar relationship was reported in breast cancer due to HPV infection (N. Zhang et al., 2016). A lower serum level of IL-17 in HPV infected women along with macrophage migration inhibitory factors were found to be related with the generation of cutaneous warts in HPV infection (El-Hamd et al., 2018). Apart from cervical cancer, HPV infection is also associated with lung tumorigenesis (Syrjänen, 2002). The expression of higher IL-17 and induced myeloid leukemia cell differentiation protein (Mcl)-1 in the presence of HPV infection is reported, which might promote tumor formation in non-small cell lung cancer by inhibiting apoptosis (Y. H. Chang et al., 2010) (-Figure 3a). High serum levels of IL-17A may induce viral persistence by deviating the immune response and lead to neoplastic progression (Mareti Bonin et al., 2019). Gene polymorphism of IL-17 plays a critical role in cervical cancer. A study done on Chinese women

reveals the association of IL-17A gene polymorphism −197G>A with cervical cancer in HPV-16 and 18 (oncogenic HPV strains) infections (Cong et al., 2015; Vidal et al., 2015). The polymerase chain reaction-restriction fragment length polymorphism results suggested that the individuals with AA and GA genotypes of IL-17A have higher risk of cervical cancer as compared to people with GG genotype (Cong et al., 2015). IL-17 was found more frequently in cervical cancer samples of women infected with HPV16/18 compared to women infected with other genotypes of HPV (Vidal et al., 2015). In summary, IL-17 mainly plays a detrimental role in oncogenic HPV infection by creating a hyperinflammatory condition leading to lesions, tumorigenesis and cancer. This indicates that blocking of IL-17 could potentially prevent the progression of premalignant lesions to cancer.

2.1.2 | Herpes simplex virus

HSV are enveloped linear dsDNA viruses with about a 150–160 kb genome (Minaya et al., 2017; Smith et al., 2014) belonging to the *Herpesviridae* family (https://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi). IL-17 promotes the cytokine-mediated recruitment of neutrophils that are associated with increased corneal opacity suggesting an indirect role of IL-17 in tissue damage (Rolinski & Hus, 2014). The absence of IL-17 leads to decreased infiltration of proinflammatory mediators in infected corneas (Molesworth-Kenyon et al., 2008). The reduced severity of corneal lesions in IL-17RA knockout (KO) mice confirms its role in disease pathogenesis (Suryawanshi et al., 2011). Apart from IL-17 expression in corneas of stromal keratitis infected patients, there is an expression of IL-17RA on human corneal fibroblasts (HCF) suggest the involvement of the IL-17 pathway. IL-17 showed a strong association with TNF-α in the recruitment of neutrophils and is thought to be a crucial immune activator in HCF (Maertzdorf et al., 2002). IL-17A plays an important role in enhancing antiviral T helper Type 1 (Th1) response in the female genital tract (Bagri et al., 2017). In IL-17A KO mice, the protective immune response against HSV-2 reinfection was impaired and the mice showed increased pathology, viral shedding and mortality as compared to wild type (WT) mice. Furthermore, the absence of IL-17A coincided with deficient interferon gamma (IFN-γ) production (Bagri et al., 2017). The generation of beta-defensin-3 in response to IL-17A induction by human herpes simplex vaccine VC2 at the vaginal mucosal surface in guinea pigs *Cavia porcellus* gave protection against HSV-2 infection. Human vaginal tissues also responded in a similar manner leading to reduced HSV-2 progeny (Stanfield et al., 2018). The role of HSV in peripheral nerve damage is debated because on one hand IL-17C secreted in response to HSV-2 infection is responsible for peripheral nerve growth (Peng et al., 2017). On the contrary, IL-17 induces the production of matrix metalloproteinases (MMPs) and oxyradicals like tissue-damaging factors and also acts as a neutrophil survival factor (Suryawanshi et al., 2011). IL-17C also provided surviving signals to protect neurons during HSV infection (Peng et al, 2017) thereby indicating the dual role of IL-17, that is, both protective and pathogenic effects in host tissues (Figure 1).

2.2 | RNA viruses

2.2.1 | Coxsackievirus B3

CVB3 is a nonenveloped, linear, positive-sense single-stranded RNA (ssRNA) virus with about a 7.4 kb genome belonging to the *Picornaviridae* family. CVB3 causes human acute viral myocarditis (AVMC) (Cooper, 2009; Gupta et al., 2008; B. Liu et al., 2014) characterized by myocardial inflammation, autoimmune response and minority of dilated cardiomyopathy cases (Dennert et al., 2008). The current understanding suggests the crucial role of IL-17A and Th17 cells in CVB3 induced AVMC pathology (Kong et al., 2013; Long et al., 2016; F. Yang et al., 2011; Yuan et al., 2010). The studies in BALB/c mouse model of viral myocarditis showed the upregulation of IL-17A at both protein and flevels from the first to sixth week of infection which promotes viral replication and leads to myocarditis (F. Yang et al., 2011). Neutralization with anti-IL-17 monoclonal antibody suppressed viral replication and improved cardiac pathology, which suggests that IL-17 could be a potential target for controlling CVB3 induced AVMC (Yuan et al, 2010). Another study on C57BL/6 J mouse model demonstrated the pathogenic role of IL-17A in CVB3 mediated pancreatitis (Yan et al, 2019). In CVB3 patients, the virus induces differentiation of $CD4^+$ T cells into Th17 cells by nucleoporin (Nup) 98 (Long et al, 2016). Inhibition of Nup98 by siRNA-Nup98 in $CD4^+$ T cells resulted in increased Th17 cells, IL-17A and ROR-γT levels (Long et al, 2016). Similarly the nicotine treatment in CVB3 mouse model significantly reduced the messenger RNA (mRNA) and protein levels of IL-17A along with decreased disease severity supporting the role of IL-17 in hyperinflammation (Li-Sha et al., 2015). Fasudil, A Rho kinase inhibitor was also reported to reduce IL-17A expression, myocardial lesions, viral replication and increase survival in CVB3 infected hearts in BALB/c murine model (K. Dai et al., 2018). In summary, IL-17 plays pathogenic role after CVB3 infection leading to cardiac injury and blocking of IL-17 reduces disease severity.

2.2.2 | Coronaviruses

CoVs are enveloped positive sensed ssRNA viruses with about a 27–32 kb genome belonging to the *Coronaviridae* family (Pal et al., 2020). This family includes SARS, MERS, and recently discovered SARS-CoV-2 that caused the COVID-19 pandemic, infecting millions of people worldwide (Pal et al., 2020). Elevated Th17 cell and IL-17 responses are reported in SARS, MERS, and SARS-CoV-2 infection (Faure et al., 2014; Josset et al., 2013; Z. Xu et al., 2020). In these viruses, the disease severity is positively correlated with IL-17 mediated inflammation along with other proinflammatory cytokines such as IFN-γ, TNF-α, IL-1β, IL-6. Excessive inflammation from these cytokines can lead to lung pathology and ARDS, which can cause severe damages in other organs such as kidney, heart and liver (Huang et al., 2020; Mahallawi et al., 2018) (Figure 3c). Higher IL-17A levels along with IFN-γ are associated with the worst disease outcomes in MERS infected patients (Faure et al., 2014). In COVID-19,

patients admitted to the intensive care unit (ICU) have higher levels of Th17 cytokines as compared to non-ICU patients (Huang et al., 2020). The higher number of Th17 cells in people with severe SARS-CoV-2 infection implicates its role in the cytokine storm, one of the principal causes of disease advancement (Q. Li et al., 2020). The deteriorated clinical symptoms of COVID-19 patients are due to the hypersecretion of IL-17A and other inflammatory cytokines. In the inflammatory cytokine storm, upregulation of IL-17A is mostly responsible for the immunopathology of COVID-19 and ARDS (Shibabaw, 2020). IL-17A induces many chemokines like interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)−1α and MIP-1β, GM-CSF contributing to cytokine storm in COVID-19 (D. Wu & Yang, 2020). Also, IL-17 induces the secretion of different MMPs, leading to lung tissue damage (D. Wu & Yang, 2020). Altogether, the Th17 response is actively involved in the pathogenesis of SARS-CoV-2 and other coronaviruses infections by contributing to tissue damage and pulmonary edema (Huang et al., 2020) (Figure 3c). It has also been hypothesized that blocking of IL-17 could have the potential to improve the aberrant immune response of COVID-19 and ARDS related mortality (Bulat et al., 2021). For example, Th17 cell differentiation is also mediated through transcription factor STAT3, which is closely associated with JAK-STAT pathway (Fabbi et al., 2017). A recent study proposed that targeting JAK with its inhibitors could be used to counter the hyperinflammation of Th17 cells (D. Wu & Yang, 2020) (Figure 3c). This study used the US Food and Drug Administration approved JAK2 inhibitor Fedratinib (TG101348, SAR302503) on Th17 cytokine synthesis. Treatment of Fedratinib decreased IL-17 production in murine Th17 cells. Moreover, the addition of IL-23 increased the suppressive effect of Fedratinib. As highlighted earlier, IL-17 is actively involved in ARDS associated with CoVs. In the mouse model, the direct and indirect blockage of IL-17 transcription factor ROR-γt resulted in lung injury reduction (Yan Chen et al., 2018; Righetti et al., 2018). Thus targeting ROR-γt could also be beneficial for effective antiviral activity against CoVs. In conclusion, IL-17 is mainly associated with increasing the CoVs associated lung pathology. A detailed analysis of Th17 cell mediated pathology and targeting IL-17 signaling could be helpful in the management COVID-19 patients.

2.2.3 | Dengue virus

DENV is an enveloped positive-strand ssRNA virus with about an 11 kb genome (Wen et al., 2018) belonging to the *Flaviviridae* family. It mainly causes dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (Rodenhuis-Zybert et al., 2010). Studies on dengue fever showed elevation of Th17 and Treg cells at different phases (immunoglobulin (Ig)M^-IgG^-, IgM^+, IgM^+IgG^+, and IgG^+ phases) of infection (M. Liu et al., 2016). Furthermore, IL-17 levels were considerably higher in dengue patients with secondary DENV infection compared to primary infection. The analysis done in various age groups showed high IL-17 levels in children with severe dengue (Jain et al., 2013). Similar results of elevated IL-17 level in DENV infection was reported by Becquart et al. (Becquart et al., 2010). A positive association of increased IL-17 level was also reported in respiratory distress and pleural effusion (Jain et al., 2013). Although the direct role of IL-17 is still under investigation, few reports have shown that IL-17 promoted the production of proinflammatory cytokines IL-6 and IL-8 which contributed to the pathogenesis of DHF (Raghupathy et al., 1998; Restrepo et al., 2008). IL-17 stimulates the secretion of another proinflammatory cytokine IL-1β, by human macrophages (Friedlander et al., 1996). Similarly, IL-17 induced upregulation of TNF-α in severe dengue infection. This caused overexpression of proadhesive molecules on the endothelium, which resulted in the migration, adhesion and accumulation of leukocytes to the capillaries (Jovanovic et al., 1998). In addition, IL-17 was associated with neutrophil recruitment in all DENV serotypes via induction of growth regulated oncogene-α (GRO-α) (Moreno-Altamirano et al., 2004; Witowski et al., 2000). However, no difference in the level of IL-17 were observed between patients with DHF who developed shock and those who did not (Malavige et al., 2012). Thus, the direct role of IL-17 in DENV infection and pathogenesis is currently unclear, nevertheless it is indirectly linked to the DENV associated pathology.

2.2.4 | Hepatitis C virus

HCV is an enveloped positive-strand ssRNA virus with about a 9.6 kb genome belonging to the *Flaviviridae* family. It causes chronic hepatitis, which progresses to liver cirrhosis and HCC (Kato, 2000). The hepatic disease due to HCV infection is believed to be the outcome of the immune response against HCV (Cachem et al., 2017). Th17 cells are associated with protective and pathogenic role in HCV infection (Gomaa et al., 2019) but the involvement of Th17 associated cytokines in HCV infection is rarely investigated (Hassan et al., 2014). Thus, among different components of the immune system, Th17 cells can be used as a biomarker in the HCV disease progression (Q. Chang et al., 2012; Paquissi, 2017). The precise profile of Th17/IL-17 in chronic hepatitis C (CHC) and the role of IL-17 in HCV infection is not known (Hassan et al., 2014). However, a positive correlation between HCV-specific Th17 cell response with the severity of liver injury in CHC patients was present. In contrast, an inverse correlation with HCV RNA load was reported in the same study (Q. Chang et al., 2012). The Th17 cells are inhibited by immunosuppressive cytokines (IL-10 and TGF-β) secreted by HCV. The TGF-β neutralization has been shown to increase IL-17 production in response to hepatitis C nonstructural protein 4 (Gutkowski & Hartleb, 2009). The increased levels of IL-17 and IL-17 producing cells were observed in HCV infected patients which were closely associated with the extent of liver inflammation. This provides the basis for the potential use of Th17 cells as a bio-marker for CHC disease advancement (Abou El-Khier et al, 2018) (Figure 3b). The higher serum concentration of IL-17 in chronic liver disease is positively correlated with viral load (Hassan et al., 2014). A study

reported an increased level of IL-17A in HCV infected patients and was correlated to viral load and proposed IL-17A to be a better biomarker in HCV infection (Gomaa et al., 2019). The IL-17A −197G>A SNP is previously discussed in different viral infections. In HCV infection, the GG and GA genotypes of IL-17A −197G>A are more prominent in HCV infected HCC and non-HCC patients. This highlights the role of IL-17A −197G>A SNP, a major risk factor associated with HCV mediated HCC progression (ELBassuoni et al., 2015). In nutshell, IL-17 plays both detrimental and protective role in HCV infection. On one side, it induces viral persistence while on the other hand the concentration of circulating Th17 cells was reported to be inversely related to HCV RNA load. Moreover, the immunosuppressive cytokines secreted during viral infection inhibited the Th17 cells suggesting their protective role in HCV infection.

2.2.5 | Zika virus

ZIKV is an enveloped positive-sense ssRNA virus with about an 11 kb genome belonging to the *Flaviviridae* family (Kuno & Chang, 2007). It mainly causes zika fever with headache and joint pain like symptoms (L. H. Chen & Hamer, 2016; Musso & Gubler, 2016). ZIKV infected patients display an early immune response with an increased serum level of IL-17 (Zuñiga et al., 2020). The elevated level of IL-17A is associated with the acute phase of human ZIKV infection (Zuñiga et al., 2020) and involved in onset of clinical symptoms. For example, patients with headache had higher IL-17A level as compared to people without headache (Zuñiga et al., 2020). The chemokine ligand IP-10, one of the downstream targets of IL-17A is also increased after ZIKV infection along with IL-17A (Zuñiga et al., 2020). In ZIKV induced microcephaly, the in situ immune response is associated with increased IL-17 level and IL-17 is associated with neuroinflammatory response by promoting the expression of inducible nitric oxide synthase (iNOS) which mediate neural cell damage (Azevedo et al., 2018). Thus the elevated level of IL-17 and its downstream target suggest that IL-17 could be used as a biomarker of acute ZIKV infection (Fares-Gusmao et al., 2019; Lum et al., 2018; Zuñiga et al., 2020). Although the exact mechanism of IL-17 mediated ZIKV pathogenesis is yet to be explored.

2.2.6 | Influenza virus

Influenza viruses are enveloped negative-sensed linear ssRNA viruses with about a 13.6 kb genome belonging to the *Orthomyxoviridae* family (Bouvier & Palese, 2008). They are associated with flu, viral pneumonia and secondary bacterial pneumonia. Influenza viruses are a major cause of respiratory infections. They are broadly divided into four main types, namely A, B, C, and D. Influenza A and B are mainly involved in human infections. Influenza A is further divided into 12 different subtypes (H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9, and H6N1), out of which H1N1 and H3N2 circulate annually in humans. Influenza B virus has no subtypes and can only infect humans (https://www.who.int/en/news-room/fact-sheets/detail/influenza-[seasonal]). The influenza A viruses are historically known to cause pandemics causing serious damage to mankind. The major pandemic associated influenza subtypes include- H1N1 that caused the Spanish influenza in 1918–1919 and second pandemic in 2009, H2N2 that caused Asian influenza in 1957–1958 and H3N2 associated with Hong Kong pandemic in 1968–1969. In addition, the H5N1, H7N9 avian influenza and H9N2 influenza strains possess a high pandemic potential (Shan et al., 2019; Song & Qin, 2020; Taubenberger & Morens, 2010). Cytokine dysregulation is associated with severe disease outcomes in influenza infection (https://www.who.int/en/news-room/fact-sheets/detail/influenza-[seasonal]; Keshavarz et al, 2019). As compared to seasonal influenza the pandemic H1N1 influenza causes increased extrapulmonary complications and without timely treatment, the mortality risk was increased in pandemic H1N1 infection (N. Lee, Chan, et al., 2011). In addition, the patients infected with pandemic H1N1 had slower viral clearance in the lower respiratory tract during antiviral treatment (N. Lee, Chan, et al., 2011). The bacterial superinfection along with pandemic H1N1 infection exacerbates the severity (N. Lee, Chan, et al., 2011). Seasonal influenza is associated with a strong cytokine response including IL-17, while pandemic H1N1 influenza is known to suppress the immune response (N. Lee, Wong, et al., 2011). As compared to seasonal influenza, in pandemic H1N1 infection, the Th17 mediated adaptive immune response was suppressed with a decreased IL-17A level. An increased IL-17A response was observed in influenza B as compared to in pandemic and seasonal influenza A patients (N. Lee, Wong, et al., 2011). On the contrary, another study reported an elevated Th17 response during early phase of pandemic H1N1 infection (Bermejo-Martin et al., 2009). The variations in these two studies may be due to the difference in patient profile and disease severity included in the two studies. Pandemic influenza is associated with reduced Th17 cell response however, some studies suggest the protective role of IL-17 in critically ill patients suffering from pandemic influenza in 2009 (Almansa et al., 2011). The immunosuppressed patients are more vulnerable to Influenza infection. Recently, for a better understanding of pathogenesis and for evaluating the potential of antiviral treatment in immunosuppressed environment an immunosuppressed mouse model was developed. However, in the immunosuppressed mouse model of influenza B infection, developed by pharmacological intervention using dexamethasone and cyclophosphamide no significant contribution of Th17 cells was observed in terms of pathogenicity (Marathe et al., 2017). A pilot study of patients with symptoms of respiratory tract infection demonstrated that the H3N2 influenza infection exhibited increased levels of Th17 cytokines concerned with pathogenesis and immune regulation (Antalis et al., 2019). In the patients infected with avian influenza A (H7N9) virus, the decreased Th17 and Tc17 cell levels are associated with disease severity however, the mechanism remains unknown (Bao et al., 2019). In PR8 H1N1 infected BALB/c mice the IL-17A and IL-17F mRNA levels were detected after 2 days

postinfection. Similarly, the protein levels of IL-17A and IL-17F were detectable from 2 to 7 days postinfection and after 7 days there was significant mortality in infected BALB/c mice. In H1N1 infected IL-17RA KO mice the weight loss was comparatively less than the WT mice which implies an increased survival rate among the IL-17RA KO mice. The IL-17RA KO mice had higher viral burden after 6 days postinfection but ultimately recovered from the infection. In addition, the neutrophil infiltration in IL-17RA KO mice abridged secretion of an oxidized phospholipid responsible for inducing lung injury. Furthermore, the IL-17RA KO mice had reduced inflammation, less capillary leakage in total BAL fluid protein, and reduced lung injury as compared to WT mice. Altogether, these findings suggest a damaging role of IL-17 in H1N1 infection (Crowe et al., 2009). In another C57BL/6 mouse model of PR8 Strain of H1N1, the level of IL-17 cytokine was reported to be elevated during infection, but on the contrary deficiency of IL-17 could not reduce virus-induced lung injury (C. Li, Yang, et al., 2012). It has been proposed that Influenza infection could alter the intestinal microbiota composition. Th17 cells markedly increased in the small intestine after severe PR8 H1N1 infection, and neutralizing IL-17A reduced intestinal injury. Furthermore, antibiotic depletion of gut microbiota reduced IL-17A production and impaired influenza-caused intestinal injury (J. Wang, et al., 2014). IL-17 is also involved in post influenza superinfection (Er et al., 2019; Kudva, 2011). IL-17 immune response is involved in the regression of post influenza *Staphylococcus aureus* superinfection. *S. aureus* infection in skin and lungs marked a mutated STAT3 transcription factor that is crucial for Th17 cell response. The IL-17RA KO mice showed decreased bacterial clearance as compared to the wild-type mice. Mice infected with PR/8/34 H1N1 and *S. aureus* displayed more viral and bacterial load and elevated inflammation. The H1N1 coinfection showed a reduced level of IL-17 after *S. aureus* challenge, thereby implying a protective role of IL-17A in post influenza superinfection (Kudva, 2011). Similarly, IL-17 mediated protective immune response is involved in influenza virus and *Streptococcus pneumonia* superinfection (Er et al., 2019). In influenza infected T-bet KO mice, the elevated level of IL-17 promotes their survival against subsequent *S. pneumonia* infection. IL-17 neutralization in T-bet KO mice was positively correlated with decreased neutrophil infiltration and increased bacterial load in pulmonary region (Er et al., 2019). Altogether these findings support the role of IL-17 in protection against post influenza bacterial superinfections. H1N1 mouse model studies suggested that IL-17A is also involved in mediating B cell-associated adaptive immune response in influenza infection (X. Wang et al., 2011). IL-17A mediates the B1A cells associated IgM antibody production by inducing NF-κB and B-lymphocyte induced maturation protein-1 (Blimp-1) (Figure 2). The reduced IL-17A concentration leads to tampered antibody production and impaired viral clearance (X. Wang et al., 2016). IL-17A is also crucial for B-cell migration into the lungs during the H5N1 influenza infection. The lung tissues of IL-17A KO mice infected with the H5N1 virus displayed reduced chemokine (C-X-C motif) ligand 13 (CXCL13) expression leading to reduced chemotaxis (X. Wang et al., 2011). IL-17 gene has different SNPs which are associated with many human diseases (Z. M. Dai et al., 2016). The presence of allele A in IL-17A −197G>A SNP increases IL-17A secretion (Rolandelli et al., 2017). Keshavarz et al. (2019) demonstrated that GG, AA, and GA genotypes of −197G>A of IL-17A are significantly associated with influenza A and B infection in Iranian population. Also, the absence of A allele in −197G>A increased the risk of H1N1 infection. IL-17 plays both protective and pathogenic role in influenza virus infection. It causes inflammation associated lung injury as well as is involved in B cell mediated adaptive immune response.

2.2.7 | Respiratory syncytial virus

RSV is an enveloped linear negative-sense ssRNA virus of about a 15.2 kb genome (Ha Do et al, 2015) belonging to the *Pneumoviridae* family. It mainly causes lower respiratory tract infections. Currently, there is no vaccine available against RSV and its precise mechanism of pathogenesis is not fully explored (Cheon et al., 2019). Upregulation of Th17 cells and IL-17A responses in RSV infection are associated with increased neutrophil recruitment and pulmonary pathogenesis in infants as well as in BALB/c mouse model of RSV (Mukherjee et al., 2011). Also, the ratio of Th17 cells and Treg cells is linked with RSV induced pathology (Mangodt et al., 2015). In an RSV infected C57BL/6 mouse model, the balance of Th17/Treg ratio was related to the pathogenesis of RSV induced bronchiolitis (Mebratu & Tesfaigzi, 2018). There is less information about IL-17A induced lung injury, but IL-17A level was increased in the bronchial submucosa site in chronic obstructive pulmonary disease, leading to mucus cell emphysema after RSV infection (Ishioka et al., 2013). RSV infection is a prominent cause of exacerbation of asthma (Ishioka et al., 2013; Sigurs et al., 2005). The reduced tolerance to asthma is caused by increased IL-17A producing cells in lungs via chemokine receptor 6 (CCR6) and chemokine ligand 20 (CCL20) signaling (Shi et al., 2017). IL-17 induces the mucin 5ac (Muc5ac) expression which is directly related to mucus production in the respiratory tract (Figure 2) (Yin Chen et al., 2003). The elevated level of IL-17 in STAT1 KO mice infected with RSV increased the mucus production and airway distress (Hashimoto et al., 2005). Apart from increasing the disease severity, a protective role of IL-17A has also been reported in RSV infection (Faber et al., 2012; Newcomb et al., 2013). Although respiratory tract remains the primary target of RSV, there are evidence of RSV mediated kidney damage (X. Hu et al., 2019). Immunoglobulin A nephropathy is a common disease characterized by prominent immunoglobulin A deposits in the renal mesangium. In BALB/c mice model of immunoglobulin A nephropathy, the RSV infection exploited the complement component and their receptor, C5a-C5aR1 axis leading to increased Th17 cell frequencies. Further, the treatment of C5aR antagonist significantly reduced the Th17 frequencies, thereby limiting the RSV induced kidney damage (Figure 1) (X. Hu et al., 2019). The acute and recovery phases of RSV bronchiolitis in children were marked with an elevated level of IL-17A, indicating the role of IL-17A in disease recovery (Faber et al., 2012). In RSV infected BALB/c mice with ovalbumin (OVA)-induced allergic airway

inflammation (OVA/RSV), IL-17A level significantly increased after 6 days postinfection. Also, IL-17A KO OVA/RSV mice had increased airway reactivity (AR) as compared with WT OVA/RSV mice, implying a negative correlation between IL-17A and RSV induced AR (Newcomb et al., 2013). A recent study on RSV infection reported a protective role of IL-17A in viral clearance during early phase of infection (Habibi et al., 2020). The RSV infection is associated with IL-17 mediated increased mucus production, neutrophil infiltration and bronchiolitis. On the contrary, IL-17 also leads to viral clearance, reduces the AR in RSV infection and promotes disease recovery.

2.3 | Retro viruses

2.3.1 | Human immunodeficiency virus/Simian immunodeficiency virus (HIV/SIV)

HIV/SIV are enveloped positive sensed ssRNA viruses with about a 9 kb (Feinberg & Greene, 1992) genome belonging to the *Retroviridae* family (Fanales-Belasio et al., 2010). HIV preferably depletes Th17 cells during the acute phase of infection even in lower viremia but, there is no consent regarding frequencies of Th17 cells in peripheral blood at different stages of HIV (Christensen-Quick et al., 2016; Dunay et al., 2016). Th17 cells make up a significant T cell subset in female reproductive tract tissues. Th17 cells expressing C-C chemokine receptor type 5 (CCR5) and cluster of differentiation 90 (CD90) showed increased susceptibility to HIV infection in the human female reproductive tract (Rodriguez-Garcia et al., 2014). The activated Tc17 cells possess the potential to produce IL-17A in healthy individuals, but not in patients living with HIV, even with highly active antiretroviral therapy. This dysfunction of Tc17 cells is related to persistent immune activation and can be restored partially by antiinflammatory agents (Perdomo-Celis et al., 2018). Th17 cells express higher levels of CD4 protein, C-X-C chemokine receptor type 4 (CXCR4), and $\alpha4\beta7$ viral receptors which increases virus and Th17 cell association. HIV infected Th17 cells lack viral inhibitory RNase and also the synthesis of CCR5 ligands, which altogether facilitate viral persistence and replication (Alvarez et al., 2013; Christensen-Quick et al., 2016) (Figure 2). (Falivene et al., 2015) reported a reduced Th17/Treg ratio in HIV-infected individuals which were similar to previous findings (Favre et al., 2009). In SIV infected pigtailed macaques *Macaca nemestrina* showed decreased Th17 cells and disturbed Th17/Treg ratio (Favre et al., 2009). Some studies also suggested the role of sex difference in Th17 cells mediated immune response against HIV infections. A comparatively higher level of Th17 and Tc17 cells are present in HIV infected females as compared to HIV infected males (D'Ettorre et al., 2019). There is an imbalance of Th17/Treg ratio in HIV infected patients with tuberculosis which leads to increased HIV replication (Y. Li & Sun, 2018). HIV infected patients were reported to have a higher risk of active tuberculosis (TB) as compared to uninfected. There is preferential depletion of Th17 cells in HIVinfected TB patients increasing their susceptibility (Murray et al., 2018) and a reduced IL-17A production in HIV^+ Latent TB patients and HIV^+ active TB patients (Devalraju et al., 2018).

There is a positive correlation between HIV-1 RNA levels and IL-17 in seminal plasma signifying the involvement of Th17/IL-17 associated inflammation in increasing HIV replication (Hoffman et al., 2014). Maek-A-Nantawat et al. (2007) reported a substantial increase in IL-17 in peripheral blood during HIV infection. The expression of IL-17 was dependent on the degree of infection in HIV-1^+ children. The plasma viral load of HIV-infected patients with a lesser than 50 copies/ml had measurable IL-17 expression (Ndhlovu et al., 2008). Also, IL-17 is involved in disease progression of oral candidiasis in HIV infected individuals (Mousavi et al., 2016). The loss of IL-17 producing cells during SIV infection in intestine increased viral persistence both on and off antiretroviral therapy (Ryan et al., 2016). Thus, the preferential loss of Th17 cells in HIV infection indicates its defensive role while the expression of viral ligands by Th17 cells and lack of viral inhibitory RNAase contributes to viral persistence, altogether indicating both supportive and damaging role of IL-17 in HIV/SIV infection.

2.3.2 | Hepatitis B virus

HBV is an enveloped circular partially dsDNA virus with about a 3.2 kb genome belonging to the *Hepadnaviridae* family. It causes liver cirrhosis and hepatocellular carcinoma (Liang, 2009). The Th17 cells are reported to be associated with liver damage in HBV infection. An increased level of IL-17 and Th17 cells was observed in peripheral blood mononuclear cells (PBMCs) of patients with chronic hepatitis B (CHB) and HBV induced acute to chronic hepatitis (B. Yang et al., 2013). Change in the Th17/Treg ratio leads to disease progression of HBV associated liver cirrhosis. The Th17/Treg ratio increased while the Th17 frequency and TGFβ/IL-17A ratio reduced in the survival group as compared to the nonsurviving group of liver cirrhosis patients (Yu et al., 2014). These results were consistent in conditions such as HBV induced CHB (J. Li, Qiu, et al., 2012; J. Y. Zhang et al., 2010), acute to chronic liver failure (Zhai et al., 2011), and HCC patients (J. P. Zhang et al., 2009). IL-17 increases the proliferation of hepatocytes by STAT3 phosphorylation via IL-6 induction in HCC patients (Z. Hu et al., 2017) (Figure 3b). The frequency of circulating Th17 cells in HBV infected patients is correlated with disease progression of chronic hepatitis B and the circulating Th17 cells are associated with liver inflammation rather than the viral replication (W. Wu et al., 2010). The proinflammatory activity of Th17 cells and IL-17 is downregulated by inflammation inhibitory mechanism of Treg cells and IL-23. In HBV induced hepatitis, the IL-17/IL-23 inhibitory machinery loses its efficiency and leads to disease progression (Q. Wang et al., 2011). In vitro studies demonstrated that IL-17A inhibits HBV replication, which correlated with overexpression of myxovirus resistance protein A (MxA) and oligoadenylate synthetase (OAS) mRNA (B. Wang et al., 2013). Epigenetic factors also influence HBV progression. In the PBMC samples, the methylation of IL-17A promoter gene was found to be positively related to CHB

progression (Tian et al., 2019). The genotype analysis of HBV infected patients suggested an active participation of −197G>A and 7488T>C SNP in HBV infection. The G allele of GG genotype at IL-17A −197G>A and T allele of TT genotype at IL-17F 7488T>C are associated with increased risk to HBV infection (Ren et al., 2017). In addition, the IL-17A −737C>T SNP is also associated with increased HBV persistence (Liu et al., 2014). Altogether, these studies suggest an active participation of IL-17 SNPs in HBV infection. Thus it can be concluded that IL-17 is involved in HBV induced hepatic diseases, CHB, acute to chronic liver failure, liver cirrhosis, and HCC due to dysregulation in inflammatory response but also inhibits viral replication that was correlated with secretion of MxA and OAS mRNA.

3 | DISCUSSION

Recently IL-17 has been explored as a promising and therapeutic molecule against various infections, autoimmune disorders, and cancer. IL-17 is largely considered a proinflammatory cytokine and involved in the clearance of extracellular pathogens. Its major role has been extensively studied in the field of autoimmune disorders as well as in inflammation associated malignancies. For example, the protumorigenic role of IL-17 and its involvement in cancer progression is well established. Elevated level of IL-17 and its signature genes is reported in various malignancies such as cervical cancer (Alves et al., 2018), hepatocellular carcinoma (Z. Hu et al., 2017), CRC (le Gouvello et al., 2008), esophageal cancer (D. Chen et al., 2012) and ovarian cancer (Miyahara et al., 2008). Recent reports showed that targeting IL-17 could inhibit disease severity and reduce clinical symptoms (Robinson et al., 2013). Currently there are three main biologics or neutralizing antibodies that are clinically adopted to block the function of IL-17 namely, ixekizumab, secukinumab and brodalumab. The therapeutic application of these antibodies was well explored against autoimmune disorders like psoriasis, psoriatic arthritis (Iain & Mcinnes, 2016; McInnes et al., 2014), ankylosing spondylitis (Yin et al., 2020), rheumatoid arthritis (Genovese et al., 2010) and experimental autoimmune encephalomyelitis (mouse model of multiple sclerosis) (Lock et al., 2002). ROR-γt is the master transcription factor for IL-17 secretion. Inhibition of ROR-γt has been proposed as a therapeutic target in skin pathologies and Crohn's disease (Bassolas-Molina et al., 2018; Ecoeur et al., 2019). In addition, STAT3 is also a major transcription factor required for IL-17 production. Inhibition of STAT3 by a small molecule C188-9 significantly reduced the airway inflammation and Th17 accumulation in murine asthma (Gavino et al., 2016). Recently, it was suggested that targeting the JAK transcription factor by its inhibitor Fedratinib (TG101348, SAR302503) was helpful in reducing Th17 mediated hyperinflammation (D. Wu & Yang, 2020). Fedratinib treatment significantly reduced IL-17 secretion in murine Th17 cells.

In the case of viral infections, the research on this cytokine is still elusive and in progress. Despite the multiple roles of IL-17 in viral infection, autoimmune disorders, different malignancies, the other members of this family have been barely studied. Various animal models of IL-17 for viral infection have been developed and studied. In influenza virus infection IL-17A plays a protective role by activating B1a cells mediated IgM production, and at the same time, it contributes to lung tissue damage by increased proinflammatory conditions. RSV is another respiratory virus that causes IL-17 mediated exacerbation of asthma, bronchiolitis, and also kidney damage. However, in the mouse model of RSV infection, IL-17A negatively regulated airway reactivity, implying a protective role. In CVB3 infection, IL-17A induces viral myocarditis, pancreatitis and inflammation associated cardiac injury suggesting positive correlation between IL-17A and CVB3 induced disease severity.

In contrast, the in vitro studies conveyed IL-17A mediated inhibition of the hepatitis virus that was correlated with antiviral proteins like MxA and OAS. In HSV infection, the increased neutrophil recruitment by IL-17 was associated with increased corneal opacity instead of viral clearance. Also, it provided survival signals to neurons and prevented peripheral nerve damage but on the other hand, it induces the production of MMP and oxyradicals like tissue damaging-factors. The Th17 cells are one of the targets of HIV virus. The expression of viral receptors by Th17 cells and the lack of inhibitory RNase facilitates viral replication and plays a pathogenic role in HIV infection.

The pathogenic role of IL-17 has also been investigated in ZIKV infection. It is associated with iNOS mediated neuroinflammatory response leading to neural damage. In SIV infection, the lack of Th17 cells was associated with disease progression, thus suggesting IL-17 may play a protective role in SIV infection. The function of IL-17 in a few viral infections like dengue is not fully explored. In flaviviral infections like dengue, the role of IL-17 is allied with pleural effusion and respiratory distress but the mechanism remains unknown. Furthermore, human genome sequencing along with advanced available bioinformatics tools have helped to identify multiple SNPs and established their correlation with the risk of developing human diseases. The identification in the variation of the human genome has opened the door for better diagnosis against various pathogens. The SNPs present in IL-17A promoter and IL-17F gene are reported to play the pathogenic roles in H1N1, HPV, and HBV/HCV infection and novel meta-analyses will be required to establish their association with other viral infections. The SNPs are also associated with different post-translation modifications, protein inactivation and altered receptor signaling in various human diseases (Y. Kim et al., 2015; Lokau et al., 2018; Martin et al., 2018; H. Wang et al., 2014). However, the biological role of IL-17 SNPs in different viral infections remains unexplored. Further studies on biological role of IL-17 SNPs in different viral infection will provide new insights in antiviral therapeutics. Several vaccination approaches and therapies for viral infections are being developed but due to unsatisfactory and nonspecific responses for many viruses, it is utmost to find novel therapeutic molecules. IL-17 has come up as a promising target due to its dual pathogenic and protective role. Future work on IL-17 and IL-17-producing cells in virus rechallenge models is needed for a better understanding. The antiviral immune response is a complex phenomenon and IL-17 has an important role in it. As discussed in this

review, the pleiotropic functions of IL-17 are complex and critical in different settings of viral infections.

The IL-17 mediated immune response varies in the cell and tissue microenvironment. For example, in lung epithelium, IL-17 signaling induces the secretion of CXCL-5, IL-6, and IL-8, and aids neutrophil recruitment (K. Chen et al., 2016; Kawaguchi et al., 2001). In NK cells, IL-17 induces GM-CSF for the proliferation of Kupffer cells (Wanqiu Hou et al., 2009; W. Hou et al., 2014). In the intestinal epithelial cells, the IL-17 signaling via ACT1 produces occludin crucial for tissue integrity (J. S. Lee et al., 2015). In addition, IL-17 induces the secretion of collagen I protein in the liver, thus contributing to liver fibrosis (W. Hou et al., 2014). Thus the multifaceted functions of IL-17 signaling depending upon the cell and tissue microenvironment make it a crucial factor during viral infections.

In this review, we have tried to address the pathogenic and protective role of IL-17 in different viral infections. On one side, it induces neutrophil migration at the site of infection, provides survival signals to neurons and mediates IgM production via NF-κB and Blimp-1 mediated response. While on the other side, the dysregulated IL-17 levels are associated with viral pathology. This include respiratory distress, tissue damage, viral persistence, skin lesions, and reduced viral inhibitory RNase resulting in viral persistence, tumorigenesis and finally cancer (HCC, CC). The manuscript also summarizes various SNPs of IL-17 reported in different viral infections that play a pathogenic role.

In conclusion, a better understanding of the molecular mechanisms that govern IL-17 mediated antiviral immune responses and its SNPs may lead to the development of novel treatment options. Targeting induction or suppression of IL-17 expression for protection against viral infections is an area worthy of future exploration.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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