LITERATURE REVIEW

Defining the Role of Th17 Lineage Cells in People with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is a pandemic disease which has created a serious public health threat worldwide and causes pneumonia due to infection of the host with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There remains a key gap in the understanding of what decides the outcome between an appropriate immune response and immunopathology in COVID-19. Th17 lineage cells are a distinct population of CD4+ T helper cells which mediate protection against bacteria and fungi. Th17 cells are dysregulated in patients with severe COVID-19 and are significant contributors to the systemic cytokine storm experienced by critical patients. Th17 cells have been described to mediate damage in the lungs of COVID-19 patients by encouraging the recruitment of neutrophils, contributing to acute respiratory distress syndrome and cytokine storms, causing pulmonary fibrosis, disrupting normal alveolar architecture and oxygenation processes and ultimately leading to systemic organ damage and death. Th17 cells have also been reported to contribute to immune dysfunction in conditions associated with increased risk of disease severity in COVID-19. There is a gap in our knowledge surrounding Th17-mediated protective immunity versus aberrant uncontrolled Th17-mediated pathology in the lung. This review aims to investigate and define the mechanisms of Th17 cells in COVID-19 pathogenesis by comparing the features of Th17 cells in a healthy immune response of the lung with the severe disease state in critical COVID-19.

Keywords: Th17 Cells, COVID-19, SARS-CoV-2

Introduction to Th17 Cells

Th17 lineage cells are a distinct population of CD4+ T-helper (Th) cells which mediate protection against bacteria and fungi[1]. Th17 cells produce proinflammatory cytokines interleukin (IL)-17A, IL-17F, IL-22, IL-26, tumour necrosis factor-α (TNFα), chemokine ligand 20 (CCL20) and granulocyte macrophage colony-stimulating factor (GM-CSF)[2]. These proinflammatory cytokines operate on various target cells and consequently are involved in several inflammatory diseases for example autoimmunity, chronic inflammation and infectious diseases[3]. Th17 cells support B cell function and recruit other cells, such as neutrophils, to the site of inflammation[4]. In certain contexts of inflammation, Th17 lineage cells exhibit plasticity and can produce the Th1 cytokine IFN-γ[5]. This unconventional polyfunctionality has a role in mediating inappropriate inflammation during autoimmunity but may also be critical to mediating protection against infectious diseases[6].

Induction and Differentiation of Th17 Cells

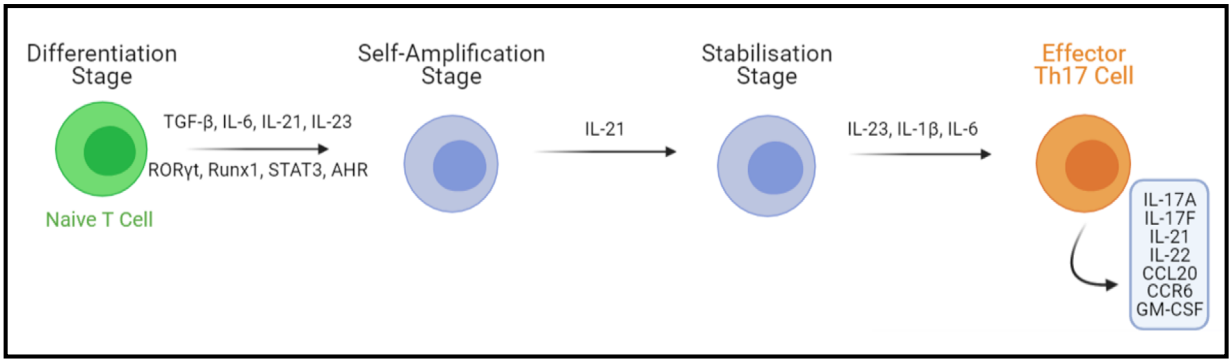
IL-6, IL-21, IL-23 and TGF-β drive Th17 cell differentiation (**Figure 1**). The master regulator of this differentiation process is the transcription factor retinoic acid receptor orphan receptor gamma-T (RORγt).

There are three stages involved in the differentiation of Th17 cells: the differentiation stage driven by TGF-β, the self-amplification stage driven by IL-21, and the stabilisation stage driven by IL-23. When TGF-β is low and IL-6 is present, this results in the differentiation of Th17, IL-21 generation and the stimulation of IL-23R. RORγt is activated through the downstream signalling of TGF-β and IL-6 and therefore stimulates the generation of IL-17A and IL-17F. Downstream signalling of IL-6, IL-21 and IL-23 leads to STAT3 activation which also contributes to Th17 cell differentiation by promoting RORγt. Runx1 is also involved in the process of Th17 differentiation as RORγt can trigger Runx1 and enhances differentiation. Transcription factor aryl hydrocarbon receptor (AHR) obstructs the negative regulators of Th17 differentiation, STAT1 and STAT5. IL-21 drives the self-amplification process and engages with TGF-β to amplify the differentiation process. The stabilisation phase is driven by IL-23 generated from antigen presenting cells and serves to enhance and sustain Th17 cell populations. Downstream signalling of IL-6 and IL-21 triggers IL-23R to be expressed on the surface of Th17 cells. IL-23 in combination with IL-1β is capable of stimulating T-bet+ RORγt+ Th17 cells without the involvement of TGF-β. Finally, effector Th17 cells produce IL-17A, IL-17F, IL-21, IL-22, CCL20, CCR6[1].

Th17 Cell Receptors and Signalling in Epithelial Cells and Fibroblasts of the Lungs

Th17 effector cytokines signal through the multimeric IL-17 receptor (IL-17R) which consists of IL-17RA and IL-17RC. IL-17R has a broad cellular distribution. In the airways, these receptors can be identified on epithelial

Figure 1. **Differentiation of Th17 cells**



cells and fibroblasts. IL-17 can mediate beneficial or detrimental effects in the lungs[7]. Mucosal epithelial cells of the lungs express IL-17 and IL-22 receptors indicating the important homeostatic role of these cytokines[8,9].

Basal airway cells contain IL-17Rs and induction of IL-17 by bronchial epithelial cells promotes a chemokine gradient which attracts an infiltration of pro-inflammatory immune cells such as neutrophils into the lungs[8,10].

Epithelial cells may contribute to lung fibrosis via IL-17, by encouraging the generation and secretion of collagen, leading to epithelial-mesenchymal transition. Autophagy in epithelial cells can be inhibited through IL-17 signalling[11]. This may contribute to lung fibrosis as autophagy regulates fibrosis[12]. However, IL-22 produced by Th17 cells can induce autophagy in epithelial cells and promote defence. IL-22 can also dampen inflammation and stimulate epithelial repair in response to injury mediated by pathogens[9,13]. Overall Th17 effector cytokines have complex interactions with epithelial cells mediating both beneficial or detrimental outcomes in the lungs.

Lung fibroblasts can shift to a profibrotic state as a result of IL-17 signalling and trigger TGF-β and collagen proteins which contributes to fibrosis[14]. IL-17 regulates the infiltration of granulocytes as well as the production of extracellular matrix from lung fibroblasts[14].

The Role of Th17 Cells in the Lungs

IL-17A plays an important role in lung immunity through initiating and driving disease or conversely ameliorating the infection process. Th17 cells are involved in neutrophil activation and triggering a cascade of immune mechanisms to eliminate pathogens and therefore are integral to host defence. However, this Th17-mediated immune response can drive a dysregulated inflammatory response and cause damage to the delicate lung tissue. Therefore, the regulation of Th17 cells in the host appears to be critical in determining disease outcome[15].

T_{RM} Cells in the Lungs from Th17 Cell Lineages

There is increasing evidence surrounding the key role of tissue resident memory T cells (T_{RM}) in various pathogenic infections[16,17] and the presence of tissue-localised T cells have been demonstrated to have specific importance in mediating lung immunity[18,19]. Investigation of T_{RM} cells in the context of human organ transplantation has displayed the importance of these cells in human lung tissue and discovered that long-term persistence of these cells was associated with reduced incidence of rejection[20]. These published studies indicate the importance of this cell population in lung immunity. Long lived T_{RM} 17 cells have displayed important protective effects against bacterial infection[21]. There is a paucity of human data surrounding the role of T_{RM} cells in health and disease and the emerging concepts regarding tissue-specific protective immunity continues to be investigated.

IL-17A tracking-fate mouse models identified that Th17 cells and its effector cytokine IL-17A give rise to the production of lung CD4 T_{RM} cells[21]. This study displayed that Th17 lineage cells capable of producing IL-10 develop into T_{RM} cells in the lungs. IL-10 producing Th17 cells encourage differentiation of macrophages into the 'anti-inflammatory' macrophage phenotype also referred to as M2 macrophages[22]. M2 macrophages are associated with immunosuppression, tissue remodelling, wound healing and fibrosis[22,23]. Th17 cells capable of producing IFN-γ but not IL-10[24], are associated with encouraging the differentiation of macrophages into M1 phenotype which have potent pro-inflammatory activities[22]. The tissue and the environment where Th17 cells are located determines whether these cells will contribute to excessive immunopathology or mediate protective effects. The cytokine milieu is a critical determining factor in this process. IL-1β inhibits IL-10 production in differentiating and in memory Th17 cells and inhibition of IL-1β result in increased IL-10 production[24]. IL-1β drives production of IFN-γ producing Th17 cells[24] and IL-27 and TGF-β drive IL-10 producing Th17 cells[25].

Coronavirus disease 2019 (COVID-19)

COVID-19 is a pandemic disease which causes a pneumonia due to infection of the host with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By December 2021, there had been over 271 million cases of COVID-19 reported and over 5 million deaths[26]. Angiotensin-converting enzyme 2 (ACE2), the primary receptor for SARS-CoV-2[27], is abundantly expressed in epithelial cells of the lungs and therefore the lungs are the major organs impacted in COVID-19 infection[28].

SARS-CoV-2 infection is initiated by the virus binding to the ACE-2 receptor in the lungs which results in viral replication (**Figure 2**). Proinflammatory cytokines IL-1β and TNF-α are triggered as a result of alveolar macrophages undergoing apoptosis and pyroptosis. The production of these cytokines triggers a loss of renin-angiotensin system (RAS) due to downregulation of ACE2. The cytokines also initiate the production of Th17 cells which further contribute to production of pro-inflammatory cytokines and encourage the attraction of additional immune cells into the site of infection. Vascular permeability and leakage are increased as a result of proinflammatory cytokine signalling[29].

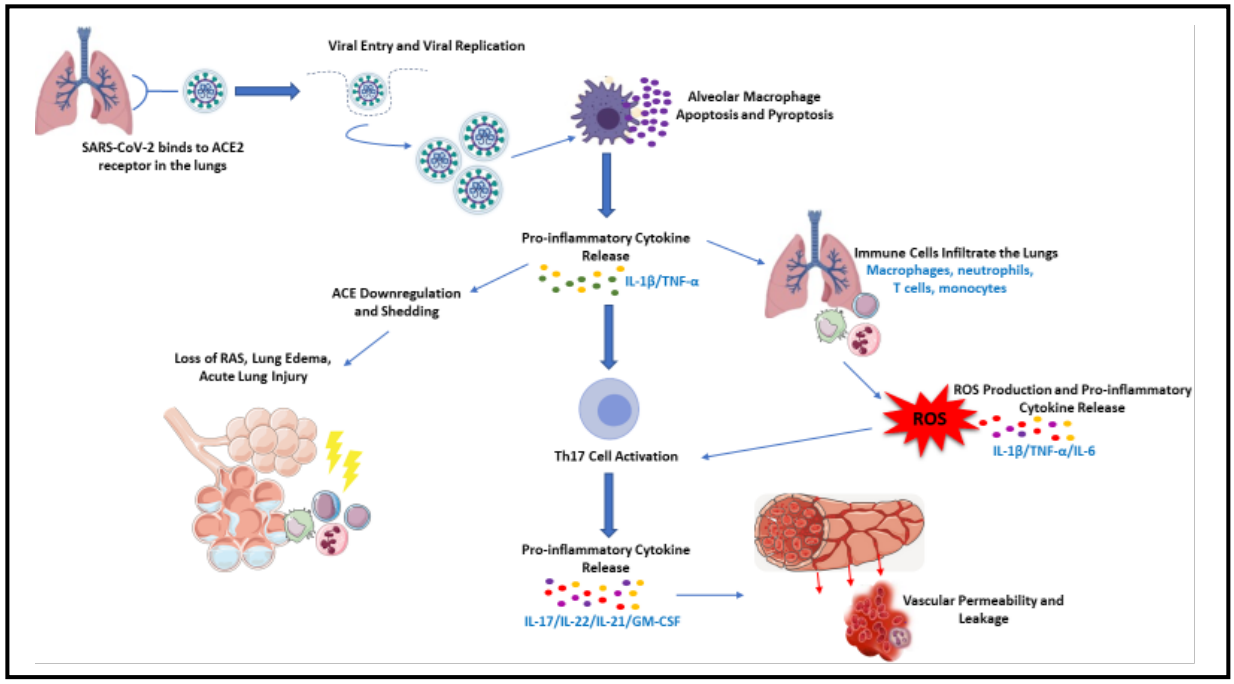
Pathogenesis and Clinical Manifestation of COVID-19 Infection

Multiple clinical symptoms have been reported in people infected with SARS-CoV-2, with most patients experiencing mild to moderate symptoms. Approximately 15% of patients can develop severe manifestations of the disease in the form of pneumonia and approximately 5% of patients may develop acute respiratory distress syndrome (ARDS) or multiple organ failure[30]. ARDS in COVID-19 infection causes diffused alveolar injury and damage to the lungs of infected patients. Patients experience breathing issues due to interstitial widening and oedema in the lungs[31]. Increased vascular permeability induces endothelial cells to become inflamed and therefore the vascular barrier of the lungs is impaired. The action of the virus binding to the ACE2 receptor induces this permeability and encourages infiltration of immune cells such as neutrophils and macrophages which in turn promotes the generation of inflammatory cytokines[32]. The production of these cytokines contributes to the inflammatory environment and drives the invasion of additional inflammatory cells into the site of infection. This severe proinflammatory immune response primarily affects the lungs but can progress to multiorgan dysfunction and cause extensive tissue damage and death[33].

Role of Th17 Cells in COVID-19 Disease

A cytokine storm drives disease severity and ARDS associated with COVID-19 (**Figure 3**). This cytokine storm is associated with increased levels of IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GM-CSF, IFNγ, TNFα, IP10, MCP1, MIP1A and MIP1B[34]. Patients who require ICU treatment are observed to have elevated concentrations of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα in serum in comparison to patients who do not require ICU treatment[34]. Many of these cytokines involved in this cytokine storm are implicated in Th17 cell activation and function. Following activation of Th17 cells, they also further contribute to the cytokine storm and pro-inflammatory environment by producing their effector cytokines IL-17, GM-CSF, IL-21 and IL-22. GM-CSF contributes to inflammation by encouraging granulopoiesis and neutrophil infiltration. IL-17 encourages the production of IL-1β, IL-6 and TNFα which are responsible for systemic inflammation and fever. IL-17 also induces chemokines KC, MIP2A, IL-8, IP10, MIP3A which are involved in enlisting additional immune cells for defence. Matrix metalloproteinases are also

Figure 2. **Viral Replication of COVID-19 in the Host and Immunopathogenesis Promoting Respiratory Infection (Adapted from Asrani and Hassan[29])**



induced by IL-17 signalling and can contribute to tissue remodelling and injury[34]. Moreover, IL-22 is proposed to be involved in the potentially fatal oedema experienced by patients as it has a role in enhancing the production of mucins, fibrinogen, anti-apoptotic proteins, serum amyloid A and LPS binding protein[34,35].

Patients with severe COVID-19 have a vast amount of CCR6+ Th17 cells in their peripheral blood, which substantiates the role of Th17 cells in the cytokine storm[36]. In addition to this, De Biasi et al. showed T cells skew towards a Th17 phenotype in COVID-19 patients[37]. A comparison between COVID-19 ICU patients and healthy controls demonstrated that the ratio of Th17/Treg cells was significantly increased in infected patients and in those who died from COVID-19 infection compared with controls[38]. Several other studies have implicated Th17 cells in exacerbating critical COVID-19 disease, causing a skewed response towards Th17 cells which results in failing to control the virus and ultimately identifies the link between impaired adaptive immune responses and the pathology of severe COVID-19 disease[39–41].

Zhao et al. identified that following viral clearance, clonally expanded tissue-resident memory-like Th17 cells ($T_{RM}17$ cells) were observed in the lungs[42]. These $T_{RM}17$ cells were identified to have a cytokine expression of IL-17A and GM-CSF defining these cells as potentially pathogenic. Interactome analysis indicated that macrophages and CD8+ T cells resident in the lung co-operate with these $T_{RM}17$ cells and correlate with lung injury and disease pathogenesis. In addition to this, high concentrations of IL-17A and GM-CSF were reported in serum of patients with severe COVID-19. Overall, this study indicates $T_{RM}17$ cells are a possible driver of hyperinflammation[42].

The complex role of Th17 cells in COVID-19 disease has also been portrayed through the investigation of clinically recovered COVID-19 patients. Yang et al. has reported that severe COVID-19 disease has a dramatic effect on lymphocytes and immune dysfunction for weeks following clinical recovery[43]. Significant reduction and repression were recorded in the levels and functions of Th1, Th2 and Th17 cells after 11 weeks of clinical recovery, suggesting long-lasting immune dysfunction as a result of severe disease[43].

Immunotyping the features of asymptomatic COVID-19 disease in comparison symptomatic disease has offered interesting insight to the protective versus pathologic contribution of Th17 cells in COVID-19. Li et al. reported that severe patients develop a non-protective immune phenotype associated with aberrant Th17 cells and reduced Tregs which was associated with increasing neutrophils and monocytes into the lungs to mediate damage[44]. However, Li et al. also identified that asymptomatic patients established an enhanced effective and protective immunophenotype which was associated with averting uncontrolled immune responses and was characterised by decreased Th17 and Tregs[44]. The reduced levels of Th17 cells and Tregs suggest their role is balancing immune responses by decreasing the Th17/Treg axis and regulating excessive immune responses which can lead to damage[44]. Chan et al. also reported a protective role of Th17 cells in asymptomatic disease[45]. However, in their study it was reported that asymptomatic patients established higher levels of virus-specific Th17 responses and weaker and sufficient neutralising antibodies. These activities suggest a role for Th17 cells in anti-viral mechanisms and contributing to controlling balancing the immune response in disease and reducing the adverse inflammatory damage experience in severe COVID-19 disease[45].

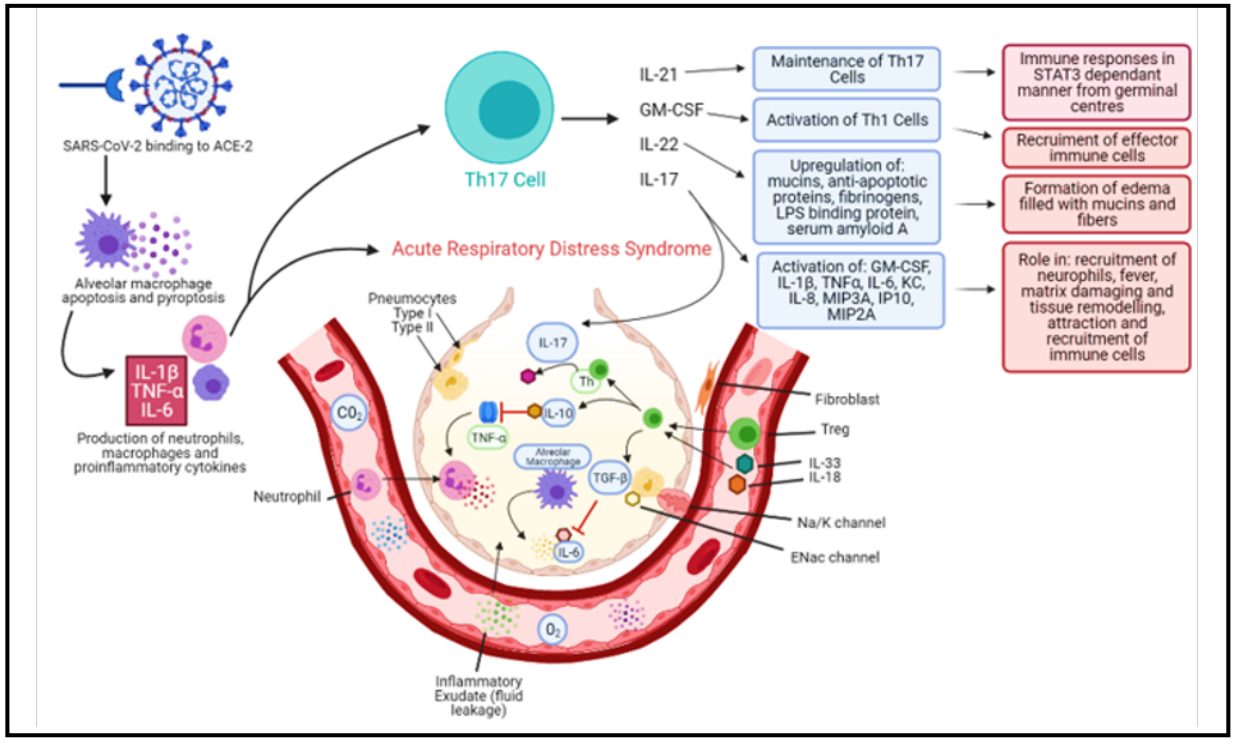
SARS-CoV-2 binds to the ACE-2 receptor in the lungs where the virus is endocytosed and interacts with alveolar macrophages stimulating an innate immune response. IL-1β, TNF-α and IL-6 are produced as a result of apoptosis and pyroptosis of macrophages. The production of these proinflammatory cytokines results in the production and recruitment of neutrophils, macrophages and additional pro-inflammatory cytokines into the site of infection. The production of these proinflammatory cytokines and inflammatory cells promotes the production of Th17 cells, as well as triggering a cytokine storm and contributing to the manifestation of ARDS[29]. Once the integrity of the epithelial cells in the alveolus become impaired, homeostasis is disrupted as epithelial sodium and sodium/potassium channels can no longer function appropriately. This leads to a breakdown in permeability of capillaries and the emittance of fluids. Th17 cells secrete IL-17 to trigger TNF-α which plays a role in damaging epithelial cells and stimulates degranulation via activation of neutrophils. Tregs in the alveolar microenvironment also contribute to ARDS by stimulating TGF-β and this contributes to fibrosis and epithelial injury[46]. The activation of Th17 cells also contributes to the cytokine storm through the production of effector cytokines IL-22, IL-21, GM-CSF and IL-17 which recruit a variety of pro-inflammatory cytokines into the environment which further mediate damage and pathology[29].

Role of Th17 Cells in Risk Factors Associated with Disease Severity in COVID-19 Infection

Age, sex, obesity, hypertension, diabetes, and chronic kidney disease (CKD) are associated with increased disease severity and increased signalling of Th17 cells and their effector cytokine IL-17A which can contribute to disease pathogenesis. Of the patients admitted to hospital with severe COVID-19, 60-80% were male[47]. Differentiation of Th17 cells can occur as a result of oestrogen deficit and decreased Treg cell frequency[48]. Oestrogen can downregulate the production of Th17 cells by obstructing RORγt signalling[49]. In murine studies of Coxsackievirus B3 infection, males display increased levels of Th17 cells compared to females and can be reduced via IL-17A neutralising antibodies[50]. These studies suggest that Th17 cells are repressed in females compared with males, proposing the potential that Th17 cells may be associated with the risk of severe COVID-19 in men[47].

Murine studies display that obesity increases polarisation of T cells towards a Th17 phenotype as a result of elevated IL-6 signalling[51]. Obese women have been reported to have greater concentrations

Figure 3. **The Role of Th17 Cells in Mediating Cytokine Storm and Acute Respiratory Distress Syndrome (Figure adapted from Asrani et al.[29] and Khadke et al.[46])**



of circulating IL-17A in comparison to lean women[52]. COVID-19 patients with BMI 27.0±2.5 present with worsened disease outcomes in comparison to patients with BMI 22.0±1.3[53]. An additional study investigating the relationship between BMI and COVID-19 displayed that 15.18% of patients who participated in this study were non-survivors and 88.2% of these patients had a BMI greater than 25[54]. These studies suggest that obesity can drive disease severity in COVID-19 which is associated with elevated levels of Th17 cells and IL-17 signalling. Dysfunctional and enhanced Th17 activities have been identified in patients with both type-I and type-II diabetes[55] suggesting that increased Th17 cells contribute to the complications of diabetes and may be a risk factor for severity in COVID-19. Similarly, CKD is a risk factor associated with COVID-19 severity and this condition is linked to dysfunctional Th17 cell activity[56,57]. Furthermore, murine models of hypertension have displayed that Th17 cells and IL-17A is increased during angiotensin II signalling. Studies on hypertensive diabetic patients, showed that there are high levels of IL-17A in their serum in comparison to healthy controls[58] and diabetic patients who are not hypertensive[59].

Finally, ageing is associated with dysregulated Th17 cell signalling. Peripheral blood mononuclear cells (PBMCs) of healthy older people contain increased Th17 cells and the effector cytokine IL-17A in comparison to control groups which are middle-aged and young[60] and the ratio of Th17/Tregs is also observed to polarise towards a Th17 phenotype in older individuals[61]. This predisposition of older individuals to have increased activity of Th17 cells may contribute towards an elevated risk of COVID-19 severity.

Conclusion

Many studies have outlined the protective role of Th17 cells against a diverse range of pathogens in the lungs by promoting infiltration of neutrophils and monocytes into the lungs. In addition to this, IL-17A regulates inflammatory responses in the tissues and host protection by triggering the induction of pro-inflammatory cytokines, chemokines, and antimicrobial peptides from various cells of the airways. These mechanisms are crucial for supporting successful protection against invading pathogens[62].

However, Th17 cells also mediate tissue pathology in various diseases and therefore responses of Th17 cells in the lung can be both protective and pathogenic. A critical balance is required to suppress the pathogenic mechanisms of Th17 cells and their effector cytokines in settings of inappropriate inflammation, but at the same time preserving their role in mediating early pathogen defence in the lungs is essential[2]. A more extensive understanding of the role of Th17 cells in lung inflammation may offer insight into therapeutic targets, which could block the pathological features of the Th17 response while maintaining the integrity of lung tissue and host defence.

There remains a key gap in the understanding of what decides the outcome between an appropriate immune response and immunopathology[63]. Th17 cells are dysregulated in patients with severe COVID-19 and are

significant contributors to the systemic cytokine storm experienced by critical patients, mediating damage in the lungs, contributing to ARDS and, causing pulmonary fibrosis disrupting normal alveolar architecture and normal oxygenation process, and ultimately leading to systemic organ damage and death[64]. Th17 cells have also been reported to contribute to immune dysfunction in other conditions associated with increased risk of disease severity in COVID-19[47]. Therefore, these mechanisms of Th17 immunopathology undoubtedly are worthy of future research. Defining the role of Th17 cells in the lungs will offer important information which can be applicable to a diverse range of respiratory diseases and inform future vaccine design and candidate therapeutics.◀

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Declarations

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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