



# A comprehensive network map of IL-17A signaling pathway

D. A. B. Rex<sup>1</sup> · Shobha Dagamajalu<sup>2</sup> · Mahesh Manjunath Gouda<sup>3</sup> · G. P. Suchitha<sup>2</sup> · Jaikanth Chandrasekaran<sup>4</sup> · Rajesh Raju<sup>1,2</sup> · T. S. Keshava Prasad<sup>2</sup> · Yashodhar Prabhakar Bhandary<sup>5</sup>

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## Abstract

Interleukin-17A (IL-17A) is one of the member of IL-17 family consisting of other five members (IL-17B to IL-17F). The Gamma delta ( $\gamma\delta$ ) T cells and T helper 17 (Th17) cells are the major producers of IL-17A. Aberrant signaling by IL-17A has been implicated in the pathogenesis of several autoimmune diseases including idiopathic pulmonary fibrosis, acute lung injury, chronic airway diseases, and cancer. Activation of the IL-17A/IL-17 receptor A (IL-17RA) system regulates phosphoinositide 3-kinase/AKT serine/threonine kinase/mammalian target of rapamycin (PI3K/AKT/mTOR), mitogen-activated protein kinases (MAPKs) and activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) mediated signaling pathways. The IL-17RA activation orchestrates multiple downstream signaling cascades resulting in the release of pro-inflammatory cytokines such as interleukins (IL)-1 $\beta$ , IL-6, and IL-8, chemokines (C-X-C motif) and promotes neutrophil-mediated immune response. Considering the biomedical importance of IL-17A, we developed a pathway resource of signaling events mediated by IL-17A/IL-17RA in this study. The curation of literature data pertaining to the IL-17A system was performed manually by the NetPath criteria. Using data mined from the published literature, we describe an integrated pathway reaction map of IL-17A/IL-17RA consisting of 114 proteins and 68 reactions. That includes detailed information on IL-17A/IL-17RA mediated signaling events of 9 activation/inhibition events, 17 catalysis events, 3 molecular association events, 68 gene regulation events, 109 protein expression events, and 6 protein translocation events. The IL-17A signaling pathway map data is made freely accessible through the WikiPathways Database (<https://www.wikipathways.org/index.php/Pathway:WP5242>).

**Keywords** Inflammation · Bleomycin · Protein–protein interactions · Fibrosis · Lung injury · Signaling pathways · Cytokines

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D. A. B. Rex and Shobha Dagamajalu have equally contributed to this work.

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✉ D. A. B. Rex  
rexpem@yenepoya.edu.in

✉ Shobha Dagamajalu  
shobha\_d@yenepoya.edu.in

✉ Yashodhar Prabhakar Bhandary  
yashbhandary@yenepoya.edu.in

Mahesh Manjunath Gouda  
maheshmg2012@gmail.com

G. P. Suchitha  
suchithajrf@yenepoya.edu.in

Jaikanth Chandrasekaran  
jaikanthjai@gmail.com

Rajesh Raju  
rajeshraju@yenepoya.edu.in

T. S. Keshava Prasad  
keshav@yenepoya.edu.in

- <sup>1</sup> Centre for Integrative Omics Data Science, Yenepoya (Deemed to be University), Mangalore, Karnataka 575018, India
- <sup>2</sup> Center for Systems Biology and Molecular Medicine, Yenepoya Research Centre, Yenepoya (Deemed to be University), Mangalore, Karnataka 575018, India
- <sup>3</sup> Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Hamburg (UKE), Martinistrasse 52, 20251 Hamburg, Germany
- <sup>4</sup> Department of Pharmacology, School of Pharmacy and Technology Management, SVKM'S NMIMS University, Hyderabad, Telangana, India
- <sup>5</sup> Yenepoya Research Centre, Yenepoya (Deemed to be University), Mangalore, Karnataka 575018, India

## Introduction

Interleukin-17A (IL-17A) is a member of a IL-17 family consisting of the other five members (IL-17B through IL-17F). IL-17A was first discovered in 1993 by Rouvier et al. (Rouvier et al. 1993). IL-17A shares similar homologs with IL-17F and operates through the same receptor called IL-17 receptor (IL-17R) composed of IL-17 receptor A and C (IL-17RA and IL-17RC) (Chen and Kolls 2017). The *IL17A* gene is located adjacent to *IL17F* on chromosome 6 in humans and on chromosome 1 in mice and is usually produced by Th17 cells (Akimzh-anov et al. 2007; Iwakura et al. 2011). The IL-17A and IL-17F exist as homodimers and can be produced as IL-17A/F heterodimers (McGeachy et al. 2019). Being the most widely studied member of the IL-17 family of pro-inflammatory cytokines, IL-17A exhibits a central role in host defense mechanisms and tissue inflammation (Chen and Kolls 2017). IL-17A studies in the past decade provide evidence that extensively studied IL-17A producing CD4<sup>+</sup> Th17 cells, are the major source of tissue inflammation and play a significant role in autoimmune diseases (Korn et al. 2009).

The discovery of the IL-17A receptor was demonstrated by isolating and cloning mouse E14 thymoma cells (Yao et al. 1995). IL-17RA is demonstrated as a predominant receptor associated with the IL-17 receptor family (Gaffen 2009; Bie et al. 2017; McGeachy et al. 2019). IL-17RA is universally expressed on a wide range of tissues and cell types. The IL-17A stimulation activates IL-17RA and initiates the activation of downstream signaling pathways to induce the production of pro-inflammatory molecules. However, IL-17RA alone is not sufficient to mediate IL-17A signaling. It was revealed that IL-17A signals through a heterodimeric receptor complex composed of IL-17RA and IL-17RC (Toy et al. 2006; Rickel et al. 2008; Song et al. 2011).

The IL-17A plays a crucial role in the host defense mechanism and it is known to control the gut microbiota and removal of extracellular fungi and bacteria such as *Mycoplasma pneumonia*, *Candida albicans*, *Klebsiella pneumoniae*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum* (Chen and Kolls 2013). While in the case of viral infections, IL-17A promotes the defense mechanism through neutrophilic inflammation (Crowe et al. 2009). The protective role of IL-17A varies depending on the type of pathogen or disease condition, and it could be a double-edged sword that could increase the risk of inflammatory diseases such as psoriasis, and chronic obstructive pulmonary disease (COPD), and various autoimmune diseases (Chen and Kolls 2017; Gouda et al. 2018c, 2018d). The lung is one of the most susceptible organ and it is prone to

be affected by regular immune reactions as it encounters various pathogens and promotes various immune cells, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), chemokines, cytokines, and interleukins including IL-17A (Gouda and Bhandary 2018; Gouda et al. 2018a). Recent studies show that the role of IL-17A is not only limited to promoting inflammation, but also plays a key mediator for various downstream pathways such as Akt, MAPKs, transforming growth factor beta (TGF- $\beta$ ), p53-fibrinolytic system, suppressor of mothers against decapentaplegic (Smad), and signal transducer and activator of transcription 3 (Stat3) signaling pathways (Gouda et al. 2018b, 2020). Besides, dysregulated IL-17A downstream signaling mechanism could result in severe tissue damage, followed by cell death and subsequent development of tissue fibrosis (Gouda et al. 2020). IL-17A role in tumorigenesis is expressed by myeloid-derived suppressor cells (MDSCs) recruitment to regulate anti-tumour immunity, and IL-17A also could enhance tumour growth by promoting IL-6 resulting in the activation of transcription factor STAT3 and overexpressed pro-angiogenic genes in tumour (Wang et al. 2009; He et al. 2010; Chang et al. 2014).

In recent years, IL-17A research has led to the discovery of its potential as a therapeutic target for various forms of inflammation and autoimmune disorders (Kuwabara et al. 2017; McGeachy et al. 2019). In the current study, we developed a resource of signaling events mediated by IL-17A/IL-17RA signaling by excerpting all research articles from the literature and compiling them in similar lines to earlier reports on comprehensive signaling maps including IL-33, IL-18 and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), C-C motif chemokine ligand 18 (CCL18) (Pinto et al. 2018; Rex et al. 2020, 2021; Aravind et al. 2022).

## Methodology

To develop a consolidated IL-17A signaling pathway map, we performed an extensive literature search for research articles pertaining to IL-17A mediated signaling. The research articles were fetched using the following search terms (“IL17A” OR “CTLA8” OR “IL-17A” OR “CTLA-8” OR “interleukin 17A” OR “IL17A” OR “Interleukin 17A” OR “IL17RA”) AND (“pathway” OR “signaling” OR “signalling”). The research articles were manually screened to select articles specifically relevant to IL-17A signaling. Manual curation was carried out for the signaling reactions that IL-17A has induced based on the previously published NetPath annotation criteria (Kandasamy et al. 2010). The IL-17A mediated signaling reactions were grouped into five categories, i.e., enzyme catalysis/post-translational modifications (PTMs), activation/inhibition events, protein/gene

regulation, molecular associations and protein translocation between cell organelles. The information, including the type of experiment performed, cell lines/tissue used, and information about the post-translational modification sites and residues were also included. PathVisio tool was used to depict and visualize the signaling pathway map using curated signaling events (Kutmon et al. 2015).

## Results and discussion

### Integration of data for IL-17A/IL-17RA signaling pathway development

The PubMed search using query terms showed 660 articles pertaining to the IL-17A signaling pathway. These articles were manually screened based on NetPath annotation criteria. Out of which, 22 articles had information involving IL-17A mediated signaling. The annotation of these selected articles provided a total of 212 molecules involved in IL-17A mediated signaling events, including 3 molecular associations, 17 enzyme catalysis, 9 activation/inhibition, 6 translocation events, 68 gene regulation events, and 109 protein expression events (Supplementary Data S1). These events were used to develop a single comprehensive map of IL-17A mediated signaling pathway (Fig. 1). The comprehensive pathway map of IL-17A signaling is made freely accessible through the WikiPathways with the ID WP5242.

### Fibrosis

In alveolar basal epithelial cells, treatment with curcumin reversed inflammation caused by IL-17A and bleomycin (BLM) induction of Akt1 (S473) phosphorylation (Gouda et al. 2018b). The BLM treatment in the mice model stimulates the secretion of IL-17A by  $\gamma\delta$ T cells at the early phase of the fibrotic process, which triggers the increased expression of B cell-activating factor belonging to the TNF family (Baff) by inflammatory neutrophils in the bronchoalveolar space and contributes to the pathogenesis of lung fibrosis (Francois et al. 2015). The BLM is a potent chemotherapeutic agent that causes damage to alveolar basal epithelial cells, triggering an inflammatory response and lung damage (Hay et al. 1991; Ge et al. 2018). Several studies have demonstrated that BLM increases the expression of the proinflammatory cytokine IL-17A in fibroblasts and epithelial cells. IL-17A serves as a critical molecule during the progression of fibrosis and lung injury (Wilson et al. 2010; Azevedo et al. 2020; Nie et al. 2022).

The BLM stimulates the expression of IL-17A, induces the phosphorylation of tumor suppressor protein (Tp53), Mapk1/3, and upregulation of mechanistic target of rapamycin (*Mtor*), plasminogen activator, urokinase (*Plau*),

PLAU receptor (*Plaur*), serpin family E member 1 (*Serpin1*), smooth muscle aortic alpha-actin 2 (*Acta2*), cleaved cysteine-aspartic acid protease 3 (cleaved *Casp3*), marker of proliferation Ki-67 (*MKI67*), and proteins including annexin A6 (*Anxa6*), proteasome 26S Subunit, ATPase 6 (*Psmc6*), alcohol dehydrogenase (*Adh1*), copine 1 (*Cpne1*), hemoglobin subunit beta-H1 (*Hbb-bh1*), UDP-Glucose glycoprotein glucosyltransferase 1 (*Uggt1*), growth associated protein 43 (*Gap43*), superoxide dismutase 2 (*Sod2*), heat shock protein family 1B (*Hspa1b*), protein phosphatase 1 regulatory inhibitor subunit 14B (*Ppp1r14b*), bleomycin hydrolase (*Blmh*), antioxidant 1 copper chaperone (*Atox1*), hemoglobin subunit-beta-2 (*Hbb-b2*), Ras-related protein Rab-10 (*Rab10*) and downregulation of Hbb-b1, transcription factor p65 (*Rela*), neutrophilic granule protein (*Ngp*), paraoxonase 3 (*Pon3*), high mobility group box protein 1 (*Hmgb1*), and hypoxia up-Regulated 1 (*Hyou1*), which are involved in response to a stimulus; increased expression of inflammation-related proteins such as *Acta2*, Ras-related protein R-Ras2 (*Rras2*), actin related protein 2/3 complex subunit 2 (*Arpc2*), G Protein subunit gamma 12 (*Gng12*), Ras homolog family member A (*RhoA*), phospholipase C eta 1 (*Plch1*), signal transducer and activator of transcription 1 (*Stat1*), Rac family small GTPase 1 (*Rac1*), *Arpc3*, P21 (*RAC1*) activated kinase 3 (*Pak3*), myosin light chain kinase (*Mylk*), cell division control protein 42 homolog (*Cdc42*), *Arpc5*, protein kinase CAMP-activated catalytic subunit beta (*Prkacb*) and downregulation of *Rela* and complement component C7 (*C7*) (Gouda et al. 2020).

In normal human primary small airway epithelial cells, IL-17A induces the upregulation of C components (*CFB*, *C3*, *GRK5*, *CXCL1*, and *CXCL2*), chemokine ligands (*CXCL3*, *CXCL5*, *CXCL6*, and *CXCL16*) and interleukins (*IL1 $\beta$* , *IL6*, and *IL8*) at the transcription and translation level which are implicated in the pathogenesis of idiopathic pulmonary fibrosis (Cipolla et al. 2017). In human fibrotic interstitial lung disease, IL-17A stimulates IL-17RA and induces the activation of Janus kinase 2 (*JAK2*), protein upregulation of ACTA2, collagen, type I, alpha 1 (*COL1A1*), fibronectin 1 (*FN1*), phosphorylation of STAT3 (Tyr705), *RELA* (Ser536), and nuclear translocation of *RELA* via NF- $\kappa$ B-mediated signaling which are mainly involved in fibroblast proliferation, extracellular matrix (ECM) generation, and promotes myofibroblast phenotype differentiation (Zhang et al. 2019). In BLM-induced mice, IL-17A stimulates the inhibition of AMP-activated protein kinase alpha (*AMPK $\alpha$* ), and increased expression of *Ptgs2* upon activation of NF- $\kappa$ B and other inflammatory molecules *Rela*, *Nfkb1*, *Nfkb2*, fibrillin 1 (*Fbn1*), platelet-derived growth factor subunit A (*Pdgfa*), *Pdgfb*, Insulin-like growth factor I (*Igf1*), CCN family member 2 (*Ccn1*), matrix metalloproteinase 3 (*Mmp3*), *Mmp9* and *Mmp14* which promotes lung fibrosis (Shaikh and Prabhakar Bhandary 2020). IL-17A stimulation

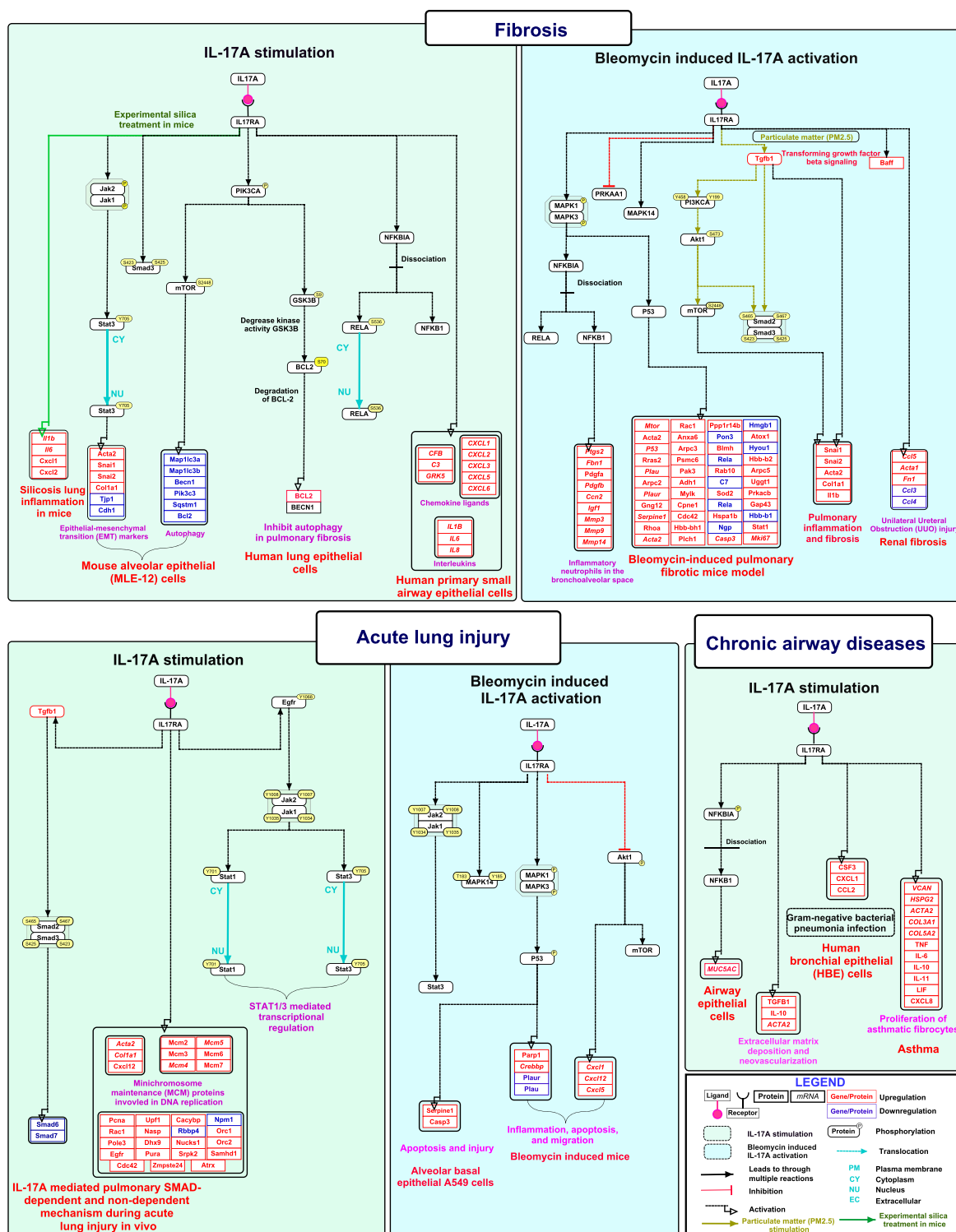


Fig. 1 Schematic representation of IL-17A signaling pathway

by particulate matter (PM2.5), activates the transforming growth factor-beta 1 (Tgf-β1) signaling pathway and induces upregulation of *Tnf*, *Il1b*, *Acta2*, and increased *Col1* deposition in lung tissue, through phosphorylation of Smad

pathway [Smad2 (Ser465/467)/ Smad3 (Ser423/425)] and PI3K pathway [PI3K (Tyr458/Tyr199)/Akt1 (Ser473)/ Mtor (Ser2448)] signaling are crucial to induce airway injury in primary bronchial epithelial cells (Cong et al. 2020).

The silica treatment in C57BL/6 mice stimulates the increased expression of IL-17A in  $\gamma\delta$ T cells and CD4<sup>+</sup> T cells, which is responsible for the upregulation of proinflammatory cytokines such as *Il1b*, *Il6* and chemokines such as *Cxcl1*, *Cxcl2* in experimental silicosis lung inflammation (Lo Re et al. 2010). IL-17A stimulates IL-17RA and induces the protein upregulation of epithelial-mesenchymal transition (EMT) markers including Snail family transcriptional repressor *Snai1*, *Snai2*, *Acta2*, and *Col1a1*, protein downregulation of E-cadherin 1 (*Cdh1*), and tight junction protein 1 (*Tjp1*) via *Tgfb1*, which promotes EMT and pulmonary fibrosis, by phosphorylation of *Rela* at S536, *Smad3* at S423/S425, *Stat3* at Y705, *Mtor* at S2448; protein downregulation of microtubule associated protein 1 light chain (*Map1lc*) 3 alpha 3a, *Map1lc3b*, *beclin 1* (*Becn1*), *Pik3c3*, *sequestosome 1* (*Sqstm1*), *B-cell lymphoma 2* (*Bcl2*), which inhibit the autophagy in the cultured mouse alveolar epithelial (MLE-12) cells (Mi et al. 2011). In cultured lung epithelial cells, IL-17A stimulation induces the phosphorylation of glycogen synthase kinase-3 beta (*GSK3B*) at Ser9 by the activation of *PIK3CA*, which in turn it decreases the kinase activity of *GSK3B*. The suppressed *GSK3B* reduces the phosphorylation and degradation of *BCL2*. Thus, increased expression of *BCL2* promotes the association of *BCL2* and *BECN1* to inhibit autophagy in pulmonary fibrosis (Liu et al. 2013). IL-17A expression promotes renal fibrosis via RANTES-mediated upregulation of *Acta*, *Fnl* and downregulation of *Ccl* and *Ccl4* in  $\gamma\delta$  T lymphocytes and Th17 cells isolated from the left kidney unilateral ureteral obstruction (UUO) operated mice model (Peng et al. 2015).

### Acute lung injury

The IL-17A plays a major role in the pathogenesis of lung disease (Linden et al. 2005). The study in BALB/c mice injected with recombinant mouse IL-17A (rmIL-17A) reported the increased mRNA expression of *Acta2*, *Colla11*, and *Cxcl12*, which resulted in activation of lung fibroblasts and translated into myofibroblast. The increased collagen secretion helps the ECM deposition and leads to the development of lung fibrosis (Wang et al. 2020). An investigation by Shaikh et al. demonstrated that the development of acute lung injury by IL-17A mediated Smad and non-Smad signaling mechanisms in a mice model in which IL-17A stimulates its receptor and induces the phosphorylation of the epidermal growth factor receptor (*Egfr*) at Y1068 which in turn activates Jak-Stat complex proteins [*Stat1* (Y701) and *Stat3* (Y705)]. The Stat complex translocates from the cytoplasm to the nucleus, where it binds to DNA and initiates the transcription of genes involved in alveolar injury. Also, IL-17A induces *Tgfb1* expression and activates the Smad 2/3 pathway; furthermore, it inhibits the expression levels of *Smad6* and *Smad7* in the acute lung injury mice

model (Shaikh et al. 2020). Additionally, IL-17A regulates the expression of mini chromosome maintenance (MCM) proteins including *Mcm2*, *Mcm3*, *Mcm4*, *Mcm5*, *Mcm6*, and *Mcm7* as well as origin recognition complex subunit (*Orc*)1 and *Orc2* proteins, which are important for DNA replication, contributing to the development of acute lung injury (Shaikh et al. 2021).

The study in BLM-exposed C57BL/6 mice results in the induction of IL-17A expression and activation of *Crebbp*, *Stat3*, *Mtor*, *Mapk14*, *c-Jun* n-terminal kinases (*Jnks*) and inhibition of *Akt* pathways, which results in activation of chemokines including *Cxcl1*, *Cxcl5*, and *Cxcl12*. In addition, IL-17A stimulates the expression of *Tp53*, which in turn induces the upregulation of the p53-fibrinolytic systems such as *Serpine1*, *Casp3* and poly [ADP-ribose] polymerase 1 (*Parp1*) and inhibits the expression of *Plau* and *Plaur* in alveolar epithelial cell apoptosis and injury (Gouda and Bhandary 2018). Furthermore, a study by Gouda et al. reported that BLM and IL-17A induce the upregulation of *TP53*, *SERPINE1*, and cleaved *CASP3*, which are involved in inflammation, apoptosis and migration of alveolar basal epithelial cells in acute lung injury (Gouda et al. 2018a).

### Chronic airway diseases

The IL-17A is one of the cytokines produced in asthmatic airways by Th17 lymphocytes and mainly contributes to the recruitment of neutrophils (Wiehler and Proud 2007; Alcorn et al. 2010; Shin et al. 2010). A study by McAllister et al. reported that IL-17A signaling is involved in the recruitment of neutrophils against gram-negative bacteria via the upregulated expression of *CSF3*, *CXCL1*, and *CCL2* in cystic fibrotic lungs. This study highlighted that IL-17A and IL-17F are the two therapeutic targets to inhibit neutrophil-mediated airway inflammation (McAllister et al. 2005). The importance of NF- $\kappa$ B activation is well documented in chronic airway diseases, including asthma, COPD, and gram-negative bacterial pneumonia infection (Hart et al. 1998; Di Stefano et al. 2002). The IL-17A stimulates IL-17RA and induces the upregulation of *MUC5AC* via activation of the NF- $\kappa$ B pathway, which induces chronic airway inflammation in airway epithelial cells (Fujisawa et al. 2009). The study by Bellini et al. reported that IL-17A stimulation in circulating fibrocytes from asthmatic patients induces the upregulation of *COL3A1*, *COL5A2*, *VCAN*, *HSPG2*, *ACTA2* gene expression, and IL-6, IL-11, leukemia inhibitory factor (*LIF*), *CXCL1*, *CXCL8*, *TNF* protein expressions, which are involved in the proliferation of asthmatic fibrocytes (Bellini et al. 2012). The treatment of IL-17A in fibrocytes induces the upregulation of *ACTA2* and downregulation of IL-10 and *TGF $\beta$ 1*, which may lead to the ECM deposition and neovascularization seen in airway remodeling (Hayashi et al. 2013).

## Conclusions

It is pertinent to note that IL-17A plays a role in the induction of inflammation and orchestrating protective responses against cutaneous bacterial and fungal infections that limit numerous pathogenic insults. Researchers will benefit from the publicly available IL-17A mediated signaling map by understanding the roles played by different molecules in regulating this pathway in both physiological and pathological conditions. The information in this resource will help translate the information available for discovering other molecules within this network and developing novel pharmacological strategies for treating diseases associated with the IL-17A molecule.

Schematic representation of IL-17A induced signaling reactions. The signaling pathway map represents molecules involved in ligand-receptor interactions and IL-17A induced downstream molecular events including molecular association, catalysis, translocation, and gene regulation events. Information regarding the post-translational modification site and the residue is also shown in the pathway.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s12079-022-00686-y>.

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