Human Innate Lymphoid Cells in Influenza Infection and Vaccination

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ABSTRACT: Influenza is a highly contagious respiratory virus that causes mild to severe respiratory illness, as well as death, and remains a serious threat to human health. Annual vaccination is the most cost-effective way to control influenza; however, the vaccine does not provide protection against emerging strains with epidemic and pandemic potential. Several antivirals have been developed to treat influenza but there is a rapid emergence of antiviral resistant strains. Therefore, there is an urgent need to understand the virus and its interactions with the host immune system so that novel strategies can be developed for prophylactic and therapeutic interventions. Innate lymphoid cells (ILCs), a family of immune cells present in the peripheral circulation and in mucosal tissues, play an important role in regulation of tissue homeostasis, inflammation, and immunity. This review examines the current understanding and therapeutic potential of ILCs during influenza virus infection in humans.

KEY WORDS: innate lymphoid cells, influenza virus, innate immunity, influenza vaccine

I. INTRODUCTION

The respiratory epithelium is constantly exposed to external airborne microbial pathogens, pollutants, and allergens. For the most part, the immune system monitors and protects the lungs from all challenges via a coordinated response by the innate and the adaptive immune pathways. Specialized types of cells of the innate immune system that have recently gained prominence in playing an important role during pathogen encounter are the innate lymphoid cells (ILCs). ILCs are characterized by the lack of phenotypic markers of lymphocytes, granulocytes, monocytes, and dendritic cells (DC) and do not express either a T- or B-cell receptor (TCR or BCR).[1] In response to a challenge, ILCs secrete cytotoxic molecules and/or cytokines to directly kill infected cells or regulate functions of other innate and adaptive cells, thereby facilitating protective immunity, tissue repair, and homeostasis. There are several recent reviews on ILC biology and functions including the role of these cells in homeostasis and in diseases such as inflammatory bowel disease, asthma, cancer, chronic obstructive pulmonary disease (COPD), and viral and bacterial infections.[2–5] Here, we focus primarily on the current knowledge about ILCs responses in influenza infection and vaccination.

II. INNATE AND ADAPTIVE IMMUNE RESPONSES TO INFLUENZA VIRUS

Influenza is a recurrent infectious respiratory disease that poses a significant threat to global public health and economy each year.[6] Worldwide, influenza epidemics are responsible for 290,000–650,000 deaths and approximately 5 million cases of severe infections every year.[7] In the United States, the CDC estimates that during the 2019–2020 season alone influenza resulted in 22,000 deaths, 400,000

hospitalizations, and 38 million illnesses.[8] Apart from the high morbidity and mortality, influenza infections inflict substantial economic damage due to the high cost of medical care and loss in productivity, which in the US alone is estimated to be USD 6.3–25.3 billion annually.[9] In addition to annual seasonal epidemics, unpredictable global influenza pandemic outbreaks also occur every 10–50 years that often result in more serious illness and fatalities with higher economic impact.[10] Novel influenza strains with epidemic and pandemic potential emerge due to the high mutation rate in the viral genome (antigenic drift) and reassortment of the genome (antigenic shifts) within the virus populations.[11,12] The virus causes a wide range of complications in humans depending upon the severity of the disease.[13] The uncomplicated influenza illness affects the upper respiratory tract while the more severe and lethal cases of influenza results in pneumonia in the lower respiratory tract. In addition, several non-respiratory complications affecting the central nervous system, musculoskeletal, and cardiac systems have been reported.[14–16] The severity of infection is attributed to the immune responses of the host where lack of preexisting immunity against an antigenically different strain and several factors such as age, pregnancy, and comorbidities, are known to augment the risk of lethal influenza infection.[17]

The influenza virus of the Orthomyxoviridae family is an enveloped virus containing a segmented single strand RNA genome.[13] There are four genera of this virus, A, B, C, and D, of which A, B, and C can infect humans.[18–20] Influenza virus A and B contain eight RNA segments that encode 12 or 11 different proteins, respectively, while C and D contain seven RNA segments that encode for eight different proteins.[21,22] The viral genome is encapsulated by a lipid membrane envelope that contains two surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA), which are the most antigenically variable proteins of the virus.[23–25] Based on the antigenic properties of HA and NA, influenza A viruses (IAVs) are further classified into 18 HA and 11 NA subtypes.[26] The HA protein facilitates viral entry by binding to cell surface sialic acid, and the NA protein causes the cleavage of new virions from the sialic acid and prevents the clumping and retention of these virions in infected cells.[25,27,28] Following virus attachment to the host cell and uptake via induced endocytosis, the viral matrix protein 2, a proton channel protein, facilitates the release of the viral ribonucleoproteins (RNPs) into the cytosol. The free viral RNA is imported into the nucleus where further replication and synthesis of the genome occurs. Several other viral proteins, including the matrix protein 1 (M1), RNA polymerase subunits composed of the polymerase basic 1 (PB1), polymerase basic 2 (PB2) and polymerase acidic (PA) proteins, viral nucleoprotein (NP), nuclear export protein (NEP), PB1-F2 and nonstructural protein (NS1) help the virus to complete its life cycle in the host cells.[29] In response to viral replication the host initiates induction of a pro-inflammatory response that is responsible for recruitment of the innate and adaptive immune cells that aid in clearing the virus.[30,31]

As the first line of defense, the innate immune system plays an important role in containing the virus infection and subsequently facilitating activation of the adaptive immune responses. Components of the viral RNA and proteins, referred to as pathogen associated molecular patterns (PAMPs), or cellular components of damaged cells, referred to as damage-associated molecular patterns (DAMPs), are recognized by a variety of cellular pathogen recognition receptors (PRRs) (Fig. 1A and 1B).[32,33] The PRRs activate the intracellular signaling pathways leading to the release of interferons (IFNs) and cytokines, resulting in the recruitment of ILCs (including natural killer [NK] cells), monocytes, dendritic cells (DCs), macrophages, and neutrophils that play important roles in early viral clearance.[34,35] In the case of the influenza virus infections, three families of PRRs are responsible for sensing the virus. These are the retinoic acid–inducible gene-I (RIG-I)-like receptors (RLRs)[36]; endosomal PRRs consisting of the toll like receptors (TLRs) 3, 7, and 8[37–39]; and nucleotide binding domain and leucine rich repeat containing proteins (NOD-like receptors or NLRs) family member NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3, also called PYRIN-containing APAF1-like protein 1).[40,41] The TLRs are type 1 membrane spanning receptors with a leucine rich extracellular domain for ligand binding and cytoplasmic tail that generally signal

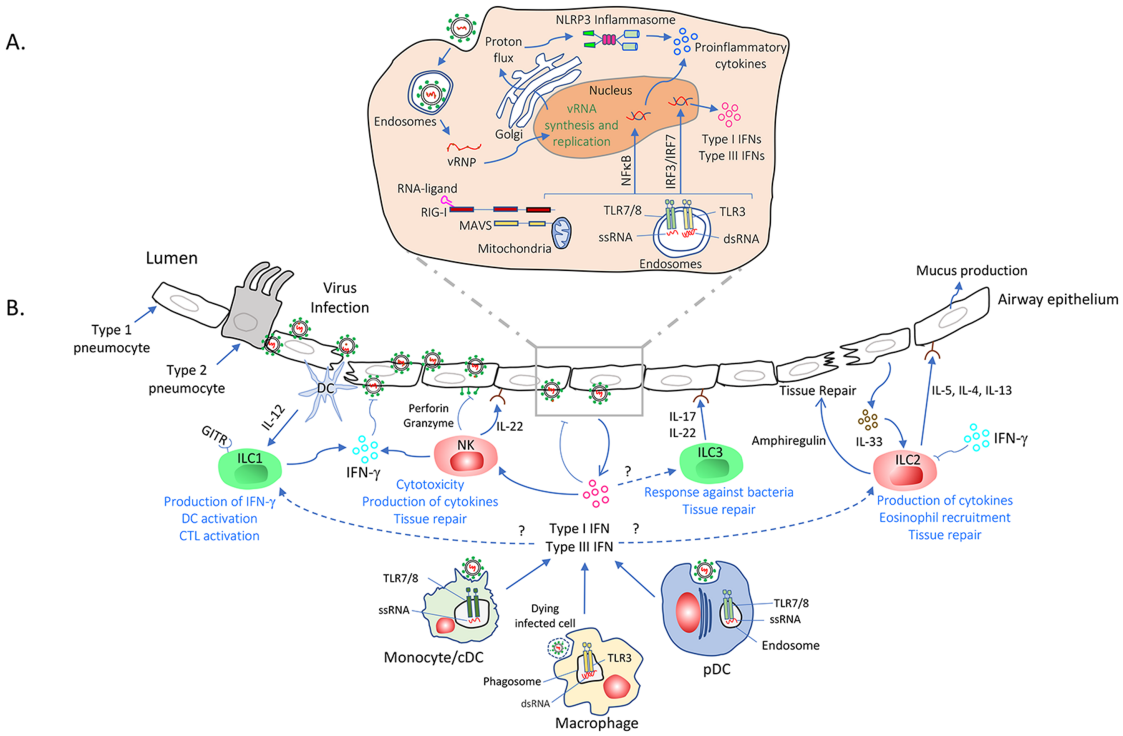

FIG. 1: The innate immune pathways (A) and the distribution of the ILCs at the mucosa of lungs (B) in response to influenza virus infection. (A) Infection of lung epithelial cells with influenza virus leads to the recognition of incoming viral genome and proteins by multiple host pathogen recognition receptors (PRRs). Ligand–PRR interaction leads to the secretion of type I and III IFNs, cytokines, and chemokines. The adaptive immune responses comprising humoral and cellular responses at both systemic and mucosal levels constitute the second line of defense against influenza viruses. The secreted cytokines and chemokines play a regulatory role in the cellular immune responses to IAVs. (B) The ILC subsets that play a role during influenza infection in lungs are illustrated and for simplicity the functions of the different subsets are emphasized. IAV infection of the lung epithelial cells results in the release various cytokines that can amplify the activation of ILC subsets. Red colored ILCs denote data derived from human studies and subsets found in human lungs or in peripheral circulation. Green denotes studies from murine models of influenza virus infection that further our understanding of these cell types in the lungs during influenza infection. Broken line indicates direct link is not established yet in either human or mice models of influenza virus infections. cDC, conventional dendritic cell; CTL, cytotoxic T-lymphocytes; dsRNA, double stranded RNA; IFN, interferon; IRF, interferon regulatory factor; MAVS, mitochondrial antiviral-signaling protein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, nucleotide-binding domain and leucine-rich-repeat-containing protein; pDC, plasmacytoid dendritic cell, RIG-I, retinoic acid-inducible gene-I; ssRNA, single stranded RNA; TLR, Toll-like receptor; vRNA, viral RNA; vRNP, viral ribonucleoprotein.

via the myeloid differentiation primary response protein 88 (MyD88) except TLR3. TLR3, normally located in endosomes and expressed by conventional DCs (cDCs) and macrophages, recognizes double-stranded RNA in infected cells. Activated TLR3 can signal either via the toll/IL-1R receptor (TIR) domain containing-adapter protein (TRIF; also known as toll like receptor adaptor molecule 1 [TICAM]) or the proto-oncoprotein, c-Src, resulting in secretion of interleukin (IL)-8, IL-6 and regulated on activation, normal T expressed and secreted (RANTES).[42,43] TLR3 has a protective role in preventing influenza virus infection, as the L412F mutation in humans increases the incidence of influenza-associated pneumonia (odds ratio = 4.5)[44] and children with TLR3 defects have an increased risk

of experiencing life-threatening pneumonia upon influenza virus infection.[45,46] In humans, TLR7 expression is restricted to airway epithelial cells (AEC), B cells, and plasmacytoid DC (pDC) and interactions with its ligands, ssRNA or imidazoquinoline family of nucleoside analogues, activates NF-κB and the IFN pathways resulting in activation of B cells and secretion of type I and III IFNs.[39,47–50] TLR8, phylogenetically most similar to TLR7, is absent in mice but in humans it is expressed primarily in myeloid cells where it mediates the recognition of imidazoquinoline resiquimod (R-848) and viral ssRNA.[38] The NLRP3 is an intracellular PRR that forms caspase-1-activating complexes termed inflammasome. In response to virus infection, the formation of the NLRP3 inflammasome is activated resulting in IL-1β and IL-18 secretion, thereby initiating an inflammatory response.[51] Mice that lack NLRP3 succumb to influenza infection suggesting a protective role of NLRP3 against influenza virus infection.[40,41] RIG-I is an RNA sensor localized in the cytosol. Upon recognition of either uncapped 5′-tri or diphosphorylated RNA, two repeats of a cysteine-aspartic protease (caspase)-recruiting domain (CARD)-like region at the N terminus of RIG-I are exposed, which allows RIG-I to interact with CARD containing adapter proteins to trigger downstream signaling events. Human PBMC samples from patients with polymorphisms in the CARD domain of RIG-I show a compromised immune response and increased immunopathology upon influenza infection.[52] PRRs are upregulated in response to influenza infection, which supports the important role they play in protecting the host. TLR8, along with TLRs 3, 7, 9, and RIG-I and melanoma differentiation-associated protein 5 (MDA5), are upregulated in monocytes and DCs and the expression of TLRs 3, 8, and 9 in myeloid DC and plasmacytoid DC correlate with lower nasopharyngeal viral RNA in influenza virus-infected patients.[53] Transcriptional profiling of PRRs in blood samples of patients infected with influenza shows an increase in the expression of TLR7 and RIG-I when compared to healthy controls.[54] The consequence of the PRR-mediated detection of influenza PAMPs and DAMPs is the activation of IFN regulatory factors (IRF) 3 and 7 and the nuclear factor kappa β (NF-κB), which leads to the production of type 1 (α and β) and III (λ) IFNs, pro-inflammatory cytokines, and IFN stimulated genes (ISGs).[55–57] Together, the IFNs and ISGs result in initiating and orchestrating the activation of the adaptive immune responses[58] (Fig. 1A).

To escape the immune surveillance system, the virus uses several proteins to attenuate activation of the innate signaling pathways. Influenza NS1 protein plays an important role in limiting the host innate immune responses[59,60] by directly interacting with RIG-1.[61,62] Ubiquitination of RIG-I by ubiquitin ligases, tripartite motif-containing protein 25 (TRIM25) or RING finger protein leading to RIG-I activation (RIPLET, also known as RNF135 or RIG-I E3 ubiquitin ligase [REUL]) has been shown to potentiate downstream RIG-I signaling pathways.[63,64] Influenza NS1 suppresses RIG-I-mediated signaling pathways and its antiviral activity by binding to TRIM-25 or RIPLET thereby inhibiting the ubiquitination of RIG-I.[65,66] In addition to regulating RIG-I activity, NS1 also attenuates RIG-I signaling by recruitment of the repressor protein, CCAAT/Enhancer binding protein beta (C/EBPs), on the RIG-1 promoter to inhibit RIG-1 transcription.[67] NS1 also regulates the functions of other host proteins. NS1 induces the levels of A20, a ubiquitin editing protein, that is known to suppress IRF-3-mediated induction of type 1 IFNs and ISGs in response to influenza virus infection.[68] Additionally, NS1 directly interacts with protein kinase R (PKR), an RNA sensor, to inhibit PKR-mediated phosphorylation of eukaryotic initiation factor-2 α-subunit (eIF2α) to facilitate viral protein synthesis.[69] Furthermore, NS1 is also known to attenuate innate responses by enhancing ubiquitin-mediated degradation of sphingosine 1-phosphate (S1P) lyase, a protein that has antiviral activity during IAV infection.[70] In addition to the NS1 protein, another viral protein, the PB1-F2, encoded by the alternative (+1) open reading frame (ORF) in the PB1 gene, also plays an important role in counteracting the host innate immune responses. PB1-F2 demonstrates strain-specific pathogenicity attributed to expression of protein of different length, amino acid sequences, and subcellular localizations in different strains. PB1-F2 interferes with the innate response by directly binding to an adapter protein mitochondrial antiviral-signaling protein

(MAVS; also known as IFN-β promoter stimulator I (IPS-1) or caspase activation recruitment domain adaptor inducing IFN-β (CARDIF) or virus-induced signaling adaptor (VISA), resulting in reduced IFN production.[71,72] PB1-F2 can suppress the RIG-I signaling pathway and the activation of the NLRP3 inflammasomes by attenuation of the mitochondrial membrane potential.[73,74] PA-X, a viral fusion protein translated as a +1 frameshift ORF in the PA gene, counteracts the antiviral response in the host by selectively degrading host RNA polymerase II–transcribed mRNAs and noncoding RNAs in the nucleus of infected cells, thereby allowing successful replication of the viral RNA in the host.[75,76] Collectively, the interactions between the influenza viral and host proteins control the IFN-mediated antiviral responses and the outcome of the influenza virus infection.

The induction of the initial innate immune response forms a formidable barrier to the influenza virus as a result of secretion of different types of cytokines and interferons including IFN-α/β, IFN-γ, and IFN-λ that control the infection during the early phases. IFN-α/β, secreted by infected cells, is known to induce an anti-viral response and viral resistance in neighboring uninfected cells through a paracrine mechanism to limit the viral replication.[77] IFN-λ secreted by the epithelial cells and the pDCs upon influenza infection correlates with protection against influenza challenge in IFN-α/β receptor gene knock-out mice, and *in vitro* cell culture studies.[78–80] Although epithelial cells are the main targets of influenza virus infection, monocytes, macrophages, and DCs also get infected,[81,82] which is important for their activation and secretion of proinflammatory cytokines to further recruit other innate immune cells to control virus infection (Fig. 1B).[29]

Adaptive immunity, the second line of defense, has two components: humoral immunity (antibody-mediated) and cell-mediated immunity (macrophages-, cytotoxic T-lymphocyte [CTL]-, NK cell-, and cytokine-mediated). The replication of the virus and activation of the innate pathway in the epithelial cells alerts the immune sentinel cells, macrophages, and DCs to act as antigen presenting cells to initiate adaptive immune responses. Influenza infection induces $CD4^+$ and $CD8^+$ T cells that have been shown to aid in viral clearance through the cytolytic activity of $CD8^+$ T cells or cytokines secreted by $CD8^+$ and $CD4^+$ T cells.[83–89] In case of IAV infection, most of the virus-specific antibodies secreted by B cells, which can be either neutralizing or non-neutralizing, are targeted against the surface protein HA and NA, and to a lesser extent to matrix protein and NP.[90] The non-neutralizing antibodies participate in virus clearance through interactions with other immune cells. The HA-specific neutralizing antibodies, used as a correlate of protection, bind to the immunodominant globular head and inhibit the virus attachment to host cells.[91,92] Some HA-specific antibodies are directed against the highly conserved HA stem region, though these are present in low titers, and may function by restricting the conformational changes required for membrane cell fusion.[91,92] Antibodies against the surface glycoprotein NA also confer protection against influenza virus infection.[93] However, these antibodies are not neutralizing; instead, these limit the spread of viral infection by interfering with sialidase activity of NA.[94,95] The presence of antibodies to NP have been reported after natural infection and vaccination. Although these are not neutralizing, they have the potential to elicit antiviral responses.[96] Different antibodies interfere with different stages of the viral life cycle, either neutralizing the virus infectivity by binding to the proteins required for virus entry or reducing viral titers by interfering with virus budding or by triggering antibody-dependent cell-mediated toxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) to kill infected cells.[97] Collectively, the innate and the adaptive response aid in induction of a protective antiviral immunity that facilitates the clearance of the virus.

The cytokine response that is typically activated by the initial sensing of pathogen invasion also regulates the recruitment, maturation, and functionality of ILCs, and in turn ILCs also regulate several components of the innate and adaptive immune pathways (Fig. 1B). In the recent past, ILCs have received considerable attention and many studies provided insight into the mechanisms of ILC responses to human pathogens and their role in protection in animal models. However, there is a major gap in our fundamental knowledge about ILCs and their role in

human infectious diseases, largely related to the difficulty in accessing human tissue for experimental analysis. In this review we examine the current literature on ILCs in the lungs with emphasis on their roles during influenza infection and vaccination.

III. CHARACTERIZATION OF THE ILCs

In the last 50 years since the identification of NK cells, a class of lymphocytes that lack an antigen-specific receptor but with cytotoxic potential, ILCs have been at the forefront of understanding the immune surveillance during homeostasis, immunity, and inflammatory states at the barrier surfaces.[4,5,98–101] Based on lineage defining transcription factors and distinct cytokine profiles, NK cells are now classified as one of the six subsets within this group that also consist of the lymphoid tissue inducer (LTi)-like cell that are responsible for secondary lymphoid organogenesis, and the three subsets of ILCs (ILC1, ILC2, ILC3) that are referred to as helper ILCs since they function like T-helper cells (Fig. 2), and the regulatory ILCs (ILC_{Reg}) similar to regulatory T cells that are beginning to be identified in the field.[102] All classes of ILCs originate from hematopoietic stem cells (HSCs) in the bone marrow, though studies in murine models suggest that fetal liver can also serve as point of origination for the progenitor cells.[5,103] Although distributed in both lymphoid and non-lymphoid organs throughout the body, ILC subsets populate barrier surfaces, notably the skin, lung, and gut, where they are activated to control viral and intracellular bacterial infections, inhibit tumor growth, and maintain

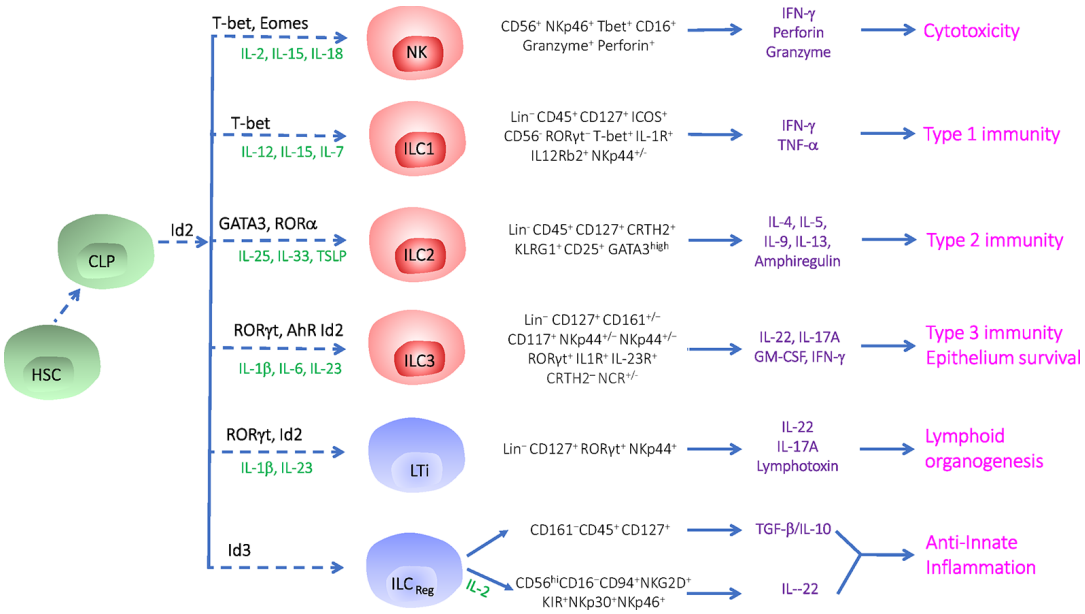

FIG. 2: Developmental heterogeneity, subsets, effector cytokines and functions that define the ILC family in humans. ILCs initially originate from the HSC in the bone marrow that differentiates into CLPs in a multistep process in response to the transcription factors and cytokines to mature into six different classes. Different transcription factors and cytokines that mediate differentiation of the ILC subsets are included before the subset, and the distinguishing markers of each subset, and known functions of each subset are indicated to the right of each subset. Red indicates the subsets found in lungs or in the peripheral blood; green denotes subsets found in the peripheral blood or in the bone marrow; blue denotes subsets found in tissue (LTi, progenitor liver) or in tissue (ILC_{Reg}). AhR, aryl hydro-carbon receptor; CLP, common lymphoid progenitors; Eomes, Eomesodermin; GATA3, GATA binding protein 3; HSC, hematopoietic stem cell; LTi, lymphoid tissue inducer; RORα, RAR-related orphan receptor α; RORγt, RAR-related orphan receptor γt; T-bet, T-box transcription factor.

homeostasis.[5,98,104,105] Influenza virus primarily infects the respiratory epithelium, however, due to the limitations in accessibility of human tissue, our understanding of the helper ILCs in the lung is limited to bronchoalveolar lavage fluid (BALF) or biopsy samples obtained from patients with lung conditions. Also, the phenotypic markers and ILC subsets vary between humans and mice. Therefore, for the purposes of this review, we limit our discussion to subsets identified in human lungs and discuss data from murine studies when information in humans is lacking. Several reviews are available on the origins of the ILCs in human tissues.[10,102,104,106,107] Briefly, the common lymphoid progenitors (CLPs) differentiate into cells of the innate and the adaptive immune pathways, i.e., T cells, B cells, monocytes, granulocytes, and DCs, and a subset of CLPs also give rise to ILCs (Fig. 2).[4,102] All ILC subsets are identified as negative for markers that are used to identify common immune cells in humans such as, CD3, CD19, CD56, CD14, HLA-DR, and CD34, to respectively identify T, B, and NK cells, monocytes, DCs, and hematopoietic progenitor cells.[108] Development of the ILCs from CLPs is independent of recombination-activating genes (RAG)-dependent rearrangement of antigen receptors and mediated by several transcription factors and cytokines as denoted in Fig. 2.

The NK cells, the most studied class, are the primary counterpart of CD8-T lymphocytes of the adaptive immune system and are identified as $Lin^{-}CD56^{bright/dim}CD117^{\pm}CD16^{-}CD94^{+}NKp46^{+}KIRs^{-}CD127^{\pm}NKp30^{-+}$.[102] They depend on T-box transcription factors (T-bet) and Eomesodermin (Eomes) for maturity and are activated in response to IL-12, IL-15, and IL-18 to produce effector cytokines IFN-γ, TNF-α, and GM-CSF and cytotoxic molecules, perforin and granzyme. In the human peripheral circulation, two populations of NK cells have been identified based on the relative expression of neural cell adhesion molecule, CD56 and the low affinity FcγR, CD16. The $CD56^{bright}CD16^{dim}$ population is a cytokine producer, while the $CD56^{dim}CD16^{bright}$ cells are frequently found in higher numbers and are associated with cytotoxic function.[109] Tissue-resident NK cells are more specialized in function and have primarily been studied in the human uterus and liver, where they represent up to 50% of the total lymphocytes in the liver[110] and a larger percentage of lymphocytes in the pregnant uterus.[111] In response to pathogens, NK cells transdifferentiate into a memory population that can be identified by surface expression of the terminal differentiation marker, CD57 and PD-1.[112–114] These memory cells primarily reside in the liver and expand following re-stimulation, as has been observed following vaccination with the hepatitis B virus vaccine or influenza virus-like particle (VLP) vaccine, human immunodeficiency virus (HIV), or human cytomegalovirus (HCMV) infection.[113,115,116]

NK subsets are classified generally as the cytotoxic subset while the other classes of the ILCs, which consist of ILC1, ILC2, and ILC3, are classified as helper ILCs.[2] The ILC1 subset, like the NK subsets, depend on T-bet for maturation and secrete high levels of IFN-γ and TNF-α, but unlike the NK cells, they express little to no granzyme or perforin. ILC1, considered to be the innate equivalent of Th1 cells, are identified as a distinct population that are $Lin^{-}CD127^{+}CRTH2^{-}CD117^{-}NKp44^{-}CD56^{-}CXCR3^{+}T\text{-}bet^{+}Eomes^{-}IFN\text{-}\gamma^{+}$ cells in humans. These cells can be further divided into two groups, based on the expression of CD127 and their localization in tissues. The first subgroup identified as $CD127^{+}CD117^{-}NKp44^{-}$ do not express C-C motif chemokine receptor 6 (CCR6), CD103, or CD25, and a second subgroup, $CD127^{low}$ ILC1s, is $CD127^{-}NKp46^{+}$.[117–119] An ILC1-like subset that is $EOMES^{+}$ is found in peripheral blood of healthy subjects and tonsils and those cells have rearranged TCR α and β chains, and express CD8α without surface expression of TCR or CD3 though the functionality of these cells is unknown.[120] In addition, the presence of another subset that is $Lin^{-}CD56^{-}IL12R\beta2^{+}$ and secretes IFN-γ has been reported in human lungs from healthy tissue away from tumors, though its functional role remains undefined.[121] The intraepithelial (ie) ILC1 cells, $Lin^{-}CD127^{+}c\text{-}kit^{-}NKp44^{-}$ are present in the mucosal tissues of tonsils and intestines and secrete IFN-γ and TNF-α in response to IL-12 and IL-15.[117] The frequency of ILC1 is much higher in inflamed mucosal tissue, suggesting a role for these cells in pathological conditions.[119] A functional role for ILC1 in infection

comes from a study showing that the ILC1 cells protect the mice from intestinal infestation with an intracellular parasite by producing IFN-γ and facilitating macrophage recruitment.[122] Traditionally, ILCs with adaptive like responses against viruses were thought to originate from the conventional NK cells. By using single cell analytical tools, a different class of ILC1-like cells has been characterized from spleen of mice infected with murine cytomegalovirus (MCMV).[123] This class of ILC1 cells, named ILC1-like NK cells, produces cytokines, recognizes and kill MCMV-infected cells, and modulates the functions of the DCs to prime T cells early during virus infection.[123] While this subset still needs to be identified in humans, these results suggest that ILC1-like adaptive cells are early sentinels of viral infection that link the innate and adaptive immune responses.

The ILC2 subset, traditionally classified as $GATA3^+$ and RORα-dependent, represents the innate counterpart of Th2 lymphocytes. They are commonly identified as $Lin^-CD127^+CD45^{high}CD161^+CRTH2^+$ cells and express ST2 (receptor for IL-33) and IL-17 receptor B (IL-17RB) in humans. This subset of cells responds to IL-25, IL-33, IL-4, thymic stromal lymphopoietin (TSLP), and prostaglandin D2 (PGD2). The functionally active ILC2 release IL-4, IL-5, IL-9, and IL-13 and amphiregulin.[4,124–126] ILC2 regulates both homeostatic functions and immune responses to pathogens and plays a role in chronic diseases such as obesity and asthma.[127] A human $Lin^-CD127^+CD161^+$ ILC population characterized by the expression of chemoattractant receptor-homologous molecules expressed on T-Helper type 2 cells (CRTH2) and CD161 responds *in vitro* to IL-25 and IL-33 by producing IL-13 and IL-5. These cells are present in fetal and adult lungs and gut.[128] IL-33R-responsive ILCs were isolated from the nasal polyps and peripheral blood of patients with chronic rhinosinusitis, suggesting that human peripheral blood also contains a population of cells that shares features of tissue resident ILC2.[128]

The ILC3 mirror the Th22 and Th17 cells through the production of cytokines IL-17A, IL-17F, IL-22, and GM-CSF.[129–131] This class of cells depends on transcription factor Retinoic-acid-receptor-related orphan nuclear receptor gamma (RORγT) for maturation and responds mainly to IL-1β and IL-23 in response to bacterial and fungal infections.[132] In humans, adult ILC3s are defined as $Lin^-CD127^+CRTH2^-CD117^+$; they also express NKp44, NKp46, CD56, and NKp30.[130,131,133] ILC3s are further subdivided into two classes based on the expression of NKp44. $NKp44^+$ ILC3 produce IL-22 whereas $NKp44^-$ ILC3 produce limited amounts of IL-17.[134] In addition to γδ-T cells, and Th17 cells, ILC3 cells are involved in the maintenance of epithelial barrier function, mucus production, and tissue repair.[105,125]

While the helper subsets of ILCs, comprising ILC1, ILC2, and ILC3, have been identified as distinct populations in humans, the identification of an LTi subset in humans as a distinct population has been challenging. In mice, the LTi family of ILCs localize to the embryonic tissues and resemble the NKp44$^-$ILC3 subset. LTi depends on RORγT for development and the LTi secreted essential factor, lymphotoxin-α1β2, is important for lymph node organogenesis, development of secondary lymphoid tissues, and the development and function of the adaptive immune system.[135–138] LTi cells express CCR6 and produce IL-17A, IL-17F, and IL-22 along with lymphotoxin upon activation with IL-1β and IL-23.[139] In adults, a distinct population of cells that develop from a progenitor that is distinct from the NK progenitor are identified as the LTi-like subset.[140]

Finally, the regulatory ILCs (ILC_{Reg}) have been identified in inflamed human and murine intestinal tissue. They originate from the common helper like innate lymphoid cells under the influence of transcription factors the inhibitor of differentiation 3 (Ide3) and SRY-Box transcription factor 4 (SOX4) and express markers $Lin^-CD45^+CD127^+$, which are distinct from the typical phenotypical markers associated with ILC1, ILC2, and ILC3. Functionally the cells are shown to inhibit the activation of ILC1 and ILC3 via secretion of IL-10 and contribute to resolution of intestinal inflammation.[141] A second type of ILC_{Reg} called follicular regulatory ILC (ILC_{FR}) has been isolated from human tonsils and lymph nodes within the germinal center follicles.

ILC_{FR} suppress the interactions between T and B cells via production of TGF-γ, resulting in a decrease in production of IgG as well as cytokines. Further, these cells expand during HIV infection,[142] suggesting a role for these cells in pathogenesis. In humans, regulatory ILCs have also been identified from tumor infiltrating lymphocytes cultures obtained from primary high-grade serous cancer. These cells were identified as $CD56^{bright}CD16^{-}$ $CD94^{+}NKG2D^{+}KIR^{+}NKp30^{+}NKp46^{+}$, shown to produce IL-22 *in vitro*, and likely originating from NK cells. Functionally these cells suppress T cell expansion and cytokine production. Their presence correlated with a reduction in time to disease recurrence, suggesting that depletion of these cells may improve immunotherapy.[143] More studies are needed to decipher the origination, maturity, and functionality of the ILC_{Reg} cells and how they exert their immunosuppressive functions in human health and disease.

IV. ILCS IN THE LUNGS

In response to pathogen encounter and inflammatory signals, the ILCs demonstrate considerable plasticity by transdifferentiating into different subsets in tissues or migrating from adjoining tissue to fine tune their effector functions.[144] Under steady state, the lung is predominantly composed of conventional lymphocytes and myeloid cells and a much lower frequency of ILCs that are $Lin^{-}CD45^{+}CD127^{+}$ cells.[121] In the biopsies of human lungs from patients with solitary pulmonary tumors, the NK subset accounts for > 95% of the total ILC subsets.[121,145] Although the tissue collected is far away from the lung lesion, which did not show tumor invasion, it is not surprising to have a higher number of NK cells given their role in tumor surveillance. Results from another study show that within the ILC subset the frequency of NK cells is higher than the helper subsets.[146] Type I and Type III IFNs are known mediators of NK cell homeostasis, activation, and function,[147,148] as are proinflammatory cytokines, IL-12, IL-25, IL-18, and TLR ligands.[149] The lung tissue–resident NK cells are primarily mature and terminally differentiated $CD56^{dim}CD16^{+}$ and are hyporesponsive to stimulation with phorbol myristate acetate (PMA), and ionomycin, with impaired cytotoxicity and ADCC functions.[150,151] A small percent of the NK cells in the lungs express $CD49a^{+}CD103^{+}CD69^{+}$ activation and homing markers.[150] This suggests that the lung NK cells are primarily derived from circulating cells. Further analysis reveals that $CD56^{dim}CD16$ NK cells in the lungs are enriched for effector functions, while $CD56^{bright}CD16^{-}$ NK cells are enriched for cell-adhesion and chemotaxis pathways.[151] NK cell subsets, i.e., $CD56^{bright}CD16^{-}$, $CD56^{dim}CD16^{+}$, $CD56^{dim}CD16^{-}$ are present in the lung parenchyma and blood, and the circulating and lung resident cells express similar levels of CD57, CD158b, and NKG2C.[152] These findings suggest that the lung NK cells mirror the phenotype of the peripheral blood and are highly mature and terminally differentiated.

The helper ILCs, ILC1, ILC2, and ILC3 have also been identified in lung biopsy samples that are obtained at a maximum distance from lung lesion and show no signs of disease from COPD patients or from deceased organ donors. Stimulation of $CD45^{+}Lin^{-}CD127^{+}$ cells obtained from the lung tissue with PMA/ionomycin, resulted in secretion of IFN-γ, IL-5, IL-17A, IL-22, and GM-CSF, indicative of the presence of all classes of helper ILC subsets though their frequency in the lungs is very low.[121] Within the $Lin^{-}CD45^{+}CD127^{+}$ cells obtained at a distance from diseased tissue, the frequency of ILC1 subset was 9.8%, 33% ILC2, and 60% ILC3.[121] Similar results are reported in another study in which the population of the helper subsets in healthy lung tissue was reported to be less than 3% of total ILCs.[145] In lung samples from deceased donors the frequency of helper ILCs is reported to be around 5–6% of total $CD45^{+}Lin$ populations.[146] These suggest that helper ILCs are also present in the lung during both healthy and diseased states.

The ILC2 cells are primarily tissue resident and situated within the lung parenchyma.[153] In the healthy human lungs, there is a population of $Lin^{-}CD127^{+}$ that express CD25 (IL-2Rα) and the IL-33R subunit ST2 that are also found in BAL of seven out of nine lung transplant recipients.[154] IL-33 secreted by epithelial cells and stromal cells in lungs facilitates the expansion of neonatal ILC2 to reach adult levels and their long residence to respond to biotic and abiotic challenges in later life.[155–157] After infection or

allergen insult in the lung, airway epithelial cells are damaged and produce IL-33, which activates ILC2 to produce amphiregulin, which promotes the repair of the airway epithelium.[158] An additional subset in the humans identified as $Lin^{-}CD127^{+}CD161^{+}$ expresses a chemoattractant receptor- CRTH2, responds *in vitro* to IL-25 and IL-33 to produce IL-13 and IL-5. This cell population is present in the fetal and adult lung and is enriched in nasal polyps of patients with chronic rhinosinusitis.[128]

ILC3s are prolific producers of IL-17, IL-22, and GM-CSF, thereby regulating inflammation or repair of lung tissue after infection or autoimmune disease.[105] In healthy lung tissue, NCR^{-}ILC3s represent the predominant subset (41.7%) with NCR^{+}ILC3 subset as the third predominant (15.5%).[121] ILC3 cells play important roles in lung health, especially in patients with COPD who had increased frequency of $NKp44^{-}$ILC3 population as well as increased levels of IL-17A and IL-17F produced by $NKp44^{-}$ ILC3.[105,121]

Single cell RNA (scRNA) analysis has opened the field of examining the ILC subsets from few cells in biopsy samples as conventional flowcytometry requires more cells, which is a limiting factor. Mazzurana et al.[120] obtained lungs tissues from four patients undergoing lobectomy for lung cancer and subjected the $CD127^{+}$ cells from lungs, blood, and colon to scRNA analysis. Although the markers used to identify these clusters were not those traditionally used for protein expression, using transcriptional markers, the authors reported that in the lung tissue all classes of ILCs are present, and some of the subsets also express tissue residency markers. The peripheral blood and the lungs contained $CRTH2^{+}$ILC2 subsets. Exposure of the blood ILC2 to a cocktail of IL-2, IL-25, IL-33, and TSLP induced the expression of IL-1RL1 and IL-17RB, suggesting the plasticity of the blood ILC2 subsets.[120] Zeis et al.[159] explored the ILC populations in human lungs and the peripheral blood, and identified a population of ILC progenitor cells (ILCp) $IL7R^{+}IL\text{-}18R1^{+}TCF1^{+}$ that express GATA3 and show graded expression of IL18R1, TCF1, GATA3, c-kit, ICOS, and CD103 markers but lack markers of mature NK, ILC1, ILC2, and ILC3. They further explored the functionality of these cells in the pathogenesis of parasitic diseases in mice and demonstrated the presence of similar ILCp cells in murine lungs that continuously differentiate to give rise to ILC2 cells that have protective effects against helminth infections.[159] This suggests that, in addition to the presence of mature subsets in lung tissues, there are ILCps present in the lungs and, upon infection, these cells can differentiate to mature ILC phenotypes in adult lungs.

V. ILCS AND INFLUENZA INFECTION

Activation and function of NK cells in virus clearance is documented with many viral diseases.[160–167] Following influenza virus exposure, NK cells are the first immune cells to directly lyse virally infected cells by either releasing cytotoxic granules containing perforin and granzymes or induction of apoptosis of infected cells by engaging various activating receptors. NK cells recognize stress- or infection-induced MHC class I-chain-related (MIC) molecules MICA and MICB as well as UL16-binding protein on the target cells by the activating receptors such as NKG2D or HA on infected cells with natural cytotoxicity receptors (NCR) or through Fc-receptor (FcR)-mediated ADCC.[168,169] After infection with the influenza virus, an increase in the NK cells in the lungs is observed during the early stages of infection in mouse models of the disease.[170,171] In humans, there is a reduction in the levels of the NK $CD56^{+}CD16^{+}$ in the peripheral circulation upon influenza virus infection,[172,173] although no statistical changes were observed between the severe and the moderate infections. Similarly, there were no correlative changes in cytokine levels to a pandemic influenza virus strain.[173] In another study, 35 healthy individuals were challenged with A/California/2009 (H1N1) and their immune profile indicated that the total NK cells abundance did not change. NK cells with marked changes in expression of the marker Ki67, which is associated with proliferation, steadily increased until day 8 after challenge with H1N1 infection in NK subsets $CD56^{lo}CD16^{+}$ and $CD56^{+}CD16^{-}$.[174] Jost et al. observed a drop in $CD56^{+}CD16$ and $CD56^{-}CD16^{+}$ in peripheral blood NK cells numbers after seasonal and pandemic H1N1 influenza infections,[175] suggesting that there is a general NK cell lymphopenia

associated with influenza infections. The phenotype of NK cells isolated from human lung tissue collected from distal tumor sites of lobectomy patients is similar to NK cells in the peripheral blood. NK cells co-culture with influenza virus-infected macrophages or epithelia of lung explants, the CD-56^{bright}CD49a^{+} NK subset expressed more 107a. These changes were mirrored by an increase in the release of granzyme and IFN-γ compared to CD-56^{bright}CD49a^{-} NK cells indicating NK cell residency within this organ.[152] In murine models of influenza infection where the NK cells have been studied in the lungs, the frequency of the NK cells did not change. However, there was a significant increase in the expression of NKp46 and CD69 after infection.[176] Antibody-mediated depletion of NK cells also results in impairment of the response to influenza virus in mice suggesting NK cells are essential in controlling virus titers in lungs.[177,178] Furthermore, the function of NK cells was mediated via IFN-γ.[179,180] In contrast to depletion experiments, adoptive transfer of NK cells shows protective effects after influenza virus infection. Conventional NK cells (NCR1^{+}NK1.1^{+}CD127^{-} RORγt^{-}) in murine lungs are the predominant cell types generating IL-22 at day 7 post–influenza virus infection and infection in IL22$^{-/-}$ mice results in more severe impairment of the regeneration of tracheal epithelial cells.[181] Further, adoptive transfer of conventional NK cells (NK1.1^{+}CD3^{-}NCR1^{+}) isolated from B6.SJL (CD45.1^{+}) to IL22$^{-/-}$ (CD45.2^{+}) mice confers protection as observed by minimal weight loss, improved epithelial regeneration, as well as improved protection post-challenge with PR8 virus.[181] These results establish a role for NK cells in lung epithelial regeneration post-influenza virus infection in the mouse model of disease. Similar results are also seen in the Syrian hamster model of influenza virus infection in which NK cell cytotoxicity was detected in cells isolated from lungs three days after infection.[182] Antibody-mediated depletion of the NK cells in the hamsters rendered the animals more susceptible to the virus infection as observed with increased morbidity and mortality.[178] Together, these results suggest that NK cells in the lungs facilitate clearance of the virus from the lungs, however, further investigations are required in humans.

Given the evidence from animal models that NK cells may be involved in clearance of the virus-infected cells, the mechanisms by which NK cells facilitate their activity have been tested in the human peripheral blood samples. Activated NK cells secrete cytokines and cytotoxic molecules, which target unhealthy or infected cells by either killing them or altering the homeostatic functions of other immune cells to enhance pathogen clearance. The cytotoxic functions of the NK cells are regulated by the expression of several activating and inhibitory receptors that can recognize cognate ligands on damaged or infected cells and mediate either killing or prevent killing of the cells, respectively.[183] Stimulation of NK cells, i.e., human large granular lymphocytes (LGLs), showed increased NK cytolytic activity against K562 cells after incubation with influenza. This was associated with increased IFN-α, β-, and γ-production.[184] NK cells respond to virus infections by upregulating their activation markers (killer cell Ig-like receptors [KIRs], NKG2A, NKG2D) and natural cytotoxic receptors (NKp30, NKp44, and NKp46).[185,186] NKp46 binds specifically to the influenza HA proteins of both A and B viruses on the surface of infected cells *in vitro* and lyses the infected cells, thereby reducing viral load.[187,188] Cooper et al. demonstrated higher cytotoxicity of NK cells due to up-regulation of surface CD107a expression and the release of IFN-γ and granzyme B in response to influenza virus infection in the lung explant model.[152] *In vitro* infection of lung cells isolated from human lung biopsy samples demonstrate that influenza infection can induce the expression of CD69 on both CD56^{dim} and CD56^{bright} populations of NK cells, which also show strong degranulation activity and induction of cytokines IFN-γ and TNF-α.[177] In mice, increased NK cells show exacerbation of the influenza disease but mice with depleted NKp44 are resistant to influenza infection, suggesting a causal link of NK cells with both viral clearance as well as pathogenesis. NKp46 binds to HA of influenza virus infected cells. Blocking interactions of the NKp46-Ig fusion protein inhibits NK cell–mediated lysis of influenza virus–infected cells.[189] Similarly, NKp44-Ig fusion protein binds to influenza virus–infected cells in a HA-dependent manner as HA reduces the

NK cell–mediated lysis of infected cells.[190] Binding of KIR2DL1-Ig to HLA-Cw4 on influenza virus–infected cells increases in a HA-independent manner suggesting that several NK cell receptors are involved in target cell recognition.[191] NK-mediated protection post-influenza infection is observed in murine model as mice immunized with ADCC stimulating HA peptides had reduced viral titers in lungs.[192] Viruses have also acquired an escape mechanism to overcome NK cell-mediated killing of virus-infected cells as purified NK cells from healthy subjects demonstrated reduced cytotoxicity when incubated with purified HA protein or infected with influenza virus due to downregulation of NKp46 and NKp30 signaling pathways and degranulation *in vitro*.[186] Reduced NK cell numbers in circulation of influenza-infected patients with severe and moderate disease have been reported[193,194]; however, this decrease in the peripheral blood could be due to the recruitment of NK cells into lungs of infected patients. Additionally, NK cells can be directly infected by the influenza virus *in vitro* leading to apoptosis and reduced cytotoxicity.[195] TLR7 plays an important role in activation of the NK cells in response to influenza virus infection as TLR7KO mice show a reduced frequency of IFN-γ and $CD69^{+}$NK cells after influenza virus challenge.[196] Activation of TLR7 results in IL-12p70 secretion leading to NK cell activation.[197] Studies in humans show that the NK cells are robust producers of cytokines in response to influenza infection, and NK-mediated release of IFN-γ *in vitro* from immune donors upon influenza virus infection requires the presence of T cells that secrete IL-2.[198] In contrast, NK cells prime the CTL responses upon stimulation with influenza virus as depletion of NK cells results in attenuation of influenza virus–specific CTL activity *in vitro*. Additionally, NK cell depletion leads to reduction in CTL activity and induction of memory responses *in vivo* in a murine model.[199,200] In a mouse model of influenza virus infection, overexpression of type III receptor (IL-28B) results in higher proliferation and activation of NK cells that is dependent on macrophages, suggesting the type III interferon plays a key role in activation and functions of NK cells during viral infection.[201] In murine lungs conventional NK cells produce IL-22 that drives regeneration of damaged tracheal and bronchial epithelial cells caused by influenza virus infection.[181] Overall, these observations suggest that NK cells play a significant role in viral clearance that is either mediated via its cytotoxic activity or cytokine production.

Demonstration of a role of the helper class of ILCs in influenza infection comes primarily from murine studies. All ILC subsets have been identified in the mouse lungs, though when compared to humans the percent of each subset varies, ILC2 subset being the most predominant ILC subset.[146,202,203] In a murine model of influenza virus infection, lung-resident ILC1 along with NK cells are the first and main source of IFN-γ production at the site of infection.[204] Rapid IL-12 production from tissue-resident DC upon virus infection promotes ILC activation and production of IFN-γ.[204] The functionality of the ILC1 (both NK cells and non-NK cells) was regulated through the glucocorticoid-induced TNFR-related protein (GITR), where high expression of GITR suppresses IFN-γ production and low expression of GITR enhances IFN-γ production.[205] Activation of ILC1 by the pegylated derivative of glycolipid alpha-galactosylceramide (GalCerMPEG), an activator of invariant NKT (iNKT) cells, is shown to modulate ILC1s by increasing the expression of "checkpoint" inhibitors, GITR and CTLA-4. Pre-activation of ILC1 with GalCerMPEG increased the absolute number of ILC1 and resulted in reduced viral titers on day 3 post–influenza virus infection.[206] In addition, influenza-activated ILC1 modulates DC activation, maturation, and DC crosstalk with $CD4^{+}$ and $CD8^{+}$ T cells to boost IFN-γ and TNF-α secretion by ILC1s. Therefore, ILC1s play a first responder role in inducing an antiviral state to limit viral replication.

In response to influenza virus infection, there is an influx of ILC2 cells in the murine lungs that precedes the recruitment of T cells.[207] Further, ILC2 deficient mice show increased susceptibility to infection with a pandemic H1N1 virus strain,[208] suggesting ILC2 plays a pivotal role during virus infection. An ILC2 subset identified in mouse (Lin^{-} $CD90^{+}CD25^{+}CD127^{+}NKp46^{-}$) that also expresses activation markers (CD44, iCOS, Sca-1, and c-kit)

has been described in humans ($Lin^{-}CD127^{+}CD25^{+}$IL-33R subunit $ST2^{+}$). In further murine studies this subset increases in the lungs following challenge with the influenza virus.[154] Depletion of ILC2 with monoclonal antibodies causes a reduction in eosinophil recruitment in the BALF and decreased lung function following an influenza virus challenge. Upon damage, epithelial and immune cell lineages produce IL-33, which leads to expansion and activation of ILC2 in lungs to produce IL-13 and amphiregulin. Adoptive transfer experiments in mice suggest that ILC2-mediated epithelial repair post-influenza infection allows restoration of airway epithelial integrity.[154] These observed effects of $CD90^{+}$ILCs were similar to blockage of the IL-33-IL-33-R signaling axis and could be restored by administration of the lung ILC product amphiregulin.[154] In neonatal mice, γδ T lymphocytes rapidly produce IL-17A after influenza infection, thereby enhancing the production of IL-33. IL-33-induced increases of ILC2s, promote lung tissue repair through amphiregulin.[209] Following influenza virus infection, ILC2 are the cellular source of IL-5 secretion leading to the influx of eosinophils into the lungs.[210] Interestingly, the protective effects of ILC2 in mediating improved tissue integrity and reduced inflammation following influenza virus infection are attenuated by influenza virus–induced IFN-γ,[208] highlighting the complex interplay between IFNs and ILCs during influenza virus infection. In murine viral infection models, an ILC2 subset, expressing an inhibitory receptor PD-1, is substantially increased in the lungs at days 4 and 7 following influenza virus infection.[211] Antibody-mediated depletion of this ILC2 subset results in reduced production of cytokines IL-5, IL-4, and IL-13 in the BALF. In the lungs there is less eosinophil accumulation and inhibition of mucus production following papain challenge[211] suggesting a role for ILC2 in mucus production following virus infection though further studies need to be conducted.

Evidence that ILC3 has a role to play in influenza virus infection comes from murine studies demonstrating that ILC3 effector cytokines IL-22 and IL-17 play a role in lung epithelial regeneration and tissue repair. Enhanced IL-22 gene and protein expression induced by ILC3 was detected in mice as early as day 2 post-influenza infection and IL-17A protein expression was detected in the BALF cells post influenza virus infection.[212] In parallel, there was enhanced levels of IL-23, a known cytokine that promotes secretion of IL-17 and IL-22 from ILC3, at day 2 and day 4 post influenza virus infection. $IL\text{-}22^{-/-}$ deficient mice exhibited impaired lung epithelial cell regeneration and failed to recover following influenza virus infection with a sublethal dose of the virus. Finally, the IAV-treated $IL\text{-}22^{-/-}$ animals are more susceptible to *Streptococcus pneumoniae* than WT.[212] These results suggest that cross talk between IL-22 and ILC3 play important role during IAV infection especially in controlling secondary bacterial infection post–influenza virus infection. Taken together, NK- and ILC1-produced IFN-γ responses may control early viral replication and ILC2 and ILC3 may mediate more homeostatic repair processes in the lungs after influenza virus infection.

VI. ILCS AND INFLUENZA VACCINATION

There are three major types of influenza vaccines in use: either egg- or cell-derived inactivated influenza vaccine (IIV), or recombinant or live-attenuated influenza vaccine (LAIV). The IIV and recombinant vaccines are approved for persons aged ≥ 6 months, including pregnant women and people with underlying health conditions, and they are known to induce a robust strain-specific antibody response with limited protection against drift variants. The LAIV vaccine is approved for healthy people between the ages of 2 and 49 years, administered intranasally, and is known to induce systemic and mucosal innate and adaptive immune responses including mucosal antibody and cell mediated immunity.[213,214] Since the vaccines have different modes of action and different efficacy that is dependent on the age of the individual, their ability to induce ILCs may vary significantly and the induction/activation of ILCs at the vaccination sites and their role in controlling influenza virus infection remain unclear.

Increases in NK cell–mediated lysis of K562 tumor cells in PBMCs after vaccination were reported as early as the 1990s, when Schapiro et al.[15]

intramuscularly immunized five healthy volunteers with the trivalent IIV vaccine, and measured NK cell activity on days 2, 3, 6, 14, and 30 post-vaccination. All subjects showed an increase in cytotoxicity activity peaking at day 6 or 14 and it was sustained until day 30. The increase in the NK activity correlated with increased hemagglutination inhibition (HI) antibody titer in these subjects, suggesting that inactivated viral components were capable of activating NK cells in peripheral blood.[215] Unlike influenza virus infection, which leads to reduced NK cells in the peripheral blood,[216] intramuscular vaccination with inactivated virus vaccine containing purified HA- results in an overall increase in $CD56^+CD16^-$ and $CD56^+CD16^+$ NK cells in peripheral circulation.[175] In another study, elderly subjects who received the IIV vaccine intramuscularly had an increase in the $CD45RO^+CD16^+$ NK cells one month post-vaccination.[217] The individuals who were protected against the influenza after vaccination had a higher frequency of NK cells with higher cytotoxic activity. Children who received LAIV had a significant increase in IFN-γ^+ producing $CD56^{bright}$ and $CD56^{dim}$ NK populations post-vaccination.[218] However, in post-LAIV and -IIV vaccination adults, $CD56^{bright}$ and $CD56^{dull}$ NK populations changes are variable. As a group, adults did not demonstrate an increase in IFN-γ^+ cells after either LAIV or IIV administration. In another study, increases in the frequency of IFN-γ^+ producing NK cells were observed in many subjects post-IIV immunization.[219] In contrast, Juarez-Reys et al. observed only a modest increase in NK cells or their receptor expression in post-seasonal or -pandemic influenza virus vaccination.[220] Additionally, there were small but significant increases in the proportions of $NKp46^+$ $NKG2A^+$ NK cells in recipients of pandemic vaccine. Transcriptome analysis of NK cells on day 28 post-vaccination indicated upregulation of perforin, Spondin-2, KLRF1, NCR1, Fc receptor-like protein 6 (FCRL6), Granzyme A, NK cell granule protein 7 (NKG7), cystatin 7 (CST7), megakaryocyte-associated protein tyrosine kinase, (MATK), and Aldo-keto reductase family 1 member C3 (AKR1C3) and these changes correlated with antibody titers.[221] A decrease in the $CD56^{bright}$ NK cell population with a corresponding increase in $CD56^{dim}$ NK cells among the $CD16^+$ subset was observed in older vaccinees when compared to their younger counterparts. Baseline NK cell cytolytic activity compared to K562 cells on a per cell basis was lower in older adults when compared to younger adults. Additionally, seasonal influenza virus vaccination had no impact on the NK cell subsets in either cohort. Vaccination of individuals with an ASO3-adjuvanted pandemic inactivated split virion H1N1 vaccine has been reported to cause a slight reduction in total NK cells that remains stable for up to day 180. The frequency of the $CD56^{dim}CD16^+$cytotoxic subset of NK cells was reduced, and there was no impact on the cytokine secreting $CD56^{bright}CD16^+$ subset. These changes in NK subsets were further associated with enhanced frequencies of memory-like $NKG2C^+$ cells that were either $CD57^+$ or $CD57^-$.[187] Furthermore, poor responders to influenza vaccination expressed lower levels of NKG2C when compared to responders. Wagstaffe et al. also observed a decrease in the $CD56^{dim}$ subset and an expansion of the $CD56^{bright}$ subset, within the NK cell population, 7 days post-vaccination, when compared to baseline or at day 30 post-vaccination with trivalent IIV vaccine. The $CD56^{bright}$ cells also showed a transient increase in Ki67 expression with no changes in expression of CD57 on either the dim or bright population.[222] Protective effects of NK cells isolated after subcutaneous immunization of $Rag1^{-/-}$ mice with noninfectious virus-like particles (VLPs) containing hemagglutinin (HA) and matrix protein (M1) together or M1 alone from influenza A/PR/8/34 has been demonstrated using adoptive transfer experiments in murine models of influenza virus infection.[116] Adoptive transfer of hepatic PR8-VLP-NK cells isolated from $Rag1^{-/-}$ immunized mice to $Rag2^{-/-}$ mice conferred protection against challenge with a lethal dose of influenza virus A/PR/8/34 but splenic PR8-VLP-sensitized NK-cells conferred very low or no protection against PR8 challenge with a lethal dose. Further, the effects of these cells were abolished by administration of anti-CXCR6 antibodies suggesting that CXCR6, a chemokine receptor for CXCL16, is essential for NK-cell-mediated adaptive immunity. These results suggest that hepatic, but not splenic memory NK cells can be activated by immunization to confer

protection in the absence of influenza-specific adaptive immune responses.

The role of NK cells in influenza virus vaccination has been established, however, a role for the helper class of ILCs after vaccination is limited to a single publication to date. Intranasal administration of an inactivated monovalent influenza virus vaccine, Fluzone or trivalent 2008-09 vaccine, Flu-Laval, combined with IL-33 enhanced ILC-2 activation with a corresponding increase in mucosal B cells and antigen-specific mucosal IgA in BALF. However, in ILC-2 deficient mice influenza vaccine with IL-33 resulted in decreased expansion of B cells and increased susceptibility of the deficient mice to heterologous and homologous challenge as compared to wild-type mice. Further, the immune BALF from the donor ILC2 deficient mice failed to protect naïve mice against heterologous challenge following incubation with challenge virus, suggesting that ILC2 play protective role initiating a vaccine-specific mucosal antibody response.[223] Even though the protective effects of ILC2 after vaccination was observed after co-delivery of the influenza vaccine with IL-33, these results establish an important role for the IL-33/ILC2 axis in establishing broadly protective and long-lasting humoral mucosal immunity against influenza. Collectively, these results suggest that activation of ILC2 cells can be exploited for the mucosal delivery of influenza but not for parenteral delivery as neither enhancement of antibody responses nor ILC2 activation was observed with codelivery of influenza vaccine and IL-33 via the intramuscular route. Much work remains to be done to understand the role(s) ILCs after vaccination.

Annual vaccination and use of antivirals remain the most effective strategies against influenza infections; however, the use of antivirals has led to the emergence of drug-resistant strains, and the vaccines are not effective against emerging new strains of the influenza virus. Therefore, there is an increasing interest to find alternative strategies to combat influenza virus infections. There are substantial challenges in developing effective vaccines and antiviral agents against influenza. Emerging strains with resistance against currently approved antivirals peramivir, oseltamivir (Tamiflu®), and baloxavir marboxil (Xofluza®) complicate effective countermeasures against influenza outbreaks. More concerning is the future specter of a pandemic associated with drug-resistant highly virulent strains against which people have no preexisting immunity. Hence, there is an urgent need to develop next generation antivirals against influenza. Poor immunogenicity of HA proteins, pre-existing immune responses, original antigen sin (OAS) due to immune imprinting, constantly evolving influenza strains due to antigenic drift and antigenic shift, vaccine dose, adjuvants, and host genetics influence the magnitude, quality, and durability of vaccine-induced immune responses. Delineating the role of each of these at the molecular level using multiomic approaches will shed more light on the host and viral factors required to induce protective anti-influenza responses in the host that are effective and durable. Accumulating evidence supports a role that increased numbers of ILCs in humans are positively correlated with improved protection against influenza viruses and other viruses. Hence, induction of ILCs provides prophylactic and therapeutic benefits. Future work in defining the distinct classes of ILC responses to influenza infection and understanding how age, sex, race, and pre-existing immunity influence ILC responses should lead to development of better control measures against influenza. Although influenza virus vaccines can induce ILCs in circulation, it is not clear if prior induction/activation of ILC would enhance the breadth, depth, magnitude, and/or durability of immune responses. Delineating the roles of ILC subsets to enhance innate antiviral immunity and modulation of influenza virus-specific adaptive immune responses will enable us to develop next generation therapeutics and molecular adjuvants for influenza vaccines.

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