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IL-17 in Neonatal Health and Disease

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Abstract

Over the last few years, scientific interest in the cytokine IL-17A has intensified as its role in human health and disease has been elucidated. Discovered almost a quarter century ago, IL-17A is known to have poor biologic activity when acting alone, but attains robust actions when working synergistically with potent mediators of proinflammatory immune responses, such as IL-6 and IL-8. IL-17A is produced by specialized innate immune cells that protect host barriers from the outside world. Like sentries, these innate immune cells can “sound the alarm” through increased production of IL-17A, causing activation and recruitment of primed neutrophils and monocytes when pathogens escape initial host defenses. In this way, IL-17A promulgates mechanisms responsible for pathogen death and clearance. However, when IL-17A pathways are triggered during fetal development, due to chorioamnionitis or *in utero* inflammatory conditions, IL-17A can instigate and/or exacerbate fetal inflammatory responses that increase neonatal morbidities and mortality associated with common neonatal conditions such as sepsis, bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC). This review details the ontogeny of IL-17A in the fetus and newborn, discusses how derangements in its production can lead to pathology, and describes known and evolving therapies that may attenuate IL-17A-mediated human conditions.

Keywords

IL-17; neonate; sepsis; patent ductus arteriosus; necrotizing enterocolitis; bronchopulmonary dysplasia; retinopathy of prematurity

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Introduction

First discovered in 1993[1], interleukin (IL)-17A (aka CTLA8) belongs to a family of six IL-17 cytokines (IL17A-F) and demonstrates diverse biologic functions[2–4]. In general, IL-17A is produced by a wide spectrum of innate immune cells that are strategically located in barrier tissues that protect the human body from the outside environment. If breached by pathogenic microorganisms, these specialized immune cells become key instigators of early innate immune responses that may negatively impact the future health of the host[5]. IL-17A-mediated fetal inflammatory responses can manifest in childhood with debilitating disease, including increased severity of respiratory syncytial virus (RSV) infection[6,7], asthma exacerbations[8], and Crohn's and inflammatory bowel disease[9–11]. In adults, IL-17A is strongly associated with disease severity and progression of psoriatic responses in the skin[12], depression[13,14], and post-ischemic phases of stroke[2,15–19]. This review will detail our current understanding of IL-17A and its association with common, debilitating neonatal conditions. In addition, the ontogeny of IL-17A-producing immune cells will be discussed, including changes in lymphocyte composition with fetal and neonatal maturation. Lastly, novel pharmacologic interventions, which target IL-17A pathways to alleviate disease will be addressed.

Cells that produce IL-17

Differentiation of naïve T lymphocytes into distinct effector T helper (Th) cells is essential for proper adaptive immune responses[20]. Naïve T helper cells are currently known to differentiate into: (i) Th1 cells, which are vital for cell-mediated immunity and have a key role initiating early resistance to pathogens, (ii) Th2 cells, which stimulate antibody-mediated responses and promote immune tolerance rather than defend against microbial infection, (iii) regulatory T (Treg) cells, which suppress immune activity, and (iv) Th17 cells, which are important in the clearance of extracellular bacteria through IL-17A production[20–23].

Th17 cells generate proinflammatory cytokines including IL-17A, IL-22, IL-26, tumor necrosis factor-α (TNF-α), chemokine (C–C motif) ligand 20 (CCL20)[24], and granulocyte macrophage colony stimulating factor (GM-CSF)[11,25]. Differentiation of Th17 cells from naïve T cells is stimulated by proinflammatory cytokines, including IL-1β, IL-6, IL-21, and IL-23, in coordination with transforming growth factor-β (TGF-β) in a RAR-related orphan receptor-γ t (RORγt) – dependent manner[11,26–29]. Whereas RORγt triggers the development of Th17 cells and IL-23 induces their maturation and expansion, TGF-β promotes Th17 cell differentiation in a dose-dependent manner[11]. At low concentrations TGF-β activates RORγt expression and Th17 differentiation, while high TGF-β concentrations stimulate forkhead box P3 (FOXP3) and Treg formation[11,30]. Because of their opposing immune responses, the Th17/Treg balance is crucial for maintaining immune homeostasis. However, in extreme inflammatory or infectious conditions, the formation of Treg lymphocytes can become defective, thereby permitting these cells to phenotypically transform into Th17-like cells[3,31,32] through a process referred to as *plasticity* or *transdifferentiation*[28].

The clinical importance of Th17 cells is apparent in preterm neonates with chorioamnionitis exposure. Chorioamnionitis is a pathologic state of inflammation of the fetal membranes and is associated with increased cord blood quantities of IL-17A-producing Th17 lymphocytes[33] and Tregs that exhibit Th17-like phenotypes[4]. Because a common lineage is shared by Tregs and Th17 cells via developmental regulation of the transcription factor RORγδ[34], extremely high levels of RORγδ expression during inflammation contributes to loss of Treg anti-inflammatory function and facilitates the conversion of Tregs to Th17 subtypes[35,36]. Likewise, cord blood T lymphocytes with effector memory (TEM) cells can also express Th17-related markers and produce IL-17A under inflammatory conditions[37]. Increased concentrations of IL-17A during early inflammatory conditions enables Th17 cells to assume Th1-like effector functions, thereby expediting the recruitment of stimulated neutrophils to the site of infection and activating of regional macrophages to promote pathogen clearance[20, 38, 39]. In the most extreme preterm neonates, however, clinically relevant deficiencies of Th17 and Th1 cellular responses, due to impaired induction of the p40 subunit common to IL-12 and IL-23, leads to decreased concentrations of these interleukins[21,40,41]. Reductions in IL-12 and IL-23 in this vulnerable patient population can heighten risks of early onset neonatal sepsis despite the presence of higher concentrations of other pro-inflammatory cytokines[21,41]. Alternatively, permutations in the normal fetal immune development towards a proinflammatory Th17 response, instead of a tolerant Th2 response, may initiate fetal inflammatory pathways that result in debilitating chronic diseases in the neonatal period or throughout a person's lifespan[33].

IL-17A is also produced by γδT cells, lymphoid-tissue inducer (LTi) cells[42], γδT cells[43], invariant natural killer T (iNKT) cells[44], natural killer (NK) cells[45], neutrophils[46], Paneth cells[47,48], microglia[49], and innate lymphoid cells group 3 (ILC3)[2,5]. These innate immune cells are strategically located in barrier tissues that protect the human body from the outside environment and provide vital host protections against foreign threats[5]. Serving primarily as sentinels, these innate immune cells can rapidly (within 4 to 8 hours) increase IL-17A production after a pathogenic challenge, luring primed neutrophils to inflamed sites to expedite the death and clearance of offending microorganisms[5].

Many of these innate immune cells constitutively express the cell surface receptors IL-1R1 and IL-23R[5,50–53] and, therefore, achieve maximal IL-17A production following exposure to both IL-1β and IL-23 cytokines[5,54]. Given the close proximity of these immune cells with the outside environment, commensal microorganisms that comprise the host's microbiome may induce IL-1R1 expression on their cell surface to enhance the biological effects of IL-17A[5,50]. As a result, this relationship may enable this group of innate immune cells to 're-shape' the gut microbiota as necessary to maintain a healthy physiologic state through increased production of IL-17, IL-22, and antimicrobial peptides that target specific groups of bacteria[5]. Dysregulation of these cells, however, may also ignite or aggravate chronic inflammatory and/or autoimmune conditions, becoming clinically relevant at any age[5,54,55].

IL-17 function

IL-17A has diverse proinflammatory effects but may be poorly active when operating alone[3,56]. IL-17A must therefore synergize with other proinflammatory cytokines, such as

TNF-α, IL-1β, IL-22, IFN-γ, and GM-CSF, to generate high levels of IL-6 and IL-8, which are potent mediators of host immune responses[4,57]. By bolstering granulopoiesis, IL-17A promotes the recruitment of large numbers of activated neutrophils to inflamed sites[58], where neutrophil cytotoxic[59] and phagocytic activities[60] are enhanced, thereby providing an amplification loop for neutrophil proinflammatory responses[61]. IL-17A also enhances the recruitment and survival of macrophages[4,62], stimulates the production of antimicrobial proteins and peptides from a variety of immune and non-immune cells[4,34,58,63,64], and promotes the secretion of IL-2 from T helper cells, which accelerates the proliferation of Treg and conventional T lymphocytes[4,65].

In general, IL-17A is important in combating extracellular pathogens including Gram-positive, Gram-negative, and fungal microbes[40,66,67]. Neonates demonstrate reduced baseline production of IL-17A compared to adults, which may diminish neonatal immune responses and contribute to their increased susceptibility to infection by group B *Streptococcus*, *Escherichia coli*[40], and *Klebsiella pneumoniae*[20,68]. Because IL-17A levels are similar between preterm and term neonates, its production is not dependent upon immune maturation or advancing gestational age[20]. In mice, IL-17A-producing γδT cells originate only within the embryonic thymus beginning at embryonic day 15[69]. This period corresponds to approximately 24-28 weeks' gestation in humans, which is associated with the highest risks of IL-17A-associated neonatal pathology including sepsis, necrotizing enterocolitis, and brain injury[70]. Although other factors contribute to the heightened susceptibility to pathology at this developmental stage, there is burgeoning evidence that IL-17 plays a prominent role in neonatal pathology.

The role of IL-17 in neonatal sepsis

The capacity for the host to respond to sepsis is strongly influenced by the patient's developmental age[71–76]. It is commonly accepted that IL-17A is important for neonatal host defense and protective immunity. Physiologic levels of IL-17A produced by type 3 innate lymphoid cells (ILCs) improved resistance to infectious challenge in healthy neonatal mice via microbiota-driven granulocyte-colony stimulating factor (G-CSF) production and neutrophil recruitment[77]. Similarly, reduced whole blood IL-17A in human preterm neonates was associated with an increased risk of bacteremia[20]. IL-17A produced by intestinal γδT cells plays an important role in maintenance and protection of epithelial barriers in the intestinal mucosa[78]. In contrast, excessive production of IL-17A during disease can be detrimental to the host and lead to organ injury and death. Emerging information implicates pathologic IL-17A signaling during experimental inflammation[79], sepsis[79–81], NEC[82], acute lung injury[83,84], and brain injury[15,17,85]. The deleterious role of excessive IL-17A, produced by many different cellular sources including γδT cells that can rapidly produce IL-17A via an IL-1R1-dependent pathway[50,86], is well established in the pathogenesis of severe inflammatory and ischemic-injury models including sepsis[15,80,87]. IL-17A mRNA was increased in the intestine following necrotizing enterocolitis in baboons[88], and excessive IL-17A impaired enterocyte tight junctions, increased enterocyte apoptosis, and reduced enterocyte proliferation in murine NEC[82]. Thus, excessive IL-17A leads to decreased intestinal integrity that, in turn, increases the likelihood of developing bacteremia, organ injury, and sepsis.

Mortality to murine neonatal sepsis was dependent upon excessive and deleterious IL-17A production by γδT cells in the lung and gut. Sepsis mortality was significantly attenuated with antibody-mediated transient IL-17 receptor (IL-17R) blockade. Notably, pathologic IL-17A production was dependent upon IL-1R1-mediated signaling and was heavily augmented by IL-18[19]. The importance of discovering the contribution of IL-18 to pathologic IL-17A production in neonates is underscored by studies that showed serum IL-18 varies inversely with age among children[89], and preterm neonates exhibited elevated blood IL-18 levels when uninfected, that rose further with infection[90]. Taken together, these data support the paradigm of a developmental age-related propensity to pathologic IL-17A production with stimulation[19,82,85].

The role of IL-17 in bronchopulmonary dysplasia

BPD develops in very low birthweight (VLBW; < 1500 grams at birth) infants secondary to abnormal growth of distal lung structures and tissue damage caused by the combination of the underlying disease pathology and injury caused by standard ventilation techniques that are lifesaving in this patient population[91–95]. Neonates destined to develop BPD demonstrate increased numbers of circulating neutrophils and macrophages, in addition to higher concentrations of leukotrienes, endothelin-1[96], IL-6[97], and IL-17A[91,98]. New studies confirm an increased number of TEMs, progenitor Th17, mature Th17, and IL-17$^+$ Treg lymphocytes in placental cord blood samples of extremely preterm human neonates who developed BPD compared to controls[98]. These same investigators previously employed a murine model of *in utero* infection to demonstrate enhanced lung expression of Th17 cells exhibiting intense proinflammatory properties resistant to Treg-mediated suppression[99,100]. The rise in Th17 cells resulted from heightened RORγt expression and transformation of Tregs into Th17-like cells via RORγt-mediated mechanisms. This phenotypic alteration of Tregs therefore contributes to both compromised Treg suppressor functions and perpetuation of Th17-mediated proinflammatory responses. The authors concluded that chorioamnionitis-mediated Th17-biased proinflammatory responses in the preterm infant attenuates immune programing during a critical developmental window resulting in “dysfunctional immune priming”. This immune modification ultimately leads to uncontrolled inflammatory processes and tissue damage that increases the risks of morbidity and mortality associated with BPD and chronic lung disease[33].

IL-17A induces airway epithelial cells to secrete chemokines and cytokines that are also important in protecting the lung against extracellular infections including: (i) CXCL1, CXCL2, IL-6, IL-8, and GM-CSF, which promote neutrophil differentiation in the bone marrow and recruitment of activated cells to the lung epithelium[101–103], (ii) CCR6, which is associated with trafficking of T, B, and dendritic cells to epithelial sites[104], (iii) IL-19, which can influence the differentiation of T helper cells into Th2 cells[105], (iv) CCL28, which enables the migration of IgE-secreting B cells[106], and (v) Th1 cell-like chemoattractants, which facilitate more effective pathogen clearance when necessary[107,108]. Furthermore, IL-17A contributes to the maintenance of a healthy respiratory epithelial border by promoting the production of adhesion and cell junction molecules through induction of ICAM-1 by airway epithelial cells[11,106,109]. Therefore, tight regulation of IL-17A appears vital for proper maintenance of the respiratory epithelial border, whereas altered production

can injure developing lung tissue resulting in detrimental pulmonary pathologies in our youngest patients.

The role of IL-17 in necrotizing enterocolitis

Necrotizing enterocolitis is a life-threatening gastrointestinal ailment that affects up to 5% of all VLBW infants admitted to the neonatal intensive care unit[110]. Devastatingly, 10% to 50% of neonates diagnosed with NEC will succumb to their illness, while one-third will suffer debilitating long-term complications, such as short-gut syndrome[111]. NEC onset is epidemiologically linked to a "window of susceptibility" with symptoms typically occurring in VLBW infants around 30-32 weeks' corrected gestational age (GA). Therefore, the youngest gestational-aged neonates will develop disease later in life than those who are older at birth[112,113]. Because the incidence of NEC is also inversely proportional to GA at birth[114], immature host defenses are thought to contribute to its pathogenesis[115]. Heightened baseline expression of Toll-like receptor (TLR)-4 and STAT3 in the intestinal mucosa of premature compared to full-term neonates[116,117], in addition to changes in microbial colonization and maturation of immune responses have been implicated in this association[115,118].

Immune homeostasis in the gut is normally maintained by the production of low-levels of IL-17A by resident Th17 lymphocytes and ILCs[119]. Secretion of IL-17A is influenced by the release of IL-1β and TGF-β from intestinal epithelial cells and functions to inhibit excessive bacterial growth in the gastrointestinal tract[6,120]. Th17 cells are also directly regulated by local Treg lymphocytes to ensure IL-17A is not disproportionally produced under basal conditions[28]. Treg control of Th17 cells is particularly important during the formation of the intestinal microbiome following birth to prevent excessive proinflammatory immune responses as the infant is newly exposed to trillions of microorganisms[28]. Disruption of the normal establishment of the neonatal microbiome through exposure to intrapartum or postpartum antibiotics, however, can alter the proper functioning of ILCs and Th17 lymphocytes. This modification can attenuate neutrophil homeostasis through altered production of G-CSF and IL-17A, which increases the neonate's susceptibility to NEC and/or sepsis by enabling the translocation of virulent microorganisms[118,119].

During a pathogenic challenge or inflammatory trigger, expression of TLR-4 by the intestinal mucosa is upregulated and accompanied by a notable rise in serum concentrations of IL-6 and prostaglandin E2 (PGE2)[6,121,122]. Together, these adaptions result in preferential differentiation of Th17 lymphocytes with a coinciding drop in Treg numbers[82,111]. Excessive IL-17A concentrations promote mucosal injury that is commonly associated with NEC, including impaired enterocyte tight junctions, increased enterocyte apoptosis, and reduced proliferation of enterocytes[82]. Hence, blocking IL-17A or inducing Treg lymphocyte differentiation can decrease or reverse NEC severity[82].

In summary, specific T helper subsets are controlled by interactions between commensal microbes and mucosal immunity[123]. Tonic TLR-4 activation by pathogenic bacteria leads to exaggerated recruitment and activation of Th17 cells but suppression of Tregs, which can alter the normal balance of gut immunity and initiate pathologic responses commonly

associated with necrotizing enterocolitis. Although specific mechanisms involved in IL-17A-mediated NEC remains elusive, continued investigation of this pathway remains intriguing. A better understanding of IL-17A-mediated actions may lead to the development of novel pharmacologic therapies or change standard clinical management to improve patient outcomes resulting from necrotizing enterocolitis.

The role of IL-17 in retinopathy of prematurity

Retinopathy of prematurity is a common, biphasic vasoproliferative disorder of the developing retina that occurs in VLBW, critically ill, and severely growth restricted infants[124]. ROP consists of initial blunting of retinal vascular growth followed by retinal vessel proliferation around 4-6 weeks of age[124]. The incidence of ROP is inversely related to gestational age, with increased risk and severity of disease in the youngest, sickest preterm infants. Recently, pre- and post- natal inflammatory conditions, including chorioamnionitis and neonatal sepsis, were shown to be positively correlated to ROP development[125,126]. Alarmingly, ROP remains a major cause of blindness in infancy despite improved screening and treatment options[90].

Fetal inflammatory responses have recently been identified as an important instigator of ROP and results from greatly increased levels of IL-6[127], but reduced concentrations of IL-17A and IL-18, shortly after birth[90]. Diminished IL-17A levels in preterm infants during critical time points may be responsible for the arrest of retinal angiogenesis, while also predisposing the infant to late onset sepsis[90].

During retinal neovascularization, however, resident immunocompetent cells of the retina, or microglial cells, secrete proinflammatory cytokines, like IL-17A, when chronically activated. These inflammatory signals stimulate vascular endothelial growth factor (VEGF) production from neuroglial cells, such as Müller and ganglion cells, to promote aberrant growth of retinal vessels [49,124,128–131]. This abnormal growth is the hallmark of ROP and can be attenuated in murine models by IL-17A neutralizing antibodies through modulation of the VEGF pathway[132]. In knockout models of IL-17A, inflammation was also alleviated and tissue repair facilitated by biasing macrophage polarization towards a M2 phenotype. This macrophage transformation leads to the production of high levels of IL-10, which dampens pro-inflammatory responses to enable wound healing[132–135]. In contrast, IL-17 drives macrophage differentiation towards a M1 subtype, facilitating secretion of TNF-α, IL-1β, and IL-6 to enhance pro-angiogenic VEGF pathways and ROP[132].

Currently, anti-VEGF agents are routinely used to treat vasoproliferative diseases, including ROP[136]. However, a substantial number of eyes do not respond adequately to these specific therapies[124,137–139]. Development of innovative therapies based on IL-17A neutralization may be an effective treatment for ROP by attenuating microglial cell density, Müller cell gliosis, and ganglion cell loss[124].

The role of IL-17 in the patent ductus arteriosus

The ductus arteriosus (ductus; PDA) is vital to the fetus allowing blood to be shunted away from the fetal lungs and into the systemic circulation. In term infants, the ductus constricts

after birth due to an increase in tissue oxygenation and decreased levels of prostaglandin[140,141]. The internal layer of the ductus becomes hypoxic with ductal constriction leading to neointimal cushion formation and extensive vascular remodeling[140,141]. This mechanism of vascular remodeling is similar to the development of atherosclerosis seen after vascular wall injury[140,142]. Cytokines, such as IL-17, play a role in vascular remodeling in atherosclerosis and may similarly mediate remodeling of the ductus[143,144]. IL-17 has also been shown to affect the aorta (large vessel) and the coronaries (small vessels) in different ways revealing that IL-17 has variable expression in different tissues[145]. Although IL-17 plays a role in vascular remodeling and in expression of prostaglandin, its role in ductal closure is presently unknown.

In contrast to term infants, the ductus may remain patent for a prolonged period in preterm infants, which can result in a shunt that leads to pulmonary over-circulation and systemic hypoperfusion. The ductus in a premature infant is thinner which can decrease vasoconstriction requiring other means of closure including platelet aggregation and thrombus formation[140,142]. IL-17 increases platelet activation and platelet adhesion which may be needed for ductal closure in the premature infant[142,146]. In addition, premature infants are more likely to have a symptomatic PDA if there is a history of chorioamnionitis[147] or history of postnatal inflammation[148] including early onset and late onset sepsis[149,150]. Of note, IL-17 is an important cytokine in inflammation and it in some cells it has been shown to stimulate the increase of prostaglandins, a potent vasodilator of the ductus[146,149,151]. The mechanistic interplay between prostaglandin and IL-17 may affect ductal closure in the setting of sepsis or other significant inflammatory states. IL-17 concentration at physiologic levels may promote vascular remodeling and platelet aggregation assisting ductal closure. However, the concentration at higher levels may induce pathologic ductal dilation due to its effect on prostaglandin production which could be the etiology of inflammatory associated symptomatic PDA. Thus, therapeutic approaches that target attenuation of pathologic IL-17 production require further study prior to implementation in the preterm population.

Pharmacologic interventions targeting IL-17 pathways

Presently, 2 monoclonal antibodies directed against IL-17A and one against the IL-17A receptor have completed phase III human trials. These agents include: (i) Ixekizumab (LY2439821), a humanized IL-17A specific antibody, (ii) Secukinumab (AIN457), a fully human IL-17A specific antibody[152], and (iii) Brodalumab (AMG 827), an IL-17A specific antibody[152]. Because the inhibition of IL-17A may increase the risks of extracellular bacterial[153] and/or fungal infections, careful attention must be paid when this cytokine is specifically targeted[152]. Adult and animal studies provide important information as we ponder the use of these therapies in neonatal patients. However, our understanding of IL-17A pathways in term and preterm infants remains incomplete and is a barrier to clinical trials that target IL-17 signaling in this unique population.

Conclusion

IL-17 is important for immune surveillance and protection of the neonate. Conversely, pathologically-elevated IL-17 plays a deleterious role in many devastating inflammatory diseases that occur in neonates including sepsis, NEC, and ROP. Targeting excessive IL-17 signaling in the setting of these diseases represents a novel therapeutic strategy that brings hope for improved outcomes in this vulnerable population.

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Abbreviations

BPD	Bronchopulmonary dysplasia
CLD	Chronic lung disease
FOXP3	Forkhead box P3
GA	Gestational age
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte-macrophage colony stimulating factor
IL	Interleukin
ILC	Intestinal group 3 innate lymphoid cell
iNKT	Invariant natural killer T cells
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
PGE2	Prostaglandin E2
RDS	Respiratory Distress Syndrome
ROP	Retinopathy of prematurity
RORγt	Retinoic acid receptor-related orphan receptor-gamma t
RSV	Respiratory syncytial virus
TEM	T lymphocytes with effector memory cell
TGF-β	Transforming growth factor β
Th	T helper lymphocyte

TLR	Toll-like receptor
VEGF	Vascular endothelial growth factor
VLBW	Very low birth weight

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