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Necrotizing Enterocolitis and the Gut-Lung Axis

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Abstract

The recently recognized connection between the gut microbiota and pulmonary disease has been termed the gut-lung axis. However, broader connections link the gut and the lungs and these organ systems are tightly interrelated in both homeostasis and disease. This concept is often ignored in the compartmentalized treatment of pulmonary or gastrointestinal disease. In newborns, the most severe gastrointestinal complication of prematurity, necrotizing enterocolitis, and the most severe pulmonary complication, bronchopulmonary dysplasia, both produce significant systemic morbidity. In this review, we highlight the often neglected pathophysiology of the gut-lung axis contributes to increased risk of bronchopulmonary dysplasia in premature infants with necrotizing enterocolitis.

Introduction

Necrotizing enterocolitis (NEC) continues to be a major cause of mortality and longer-term morbidity in very preterm infants admitted to neonatal ICUs worldwide. In the Vermont Oxford Network, of 473,895 very low birth weight infants (≤1500g or <29w GA) born 2006-2017 and admitted to 820 US centers, 36,130 (7.6%) were diagnosed with NEC, of which 58.3% were medical NEC and 41.7% were surgical NEC. In more recent years, the incidence of medical NEC was 3%, and of surgical NEC was 3.1% (1). In the NICHD Neonatal Research Network consisting of larger academic centers in 2012, 9% of the extremely preterm infants (22-28w GA) developed NEC (2). Many infants with surgical NEC are often ventilator-dependent, and are more likely to be diagnosed with bronchopulmonary dysplasia (BPD) and impairment of growth (3). It is evident that with more extreme immaturity, the risks of both NEC as well as respiratory distress syndrome and subsequent BPD are higher. The term “gut-lung” axis is often used to suggest how alterations in the gut microbiota may predispose to lung disease (e.g asthma and allergic airway disease)(4-7), but this is not the only type of interaction between these two vital systems that share a common embryonic origin. There are physiological interactions

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between therapeutic respiratory interventions and the gut, and between gastrointestinal interventions and the respiratory system. There are also more complex molecular and cellular interactions between the gut and the lung, as well as between pathophysiology in either the gut (NEC, spontaneous intestinal perforation) and lung (respiratory distress syndrome, BPD). The following is an overview of such potential and proven interactions. First, the effects of respiratory management and of lung disorders on the risk of NEC will be discussed. Next, the effects of NEC on the lung will be described, with a consideration of potential molecular and cellular mechanisms.

Effects of respiratory management on risk of NEC:

Respiratory management in preterm infants generally includes monitoring of gas exchange (e.g. pulse oximetry, blood gas analysis) and support (e.g. oxygen, CPAP, non-invasive or invasive positive pressure mechanical ventilation). The magnitude of gas exchange as well as that of respiratory support provided may impact the risk of NEC.

It is likely that oxygenation needs to be above a certain threshold and prolonged hypoxemia may increase the risk of NEC. In a meta-analysis of individual participant data from five randomized controlled trials enrolling preterm infants <28w GA and evaluating a pulse oximeter (SpO_2) target range that was lower (85%-89%) vs higher (91%-95%), it was noted that 484 of 2433 infants (19.9%) died in the lower SpO_2 target group versus 418 of 2440 infants (17.1%) in the higher SpO_2 target group (risk difference, 2.8% [95% CI, 0.6% to 5.0%]; RR, 1.17 [95% CI, 1.04 to 1.31], P = .01) (8). Importantly, severe NEC occurred in 227 of 2464 infants (9.2%) in the lower SpO_2 target group and 170 of 2465 infants (6.9%) in the higher SpO_2 target group (risk difference, 2.3% [95% CI, 0.8% to 3.8%]; RR, 1.33 [95% CI, 1.10 to 1.61], P = .003) (8). Hence, it may be advisable to maintain SpO_2 in the target range of 91-95% and not lower while the preterm infant needs oxygen supplementation.

However, SpO_2 target range may not correlate well with splanchnic tissue oxygenation (StO_2) measured with near-infrared spectroscopy. In a prospective study of 92 preterm infants (<32w GA and <1500g birth weight), mean abdominal StO_2 during the first postnatal week in those who did not NEC was higher than in those who developed NEC (77.3% ± 14.4% vs 70.7% ± 19.1%, respectively, p = 0.002) (9). StO_2 ≤56% identified preterm infants progressing to necrotizing enterocolitis with 86% sensitivity, 64% specificity, 96% negative predictive value, and 30% positive predictive value (9). By logistic regression, StO_2 ≤56% was independently associated with increased risk of NEC (OR 14.1; p = 0.01). Infants with NEC also had more variation in StO_2 both during and after feeding in the first 2 weeks of life (9). In another study of 52 extremely preterm infants of whom eight developed NEC at a median age of 15 days (range 6-35), infants with a mean StO_2<30% had a higher risk for developing NEC compared with those with StO_2>30% (crude risk ratio 5.25; 95% CI [1.19-23.01]) (10). Small for gestational age, gestational age, birth weight, postnatal age did not affect the results (10). In another observational study, ten infants who developed NEC at a median age of day 13 (range 4-43d) were compared to 20 matched controls, and Infants with cerebral rSO_2 <70% within the first 48 h after birth developed NEC significantly more often than infants with cerebral rSO_2 ≥70% (odds ratio 9.00 (95% CI 1.33-61.14) (11). Intestinal fractional tissue oxygen extraction was higher in infants who developed NEC

compared to controls during the last near-infrared spectroscopy measurement at median 2 days (range: 1-7) before NEC onset (median 0.65 vs. 0.44) (11). However, other studies have revealed comparable abdominal StO_2 and splanchnic-cerebral oxygenation ratio in patients with and without NEC (StO_2: 47.3 [20.4] vs. 50.4 [17.8], $p = 0.59$, splanchnic-cerebral oxygenation ratio: 0.64 [0.26] vs. 0.69 [0.24], $p = 0.51$) (12). Based on the available data, it may be prudent to maintain abdominal StO_2>56% and cerebral rSO_2 >70%, with intestinal FTOE <0.50.

In addition to oxygen therapy, many preterm infants also receive either CPAP/nasal positive pressure ventilation or intubation followed by mechanical positive pressure ventilation. It has been shown that infants with lower birth weight and respiratory morbidity (as measured by mean airway pressure x FiO2) are at higher risk not only of death or BPD, but also of NEC (13). It is possible that more extreme immaturity as well as shared genetic predisposition increase the risk of NEC in the infants who also have worse lung disease. One of the common issues noted with use of CPAP is abdominal distension (“CPAP belly”) (14), usually due to increased gas swallowing or ingress via the esophagus secondary to the airway positive pressure. This may be especially noticeable in infants on non-invasive intermittent positive pressure ventilation, as the positive pressure breaths may force more gas down the gastrointestinal tract. As one of the early signs of NEC is abdominal distension, clinicians may investigate infants with such CPAP-induced abdominal distension for NEC. Although CPAP-induced gaseous distension has not been shown to result in NEC (14, 15), radiologic features of NEC such as pneumatosis intestinalis may sometimes be difficult to exclude in the presence of foamy stool in the intestines, and there is the risk of occasional diagnostic error with false positive diagnosis of NEC. This fear of NEC (NEC-phobia) due to CPAP belly may result in prolongation of time to full feeds and a longer duration of parenteral nutrition (16).

A direct effect of positive end expiratory pressure (PEEP) or mean airway pressure (MAP) on cardiovascular variables such as mean arterial pressure, cardiac output, and regional blood flow to the intestines (e.g. superior mesenteric arterial flow or portal venous flow) may also be relevant to NEC, although conclusive data are lacking in the neonatal literature. Mechanical ventilation with high positive end-expiratory pressure has been found to decrease splanchnic perfusion in adults (17). Spontaneous breathing during ventilator support has been shown to improve systemic blood flow and gastrointestinal and splanchnic perfusion(17). At lower intestinal perfusion pressures (e.g. as may occur with hypotension), even moderate levels of PEEP impair local blood flow enough to cause intestinal ischemia in pig models (18). Animal studies have also shown alterations in gut mucosal and muscularis flow with the use of higher peak inspiratory pressures (19). Hence, it is preferable to permit spontaneous breathing (avoiding muscle relaxants) and use sufficient but not excessive PEEP to maintain lung inflation and functional residual capacity (FRC), with limited peak inspiratory pressures, to avoid over-distension and reduction in cardiac output that may impair gut perfusion, potentially increasing the risk of NEC. In the setting of endotoxemia (as may happen with NEC), mechanical ventilation with PEEP increases abdominal edema and inflammation (increased interleukin-6 and tumor necrosis factor-alpha) in the intestine and liver by increasing systemic capillary leakage and impeding abdominal lymph drainage

(20). Therefore, mechanical ventilation should be judiciously titrated to achieve adequate gas exchange with the least pressures.

Intestinal microcirculation is also severely compromised by hemodilution (21). Severe anemia is associated with an increased risk of NEC (22), and there is evidence from animal models that intestinal injury worsens with increasing severity and duration of anemia prior to transfusion(23). Although recent data from transfusion thresholds in preterm infants do not suggest any differences in NEC, it may be preferable to maintain sufficient systemic oxygenation (SpO_2), intestinal oxygenation as monitored by NIRS (StO_2), and adequate gas exchange capacity by avoiding severe anemia.

It is not just management of gas exchange and oxygen transport that impacts the risk for, or the diagnosis of NEC. Pharmacological management of respiratory disorders may also modulate the risk of NEC. Infants with respiratory distress soon after birth are often treated with antimicrobials, as the possibility of pneumonia /sepsis (such as with group B streptococci or *E. coli*) cannot be excluded. This antimicrobial therapy may alter the neonatal microbiome at multiple sites including the gut and lung, predisposing to subsequent NEC as well as BPD. The prolonged use of empiric antibiotics is associated with increased rates of NEC and death in extremely low birth weight infants (24). Some of these adverse effects of antimicrobials may result from alterations of the microbiome (dysbiosis). Dysbiosis in the gut has been observed in pre-diagnosis samples from infants with established NEC (25, 26). Fecal microbiome from preterm infants with NEC have increased relative abundances of Proteobacteria and decreased relative abundances of Firmicutes prior to NEC onset (26), similar to what has been observed in the airway microbiome of BPD (27). It is known that the lung microbiome plays an important role in the maturation and homeostasis of lung immunity(28). Infectious organisms such as *Ureaplasma* spp. have been associated not only with increased risk of BPD in infants needing prolonged mechanical ventilation (29-31) but also with a higher risk of NEC(32). NEC was 2.2-fold higher in *Ureaplasma*-positive (12.3%) than *Ureaplasma*-negative (5.5%) infants <33 wk (OR 2.43; 95% CI 1.13–5.2; $p = 0.02$) and 3.3-fold higher in *Ureaplasma*-positive (14.6%) than *Ureaplasma*-negative (4.4%) infants ≤28 wk (OR 3.67; 95% CI 1.36–9.93; $p = 0.01$) (32), though it is not clear if the higher risk of NEC is due directly to inflammation induced by *Ureaplasma* infection, or because of more severe lung disease. Systemic postnatal corticosteroids are occasionally used to prevent BPD, but there is no evidence to suggest that they affect the rate of NEC (33). It is possible that other medications (e.g. diuretics, bronchodilators, methylxanthines) used for respiratory indications may secondarily have effects on the gut, by modification of intestinal perfusion, motility, or the microbiome. Caffeine (or theophylline) is frequently used to stimulate the respiratory drive and reduce apnea in preterm infants. Retrospective studies have suggested caffeine may either increase NEC(34) or not influence the rate of NEC (35, 36) – the large Caffeine for Apnea of Prematurity (CAP) trial did not show a difference in rate of NEC between caffeine and placebo group (6.3% vs. 6.7%, OR 0.94 (0.65-1.34) adjusted for center and patient characteristics) (37).

Effect of NEC on the lung:

A multicenter retrospective analysis of extremely low birth weight infants in the NICHD Neonatal Research Network indicated that infants with surgical NEC (57%) but not medical NEC (51%) were more likely to have received a diagnosis of BPD, as compared to infants without NEC (43%; p=0.003 for surgical NEC vs. no NEC, and p=0.09 for medical NEC vs. no NEC)(3). A more recent larger multicenter cohort from Spain with 25,821 infants <32w GA also found that infants with surgical NEC had a higher odds ratio (OR) 2.00 (95% CI 1.71-2.33) for BPD after adjustment for gestational age, compared to infants without NEC, and that infants with medical NEC also had increased risk for BPD but to a lesser extent (OR 1.44 (95%CI 1.18-1.77)) (38). It is relatively common for neonatologists to observe that even in infants who do not have severe lung disease to begin with, an episode of necrotizing enterocolitis often leads to multiorgan dysfunction and abdominal distension, both of which cause a significant decline in gas exchange, resulting in the need for a higher oxygen concentration and higher mechanical ventilation settings that often further injures the lungs (ventilation-induced lung injury), contributing to BPD. It is also likely that translocation of gut bacteria through the compromised intestinal wall leads to systemic inflammation and induces a dysbiosis of the lung microbiome.

The mechanisms by which gut necrosis and intestinal inflammation in a preterm infant lead to lung injury, inflammation, or BPD have not been fully defined. There is data from adult models of gut injury that can possibly be extrapolated to the neonatal NEC-lung axis. There is cross-talk and collaboration between the gastrointestinal tract and respiratory tract at multiple levels (microbiome, immunity, metabolites etc.). The intestinal microbiome and its dysbiosis modulates the systemic immune response, by alteration of dendritic cell priming of T-cell subsets, changes in levels of cytokines, and perhaps changes in activation of other immune cells (39). The “intestinal cross-talk” between the intestinal epithelium, immune cells, and microbiome is normally in a state of homeostatic balance (39, 40), but during the early postnatal period in a preterm infant, intestinal epithelial injury, an immature immune system and dysbiosis may combine to a very dysregulated cross-talk in this three-way partnership. It is also possible that the “gut-lymph” theory is relevant to neonatal lung injury during NEC – macrophages and immune cells in the intestine kill the majority of translocating bacteria but surviving bacteria and their fragments/peptides may reach the lungs and activate alveolar macrophages, leading to lung injury (39, 41). Thoracic lymph duct ligation before intestinal ischemia-reperfusion has been shown to reduce pulmonary neutrophil recruitment and plasma extravasation, associated with high levels of tumor necrosis factor in the lymph but not in serum (42). It may be that microbial products rather than circulating microbes are relevant. It has been observed that gut microbiome-derived short-chain fatty acids such as propionate are regulate lung inflammation in mice(43).

There are multiple potential mechanisms by which the gastrointestinal microbiota can regulate lung immunology, and thereby inflammation and pathogenesis of BPD. Toll like receptors (TLRs) are pattern recognition receptors that recognize microbial products, and multiple immune processes, including microbiota-mediated activation of antigen-specific CD4 and CD8 T cells, T-cell priming, dendritic cell (DC) migration, microbe-specific antibodies, and inflammasome regulation are all regulated by TLRs (39). TLR4 signaling

has been shown to mediate lung injury and inflammation following intestinal ischemia-reperfusion (44). T cell homing in a tissue-specific manner is induced by direct interaction with mucosal DCs, and T cell homing to the GI tract involves induction of α4β7 and CCR9 by Peyer's patch and mesenteric lymph node (MLN) DCs in a retinoic acid-dependent manner, but it has also been shown that lung DCs also up-regulate the gut-homing integrin α4β7 in vitro and in vivo, and induce T cell migration to the GI tract in vivo (45), indicating that mucosal cross-talk is mediated by DCs. Another mechanism by which lymphocytes may be recruited to multiple mucosal sites is by induction of CCL20 (the ligand for CCR6, which mediates homing of both CD4 T cells and DCs) in either intestinal epithelial or lung epithelial cells by pro-inflammatory signals or TLR agonists (39, 46).

In addition to alterations in adaptive immunity, other pathophysiologic changes may also negatively impact the lung in the setting of ischemic gut injury as seen in NEC. Animal models indicate that neutrophil macroaggregates triggered by dying platelets promote widespread pulmonary thrombosis in the setting of gut ischemia, causing occlusion of pulmonary arteries, veins, and the microvessels (47). Depletion of alveolar macrophages has also been shown to reduce acute lung injury following intestinal ischemia-reperfusion (48).

The mechanisms just listed have been mostly demonstrated in adult animal models of gut ischemia. How relevant are they to the preterm infant with NEC, and what differences in mechanisms may be observed? It has been shown that NEC is associated with a systemic pro-inflammatory state with elevated IL-1β, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1/CC-motif ligand-2 (MCP-1), macrophage inflammatory protein-1β/CC-motif ligand-3 (MIP-1β), and C-reactive protein in the blood after the onset of NEC (49). Elevations of these cytokines are also associated with BPD or death in extremely preterm infants (50).

TLR4 expression in the lung gradually increases during postnatal development, and both mice and humans with NEC-associated lung inflammation have more pulmonary TLR4 than age-matched controls (51). NEC in newborn mice results in pulmonary injury that is prevented by TLR4 deletion from the pulmonary epithelium, indicating a role for pulmonary TLR4 in NEC lung injury (51). It was also observed that intestinal epithelial TLR4 activation induced high-mobility group box 1 release from the intestine, which activated pulmonary epithelial TLR4, leading to the induction of the neutrophil recruiting CXCL5 and the influx of neutrophils into lung (51). NEC-induced lung injury in mice and humans is characterized by an influx of Th17 cells and a reduction in T regulatory lymphocytes (52). In mice with NEC, deletion of TLR4 from Sftpc1+ epithelial cells reduced lung injury, while TLR4 activation induced CCL25, the Th17 recruiting chemokine (52). It is therefore evident that TLR4 is a regulator (and potential “druggable” target) of NEC-induced lung injury.

Sensing of commensal bacteria by intestinal mucosal dendritic cells also leads to an influx of IL-22-producing group 3 innate lymphoid cells into the lungs of newborn mice (53). Dysregulation of this process by intestinal luminal pathogens may disturb lung innate immunity. Infants with NEC often receive prolonged courses of antimicrobials, and there is evidence that microbial depletion using broad-spectrum antimicrobials may increase susceptibility to ventilation-induced lung injury (54), which may also contribute to BPD

in the setting of NEC. On the other hand, probiotics have been shown to reduce the risk of NEC in preterm infants (risk ratio [RR] 0.52, 95% CI 0.33-0.81, p=0.004), but systematic review of the data from these trials did not demonstrate any effect on BPD at 36w PMA (RR 1.07, 95% CI 0.96-1.20, p=0.203), and meta-regression did not show any significant association between the RR for NEC and that for BPD (55).

In summary, NEC is a multifactorial disorder characterized by intestinal ischemia, dysbiosis, and a state of systemic inflammation that usually results in concomitant lung inflammation and a higher risk for BPD. This effect of NEC on the lung is mediated by many physiological effects as well as molecular and cellular mechanisms related to dysregulated immune processes. Conversely, lung disease and its management in the preterm infant may also impact gut oxygenation, microbiome, and other risk factors for NEC.

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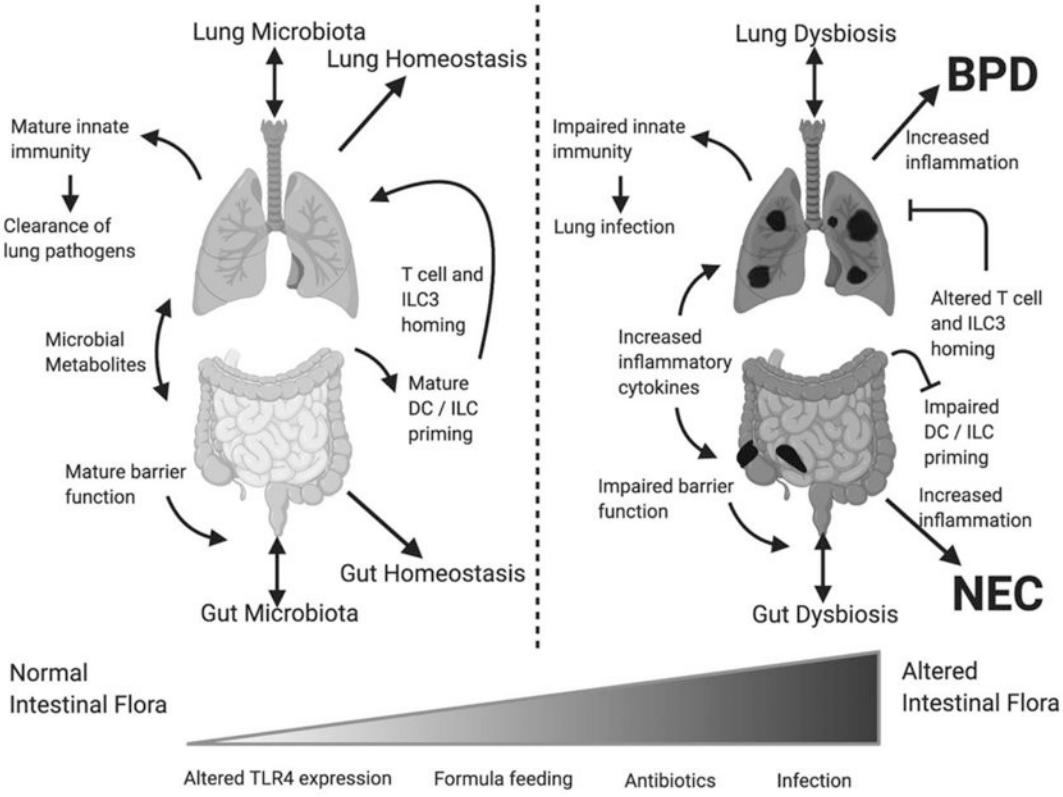

Figure 1. Dysbiosis of the lung and gut likely contribute to the development of both BPD and NEC.

Multiple, likely interrelated, mechanisms may contribute to the development of both diseases. BPD, bronchopulmonary dysplasia; DC, dendritic cell; ILC3, type 3 innate lymphoid cells; NEC, necrotizing enterocolitis.

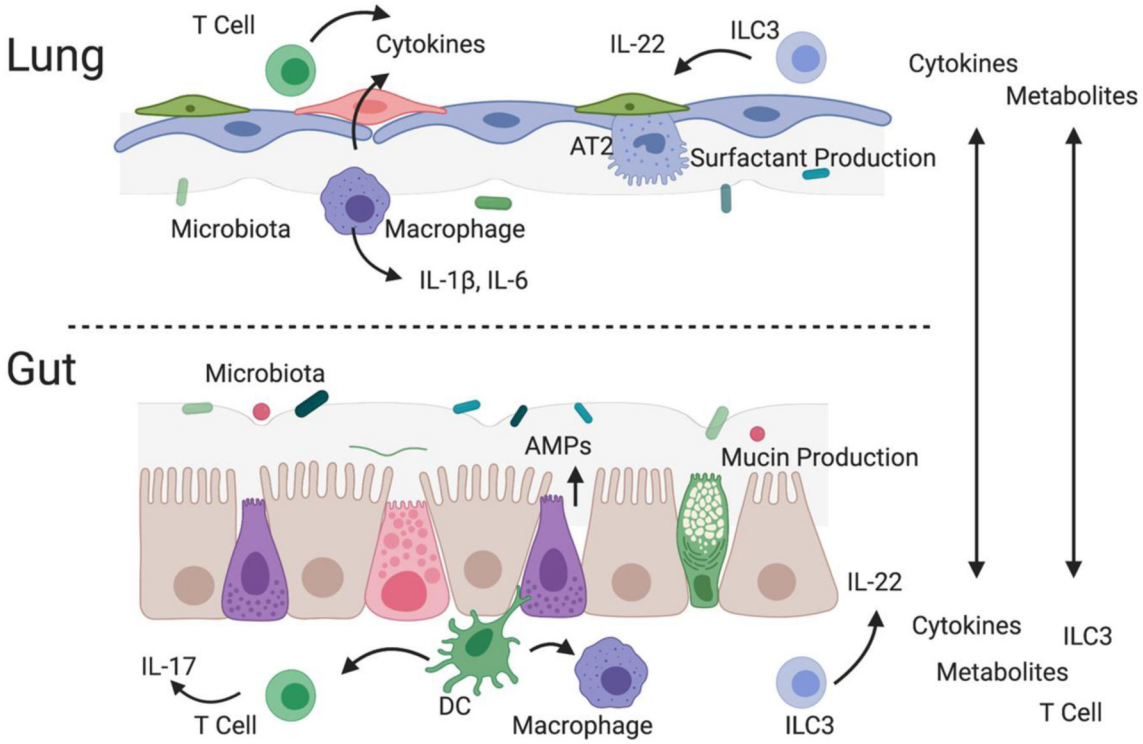

Figure 2. Immune interactions with the intrinsic microbiomes of the gut and lung are critical components of the gut-lung axis.

In addition, to direct transfer of T cells, type 3 innate lymphoid cells (ILC3), metabolites and cytokines, spill over from tissue specific interactions between the microbiota and innate immune cells may also disrupt homeostasis in the opposite organ. AMP, antimicrobial peptides; AT2 alveolar type 2 cell; DC, dendritic cells.