Early-life dysbiosis and Th17 asthma: never is better than late

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Early-life dysbiosis and Th17 asthma: Never is better than late

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When considering the innumerable environmental factors that influence respiratory health, herein the “exposome”, our attention may be drawn to the more ubiquitous irritants such as cigarette smoke, particulate air pollution, and inhaled occupational exposures. However, it would be remiss to overlook the gut microbiota and its critical role in immune homeostasis. Here, Wilburn and colleagues report findings that should redirect our attention to early-life dysbiosis and its influence on the development of allergic asthma[1].

The lung microbiome has been the subject of intense research interest during the last decade and the rapid expansion of high-throughput 16S rRNA amplicon sequencing has shattered the illusion that the lower airway is a sterile field. However, our understanding of the effects of the intestinal microbiota on airway immune development via the “gut-lung axis” is more limited [2]. The neonatal gut microbiome diversifies rapidly and early-life environmental exposures exert a pivotal role in shaping the composition of the host microbiota [3]. Early host-environment interactions can lead to distinct shifts in microbial communities, none more so than the mode of delivery which marks the infant’s first microbial exposure. Caesarean section can affect microbiome development through disruption of mother-to-neonate transmission, resulting in diminished intestinal microbial richness and diversity [4]. Antibiotics have also been shown to inhibit infant microbiota maturation via depletion of *Enterobacteriaceae, Lachnospiraceae,* and *Erysipelotrichaceae* [4,5]. Importantly, despite the transient nature of such early-life dysbiotic events they can result in lasting immune dysregulation and increased risk of atopy[5]. Consequently, we need to improve our understanding of how to support the establishment and maturation of the gut microbiota amidst a dynamic and ever-changing exposome.

Accumulating data indicates that gut microbiome profile correlates with subsequent risk of asthma [6,7]. Previous murine studies have only examined the effect of allergen challenge during an experimentally-induced dysbiotic state making it difficult to discern whether disruption of the microbiota or downstream immune dysregulation is responsible for increased airway hyperresponsiveness (AHR) [8,9]. To address the gap in our current understanding, Wilburn and

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colleagues investigated the effects of delayed microbial maturation on AHR using an acute antibiotic exposure model. The investigators induced transient dysbiosis by supplementing nursing C57BL/6 dams drinking water with an antibiotic cocktail during postnatal days 10-20. This timepoint conveniently overlaps with weaning, the introduction of solid food and murine gut microbial maturation. Faecal microbiome was longitudinally evaluated by shotgun metagenomic sequencing confirming dysbiosis in antibiotic-exposed pups. The results confirmed that house dust mite (HDM) exposure initiated during dysbiosis is associated with a significant increase in AHR. Intriguingly, despite gut microbial recovery and maturation at week 7 in antibiotic-exposed pups the total airway resistance remained significantly elevated demonstrating the durable effect of delayed microbial maturation (DMM). Thus, transient early life dysbiosis results in durable immune dysregulation that is independent of the microbial ecology at the time of allergen challenge. The authors interrogated the underlying immune signalling in DMM showing that increased induction of IL-17A-producing Th17 cells appeared to be mechanistically implicated and that blockade of this pathway using anti-IL-17A monoclonal antibody attenuated AHR in DMM. Furthermore, synergistic signalling between IL-17A and IL-13 was shown in the mesenchymal compartment.

A limitation of the current study is that the underlying mechanisms of DMM remain to be fully elucidated. In their discussion the authors speculate that short-chain fatty acids (SCFAs) may play a role and higher levels of butyrate and propionate have been associated with lower risk of childhood asthma [10]. Interestingly, SCFA supplementation has been shown to exert anti-inflammatory properties in murine asthma models [10]. Beyond asthma, supplementation of sodium propionate has been shown to attenuate zinc oxide nanoparticle-induced (ZnONPs) lung injury [11]. Consequently, these bacterial metabolites represent tantalizing mechanistic candidates not least by virtue of their potential to be therapeutically modulated.

It seems intuitive that prevention of gut dysbiosis during early-life is better than cure. However, this is a high bar to set and a more pragmatic approach may be necessary. Further

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unanswered questions include whether the gut microbiome represents a realistic therapeutic target that can influence respiratory health outcomes and what modality of treatment could be used. Recently, Zhang et al. reported that murine faecal microbial transplantation attenuated ZnONPs lung injury [11]. Probiotics represent an intriguing candidate therapy and oral supplementation of *Lactobacillus reuteri* has been shown to reduce airway eosinophil influx with lower IL-5 and IL-13 expression [12] while gut microbial development in infants at high risk of asthma may be temporarily modified through *Lactobacillus* supplementation[13]. More recently, targeted administration of maternal vaginal microbes following C-section failed to alter gut microbiome [14]. Looking further afield, probiotics have been extensively evaluated for prevention of necrotizing enterocolitis in pre-term and low birth weight infants, however, despite more than 50 trials the evidence base remains conflicting [15]. Therefore, probiotic studies targeting the gut microbiota are likely to require large high quality clinical trials adequately powered for clinical outcomes.

Improving outcomes in Th2-low severe asthma is a research priority as this patient group does not experience the same benefit from established monoclonal antibody therapies [16]. Critically, this study helps to characterize synergistic signalling of IL-17A and IL-13 potentially suggesting Th17-high asthma in the context of delayed microbial maturation represents a distinct endotype that could be targeted by immunotherapy. However, establishing a better mechanistic understanding may be a prudent first step before embarking on therapeutic trials.

The oft-quoted hygiene hypothesis of asthma somewhat flies in the face of the old adage that “cleanliness is next to godliness” where the early-life exposome is concerned. Naturally, we must balance what we can control with what we should control in the early post-natal period. In the current study Wilburn and colleagues provide strong evidence that we should strive to support the normal establishment of the fledgling gut microbiome and in this context early-life antibiotic exposure and subsequent dysbiosis is one facet of the exposome that justifies more rigorous control. Presently, we may have to concede that when it comes to maturation of the

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gut microbiota it's still a case of "better late than never". However, in regard to early-life dysbiosis it is evident that never is better than late.

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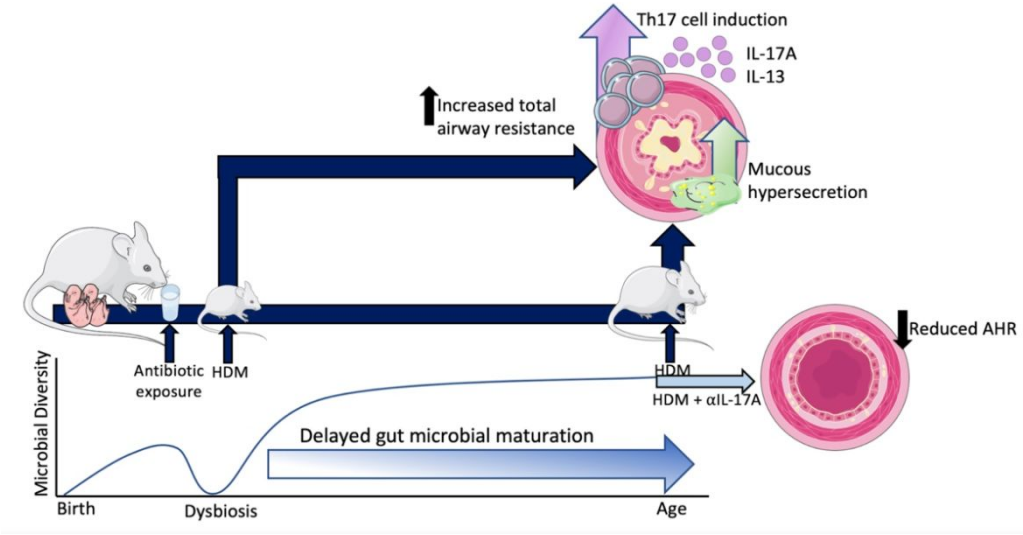

Figure 1. Delayed microbial maturation following transient dysbiosis results in durable Th17 driven asthmata phenotype. Allergen challenge with house dust mite (HDM) following transient dysbiosis and gut microbial maturation is capable of inducing features of severe asthma phenotype including airway hyperresponsiveness (AHR), Th17 frequency and synergistic signalling of IL-13 and IL-17A. Notably, blockade of this pathway using IL-17A monoclonal antibody is capable of reversing AHR.

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