Gut-Lung Axis- Implication of the Gut Microbiota beyond its niche

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Outline

1. Introduction to gut microbiota
2. Introduction to lung microbiota
3. Concept of a ‘gut-lung axis’
4. Gut-lung axis in health
5. Gut-lung axis in Disease
6. Future directions
7. Summary

Gut microbiota

- Best studied host-associated microbial ecosystem
  - Magnitude 10^{14} bacterial cells[1]
- Healthy gut dominated by four phyla: **Firmicutes, Bacteroidetes, Proteobacteria** and **Actinobacteria**
  - *Bacteroides*, *Faecalibacterium,* and *Bifidobacterium* are the most prevalent genera[2]
- Function: **Breaking down of dietary polysaccharides**, **competing with pathogens** and **modulating host immune system**
- Dysbiosis of gut microbiota associated with gastrointestinal(GI) and non-GI diseases

[1]Savage, D. C. (1977). Microbial ecology of the gastrointestinal tract. *Annual Review of Microbiology, 31*, 107-133
[2]Robles Alonso, V., & Guarner, F. (2013). Intestinal microbiota composition in adults.*107*, 17-24.

Lung microbiota

- The healthy lung is not sterile
- 10-100 bacterial cells per 1,000 human cells[1]

Two predominant phyla: **Firmicutes** and **Bacteroidetes**[2]

- Comon genera in healthy individuals: *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacteria*, *Veillonella*, *Haemophilus*, *Neisseria,* and *Porphyromonas*

- Imbalance may predispose to disease development
- Not as well studied as the gut microbiota
  - Low biomass
  - Difficulty to obtain sample

[1] Sze MA *et al.* The lung tissue microbiome in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;185:1073–1080

[2] Erb-Downward JR *et al*. Analysis of the lung microbiome in the "healthy" smoker and in COPD. *PLoS One* 2011;6:e16384

Concept of a ‘gut-lung axis’

Crosstalk between the two segregated sites?

Chronic lung and gastrointestinal tract (GIT) disease

- Inflammatory bowel disease (IBD) and Irritable bowel syndrome (IBS)
- Chronic obstructive pulmonary disease (COPD)
  - Up to 50% of patients with IBD and 33% with IBS have some pulmonary involvement[1]
  - COPD patients are 2-3 times more likely to be diagnosed with IBD[2]
- GIT and lung – part of a shared mucosal immune system
- Common Factor: **link with microbial dysbiosis** and consequent **disruption in homeostasis of host immune response**
- Microbiota of gut can influence immune response at distal sites
- Coining of term **'Gut-lung axis'**

Budden, K. F. *et al*. (2017). Emerging pathogenic links between microbiota and the gut-lung axis. *Nature Reviews.Microbiology, 15*(1), 55-63.
[1] Yazar, A.*et al* (2001). Respiratory symptoms and pulmonary functional changes in patients with irritable bowel syndrome. *The American Journal of Gastroenterology, 96*(5), 1511-1516
[2] Rutten, E. P. A.*et al*. (2014). Disturbed intestinal integrity in patients with COPD: Effects of activities of daily living. *Chest, 145*(2), 245-252

The gut-lung axis

1. “The gastrointestinal tract (GIT) and respiratory tract, although separate organs, are part of a shared mucosal immune system termed the gut–lung axis” [1]
2. “Passage of microbes, microbial products, endotoxins, metabolites as well as hormones and cytokines into the bloodstream thereby connecting the intestinal niche with that of the lung” [2]

[1]Budden, K. F. *et al*. (2017). Emerging pathogenic links between microbiota and the gut-lung axis. *Nature Reviews.Microbiology, 15*(1), 55-63
[2]Cervantes, J., & Hong, B. (2017). The gut-lung axis in tuberculosis. *Pathogens and Disease, 75*(8), ft097

Gut- lung axis in health

Early life exposures

Early life exposures modulate gut microbiota – protection or predisposition towards allergic airways disease (e.g. Asthma)[1]

more diverse gut microbiota = more protective

- **Breastfeeding**- Decreases risk of development of childhood asthma[2,3]
  - Introduces new microbial communities
  - Beneficial *Bifidobacter* and *Lactobacillus* spp.
- **Caesarean birth**: Predisposition towards childhood asthma[4]
  - Reduced diversity of intestinal bacteria
- **Early life exposure to antibiotics :** correlates strongly with development of asthma[5]

[1] Thavagnanam. A *et al.* (2008). Meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy,38:629–633
[2] Kull I, *et al*.(2004) Breast-feeding reduces the risk of asthma during the first 4 years of life. J Allergy Clin Immunol .,114:755–760
[3] Guaraldi F and Salvatori G.(2012) Effect of breast and formula feeding on gut microbiota shaping in newborns. Front Cell Infect Microbiol, 2:94
[4] Fanaro S *et al.* (2003). Intestinal microflora in early infancy: composition and development. Acta Paediatr Suppl., 91:48–55
[5] Russell SL et al. (2013). Perinatal antibiotic treatment affects murine microbiota, immune responses and allergic asthma. Gut Microbes, 4:158–164

Gut- lung axis in disease

Role of the gut-lung axis in COPD?

- No study to date has investigate the changes in gut microbiota in COPD patients
- Studies have investigated gut microbiota in smokers vs. Non smokers
  - ↑ *Bacteriodes-Prevotella* ratio[1]
  - ↓ Firmicutes/Bacteroidetes ratio[2]
  - Changes associated with inflammation and IBD
  - Smokers: ↓ *Bifidobacterium* spp. – loss of associated anti-inflammatory effects? [2]
- Require longitudinal and interventional studies- get a better understanding of gut-lung axis in COPD

1 Benjamin, J. L. *et al.* (2012). Smokers with active crohn's disease have a clinically relevant dysbiosis of the gastrointestinal microbiota. Inflammatory Bowel Diseases, 18(6), 1092-1100

2 Biedermann, L. *et al.* (2014). Smoking cessation alters intestinal microbiota: Insights from quantitative investigations on human fecal samples using FISH. *Inflammatory Bowel Diseases, 20*(9), 1496-1501

Future directions

Targeting gut-lung axis for therapeutics?

- Opens doors for new therapeutic strategies for chronic lung diseases
- Not quite there yet
  - Current studies: Pathophysiology vs microbiota composition
  - Establish causal links
- Probiotics for chronic lung conditions?
  - Asthma: Promising in murine studies[1]
    - Oral administration of probiotic in neonatal mice – suppressed asthmatic phenotype
    - Induces antigen specific T_{reg} cells
  - Data from human studies still inconsistent
  - Probiotics for COPD not investigated

[1] Feleszko, W. *et al.* (2007). Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. *Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology, 37*(4), 498-505

Summary

- Gut and lung- physically segregated sites that harbour their own microbiota
- Clues of crosstalk between the two – chronic pulmonary and GI tract diseases
- Crosstalk brought about by microbes/microbial products/microbial modulation of the immune system **(Gut-lung axis)**
- Gut-lung axis- role of gut microbiota in pulmonary health and disease
- Potential therapeutic target

Thank you!