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REVIEW

Impact of diet and the bacterial microbiome on the mucous barrier and immune disorders

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Abstract

The prevalence of chronic immune and metabolic disorders is increasing rapidly. In particular, inflammatory bowel diseases, obesity, diabetes, asthma and chronic obstructive pulmonary disease have become major healthcare and economic burdens worldwide. Recent advances in microbiome research have led to significant discoveries of associative links between alterations in the microbiome and health, as well as these chronic supposedly non-communicable, immune/metabolic disorders. Importantly, the interplay between diet, microbiome, and the mucous barrier in these diseases has gained significant attention. Diet modulates the mucous barrier *via* alterations in gut microbiota, resulting in either disease onset/exacerbation due to a 'poor' diet or protection against disease with a 'healthy' diet. In addition, many mucosa-associated disorders possess a specific gut microbiome fingerprint associated with the composition of the mucous barrier, which is further influenced by host-microbiome and inter-microbial interactions, dietary choices, microbe immigration and antimicrobials. Our review focuses on the interactions of diet (macronutrients and micronutrients), gut microbiota and mucous barriers (gastrointestinal and respiratory tract), and their importance in the onset and/or progression of major immune/metabolic disorders. We also highlight the key mechanisms that could be targeted therapeutically to prevent and/or treat these disorders.

KEYWORDS

Diet, microbiome, mucus, disease, induction, exacerbation, prevention, treatment, inflammation, IBD, asthma, COPD

ABBREVIATIONS

AAD = Allergic airway disease

AD = Atopic dermatitis

AGR2 = Anterior gradient 2

AHR – Airway hyper-responsiveness

ATG16L1 = Autophagy related 16 like 1

CCP = Cyclic citrullinated peptide

CARD9 = Caspase recruitment domain family member 9

COPD = Chronic obstructive pulmonary disease

CLCA1 = Chloride channel accessory 1

DC = Dendritic cell

FUT2 = α (1 , 2)-fucosyltransferase

FCGBP= Fc fragment of IgG binding protein

GI = Gastrointestinal

GIT = Gastrointestinal tract

Gpr = G protein coupled receptor

HFD = High fat diet

IBD = Inflammatory bowel disease

IBS = Irritable bowel syndrome

IL = Interleukin

ILC = Innate lymphoid cell

IRGM = Immunity-related GTPase family M protein

MUC = mucin

MLGs = Metagenomics linkage groups

NOD2 = Nucleotide-binding oligomerization domain-containing protein 2

pIgR−/−= Polymeric immunoglobulin receptor-deficient

PUFA = Polyunsaturated fatty acid

RA = Rheumatoid arthritis

Reg3B/3G = Regenerating islet-derived protein type 3 beta/gamma

sIgA = Secretory immunoglobulin A

SCFA = Short chain fatty acid

SOCS3 = Suppressor of cytokine signalling 3

TFF= Trefoil factor peptides

T_h = Helper T cell

TGFβ = Transforming growth factor-β

TIMP = Tissue inhibitor of metalloproteinases

Treg = Regulatory T cell

ZG16 = Zymogen granule protein 16

INTRODUCTION

Diet-gut microbiome-mucous barrier and immune disorders

The immune system is composed of a labyrinth of cellular and molecular networks that ensure adequate host defences against a range of stimuli, but during homeostasis, the body co-exists with a dense microbial ecosystem (microbiome), in a symbiotic relationship permitted by the immune environment.[1,2] A key regulator balancing this relationship is the mucous barrier, consisting of a secreted mucus layer and the underlying epithelium.[3] The mucous barrier is the primary physical defence barrier of the host, segregating internal organs and tissues, such as the gut and lungs, from microorganisms but providing a ubiquitous source of carbon and energy for commensal microbes.[3,4] Disturbance to the mucous barrier leads to the translocation of microbes into mucosal tissues, which in turn triggers inflammation and immune responses.[3,4]

The gut harbours the largest microbiome in the human body[5] and is established in three distinct phases of microbial progression: 1. Development; 2. Transitional phase, and; 3. Stable phase.[6] The developmental stage is initiated by contact with the vaginal microbiota during birth,[7] although there is the debatable possibility that the human intestines and placenta may also be colonised before birth.[8] As infants begin to consume solids, the transitional phase occurs, with changes in microbiome composition and function.[7] Microbiome composition can continue to change during adulthood, in response to diet, environmental exposures, antimicrobial use, medications and age.[9-12] However, as shown by metagenomics approaches, there is remarkable stability in the functionality of the microbiota and this stage is thus referred to as the stable phase.[9,12] This functional stability of the microbiome reflects its robust nature and importance in modulating homeostatic interactions with the host.[9,12]

Studies of the lung microbiome are challenging due to limitations of sample collection, especially in the distal airways, and technical issues with low biomass.[13] Bacterial load increases as the respiratory microbiome matures,[16] although it remains far less densely populated than the gut.[2,17]

Diet is a major but just one of many factors that affect microbiota, which in turn has a strong impact on mucous membranes and gut and lung health.[10,12,18-20] Diet, environmental and genetic factors regulate short- and long-term stability of microbiota, and in the gut, this affects energy harvest from ingested food.[21,22] The protective nature of the mucous barrier, innate and adaptive immune responses and competitive inhibition selects against poorly adapted microorganisms in the gut and lung and promotes persistence of commensal microbial communities.[11]

Chronic immune disorders such as inflammatory bowel disease (IBD), obesity, diabetes, rheumatoid arthritis, atopic dermatitis (AD), psoriasis, asthma and chronic obstructive pulmonary disease (COPD) are becoming increasingly prevalent globally, and alterations in diet, microbiota, immunity and/or mucous membranes are associated with these diseases.[10-12,18,19] However, the mechanisms involved in the interplay between these factors are unclear. Here, we review the current understanding of the dynamic nature of the microbiome-mucous barrier relationship, and how diet, host and external factors affect the pathogenesis of chronic immune disorders in the context of the gut and respiratory microbiomes. Furthermore, we highlight the importance of diet in regulating the microbiome and mucous barrier, and identify potential prophylactic and therapeutic approaches that target these interactions.

THE MUCOUS BARRIER

Mucus structure and regulation

Mucus is a biological gel that covers all mucosal epithelia in the body. Gel-forming mucin glycoproteins form the major components of mucus and are the main products of goblet cells. Mucins are divided into two subtypes; cell surface-tethered/membrane-bound mucins (MUC1, MUC3A/B, MUC4, MUC12-17 and MUC20-22), and secreted mucins.[23] Secreted mucins are further divided into two subfamilies gel-forming (MUC2, MUC5AC, MUC5B, MUC6, and MUC19), and non-gel forming (MUC7-9) mucins, which maintain the structure and organisation of the mucous gel and control its viscoelastic properties.[23] Cell-tethered mucins form a gel-like layer around cilia of the respiratory epithelium that aid normal ciliary action of moving mucus in mucociliary clearance mechanisms.[4] Biochemically, mucin structure consists of N- and C-terminal regions containing von Willebrand factor-like domains that partake in polymerisation, and central domains characterised by tandem and non-tandem repeats of serine, threonine and proline that undergo O-glycosylation and make up 80% of the molecular mass.[4,24] The specific glycosyltransferase enzymes present in a cell determine the O-glycan outcome, and therefore the same protein sequence can result in very different compositions of glycans.[25,26]

Other major mucus-related proteins include chloride channel accessory (CLCA)1, Fc fragment of IgG binding protein (FCGBP), zymogen granule protein 16 (ZG16), and anterior gradient (AGR)2 which are secreted by goblet cells.[27] Trefoil factor (TFF) peptides are a family of mucin-associated secretory molecules occurring in three types that promote defence

and protection of the gut. TFF3 enhances intestinal barrier function *via* regulating tight junctions between the epithelial cells.[28] It also is expressed with MUC2 in intestinal goblet cells and contributes to mucosal regeneration and repair.[29] Furthermore, antibodies especially secretory immunoglobulin A (sIgA) production, is induced by interactions with select commensal bacteria in the gut. They are released by plasma cells and have a polymeric nature and multi-valency that enables them to non-covalently bind microorganisms or macromolecules.[30,31] This phenomenon blocks the interactions of microbial adhesins with the epithelium and also inhibits microbial motility, both of which facilitate microbial entrapment in the mucus to protect against lethal sepsis.[30,31] IgA binding to bacterial surfaces also modulates bacterial gene expression and function to promote symbiosis between members of the microbiome and the gut.[30,32] Moreover, polymeric IgA bound to antigens in the circulation may be transported into the intestinal lumen via transcytosis across the epithelium, thereby providing a role for mucous membranes in clearing circulating immune complexes.[33]

GASTROINTESINAL TRACT (GIT) MUCOSA

The gastrointestinal mucus structure is shaped by location as well as microbiota (**Figure 1, Table 1**).[34] In the stomach, gel-forming mucins MUC5A and MUC5B produced by goblet cells in the gastric epithelium are dominant, while MUC6 is produced by mucous neck cells and in pyloric glands of the antrum.[35] In the small intestine and colon, MUC2 is highly expressed and stimulates β-defensin that has anti-microbial effects, while the colon also produces low levels of MUC5B.[36,37] Although the small intestine is covered by a single, loosely attached mucus layer, colonic mucus is much thicker due to the greater microbial density, and is comprised of two layers; an outer (luminal) viscous mucous layer and an inner stratified layer of colonic mucus that adheres firmly to the underlying columnar epithelia (glycocalyx).[38] Transmembrane mucins MUC3, MUC4, MUC12, MUC13 and MUC17 are constitutively expressed along the GIT and occur in the glycocalyx. Here, MUC17 shuttles from the epithelial surface to intracellular vesicles concomitantly with internalisation of the Na+/H+ exchanger and the recruitment of the cystic fibrosis transmembrane conductance regulator (CFTR) to the apical membranes.[39] This promotes goblet cell mucin secretion, which may be associated with increased bicarbonate diffusion.[39]

Some mucus-producing sentinel goblet cells found in the colonic crypts are stimulated when Toll-like receptors on the surface of these crypts are triggered. This activates

inflammasomes and reactive oxygen species production in these cells, which in turn stimulate MUC2 release from neighbouring cells, therefore, acting like gatekeeper cells in the GIT.[29,40]

Studies of the interactions of the gut mucosa and microbiota indicate that mucus composition is associated with specific gut microbial communities.[34,41] Jackobsson *et al*., placed two groups of mice in the same specific pathogen-free environment and observed differences in their gut microbiota and mucus phenotype.[41] One group had impenetrable mucus layer and increased abundance of *Erysipelotrichia*, whereas the other had penetrable mucus that corresponded with higher levels of *Proteobacteria* and TM7 bacteria in the distal colon.[41] Furthermore, diet and mucous membrane properties are directly linked to microbial community composition giving every mouse a distinct microbial fingerprint.[18,21,41] In human studies there is a distinct identity of enterotypes formed depending on long-term dietary patterns but their links to the mucous membrane are less clear.[18,21,41]

The disruption of oligosaccharide synthesis in the gut leads to impaired mucosal barrier function. Mice that lacked important glycosyltransferases involved in O-glycan biosynthesis had impaired mucosal barrier function, truncated mucins, and increased bacterial penetration into mucosal tissues.[42] In humans, the non-secretor polymorphism of α(1, 2)-fucosyltransferase (FUT2) is associated with increased risk of the IBD Crohn's disease, and leads to altered microbiome composition and function.[43,44] FUT2 synthesises H antigen, an oligosaccharide moiety which acts as an attachment site and carbon source for intestinal bacteria, and the effects of polymorphisms highlight the importance of genetics in regulating host-microbiome interactions at the mucosal surface.[43,44]

Similar to the regeneration mechanisms of skin epithelia, GIT epithelial tissue regenerates continuously, starting from basal progeny stem cells in the intestinal crypts that mature into four cell lineages, namely; epithelial cells (enterocytes), enteroendocrine cells, antimicrobial peptide-producing Paneth cells and mucin-producing goblet cells (**Figure 2a**).[45] These cell lineages migrate towards the luminal surface as they differentiate and mature, with the exception of Paneth cells which remain at the base of the intestinal crypts.[46] Enterocytes are the most abundant cells in the small intestine and are responsible for digestion and absorption of dietary nutrients. They are coated by a glycocalyx comprised of glycolipids, glycoproteins, proteoglycans and microvilli responsible for transport.[47] Less abundant cells include microfold (M) cells that transcytose luminal antigens and initiate immune responses and IgA production, chemosensory tuft cells that can initiate type-2 responses and drive type-2 innate lymphoid cell (ILC2) signalling circuits, and enteroendocrine cells that secrete hormones.[45,48,49] The luminal surface eventually undergoes programmed cell death and is

restored by regenerated cells.[46] All these cells are interconnected by tight junctions comprised of four integral transmembrane proteins, claudins, occludin, junctional adhesion molecule and tricelluin, which form a selectively permeable seal between adjacent cells.[50]

EARLY-LIFE SHAPING OF THE GUT MICROBIOME

As the newborn passes through the birth canal, the mother's vaginal microbiota provides the first microbial exposure.[10] Newborns delivered through caesarean section lack this vaginal inoculation and subsequently their microbiota at all body sites more closely resemble their mother's skin flora.[10] Studies with mice suggest that the newborn gut environment transitions from aerobic to anaerobic conditions within days of birth, and supports the emergence and dominance of *Bifidobacteriaceae* and *Lactobacillaceae* families,[63] with *Bifidobacterium*, *Lactobacillus gasseri* and *Lactobacillus reuteri* the most significant colonisers in early-life.[64,65] The subsequent development of the early-life gut microbiome is influenced by many factors including mode of delivery,[66] initial diets (breastmilk, formula),[67] day care attendance and the timing of the transition to solid foods (**Figure 3**).[7,68] However, the functionality of the gut microbiome, determined by metagenomics profiles, is less variable than phylogenetic composition as evidenced by similarities in breastmilk- or formula-fed infants.[69] Human breast milk contains a host of proteins, fats, carbohydrates and immune factors that may impact microbial growth, survival and metabolism.[70] Oligosaccharides are abundant and actively promote the growth of *Bifidobacterium* and *Lactobacillus,*[34,71] which may explain their dominance in early life.[34,64] Transition to solid foods promotes the transition to adult-like gut microbiota dominated by *Bacteroidetes* and *Firmicutes,*[34] and can be classified into enterotypes based on the respective dominance of genera within these phyla, and the functional and phylogenetic relationships between them.[9]

THE GUT-LUNG AXIS

Given the emerging links between the gut and lungs, the 'gut-lung axis' has become increasingly prominent in research associated with diet, the microbiome and the lungs.[1,1751] The gut-lung axis refers to the highly influential crosstalk between mucosal immune sites of the gut and lung, as well as their microbiota.[1,52] In particular, the gut microbiome is implicated in regulating immune responses to respiratory infections[53] and the pathogenesis of chronic respiratory diseases such as asthma and COPD.[1,52-54] The mechanisms by which gut microbiota influence the lung are varied, including the production of host-accessible

metabolites, penetration of mucosal barriers by bacteria and/or toxins, regulation of haematopoiesis or circulating hormones and cytokines, and direct stimulation of migrating immune cells.[1,2,17,52-54] Other events may also contribute such as induction of IL-6 and neutrophilia, and the induction of bacterial receptor expression in the lung.[55,56] Conversely, the induction of lung hypoxia may promote gut remodelling and disease.[56]

RESPIRATORY TRACT MUCOSA

Ciliated epithelial cells are responsible for mucociliary clearance of the airways and lungs, the removal of inhaled microorganisms and debris, and maintenance of unobstructed airways.[4] Interspersed between these cells are goblet cells, the major secretory cells in the apical layer of the large airways which produce highly hydrated mucus that is primarily comprised of mucin glycoproteins (**Figure 2b**).[4,23,57] Hyperplasia of goblet cells and mucus hypersecretion alter the rheological properties of mucus and are a major disease feature of asthma and COPD.[4,58-61]

Respiratory mucins are divided into three classes: mucins that are secreted but do not polymerise (MUC7 , MUC8), secreted gel-forming mucins (MUC2, MUC5AC, MUC5B, MUC19), and membrane-associated mucins (MUC1, MUC4, MUC12-16, and MUC20-22).[23] MUC5AC and MUC5B are produced in the trachea and bronchi, with MUC5B predominating over MUC5A.[62] MUC1 is produced by the surface columnar epithelial cells of the respiratory tract, as well as alveolar type 2 cells which play critical roles in the alleviation of inflammation.[57] During airway infection, the respiratory mucosa serves as a major protective barrier against pathogens by mucus entrapment and removal *via* the coordinated beating of motile cilia.[4]

MICROBIOME-MUCOUS MEMBRANE INTERACTIONS

Microbiota are necessary for appropriate production of gut and respiratory tract mucus, and is a major regulator of its composition.[18,20,34,41,72-74] Pathogenic and commensal bacteria persist in these locations through adaptations that enable them to directly interact with mucous membranes, with varying impacts on host health.[4] GI pathogens, including *Clostridium difficile*, utilise adhesion to the mucus layer to access and invade the underlying epithelia and cause disease.[75] However, commensal bacteria such as *Escherichia coli* and *Lactobacillus*

rhamnosus also adhere to mucus and competitively inhibit colonisation by opportunistic pathogens.[76,77]

Similarly, mucins in the lung and oral cavity, from where bacteria migrate to the lower respiratory tract,[2] inhibit biofilm formation and downregulate toxins and other virulence factors of pathogenic taxa, such as *Pseudomonas aeruginosa*, preventing their outgrowth and dominance and thereby promoting community diversity.[78-80] These protective effects may be subverted, as *P. aeruginosa* can utilise MUC1 for adherence[81] and reside in the mucus to evade exposure to antibiotics, particularly with mucus hypersecretion such as in cystic fibrosis.[82,83]

Many bacteria in the GI and respiratory tracts utilise the mucous barrier as a carbon source and are highly adapted to this microenvironment.[74,84-87] Colonic mucosal isolates of *Bacteroides thetaiotaomicron* in mono-colonised germ-free mice predominantly expressed N-linked glycosidases associated with mucus digestion, whereas luminal isolates predominantly expressed glycoside hydrolases associated with digestion of glycan side-chains and fibre in the host diet.[88] Some digestion of the mucus layer is essential for appropriate mucus turnover and promotes symbiotic relationships between the host and commensal bacteria such as *Akkermansia muciniphila*.[89,90] However, excessive degradation may cause attrition of mucus and expose the underlying intestinal and airway epithelium to pathogens.[74,84,91]

The microbiome plays significant roles in pathogen resistance, nutrient metabolism and development of immune responses, in part through these interactions with the mucus layer or the underlying epithelia after mucus breakdown.[1] A major factor critical to maintaining a symbiotic relationship between host, microbiota and the mucous barrier is host diet.

DIETARY EFFECTS ON MICROBIOMES AND THEIR IMPACT ON MUCUS

Human and animal studies demonstrate that dietary changes have rapid effects on the mucosa directly or indirectly through changes in microbiota (**Figure 4**).[92-95] Diets mainly consist of macronutrients such as carbohydrates, lipids and proteins, as well as trace amounts of micronutrients such as vitamins and minerals.[96,97] On a human global scale, different regional diets correspond to differences in the composition of the gut microbiota. A Western diet is characterised by excess intake of foods rich in fats, cholesterol, animal proteins, sugars and processed foods.[98] Consequently, these diets promote low *Prevotella* and higher *Bacteroides*

populations that contribute to low-grade inflammation and several diseases.[21] Conversely, the Mediterranean diet includes greater proportions of fruits, vegetables, nuts and whole grains, which promote increased abundance of *Prevotella* and fibre-degrading bacteria that ferment complex carbohydrates to produce short chain fatty acids (SCFAs) that positively influence health status.[104]

MACRONUTRIENTS: IMPACT ON MICROBIOME AND MUCOUS BARRIER

Dietary fibre

Host enzymes such as amylases in the human GIT primarily digest starches, whereas some fibres, such as galacto- and fructo-oligosaccharides, resistant starch, inulin, and pectin, are poorly digested.[85,98] Rather, members of the gut microbiota (including *Firmicutes*, *Bacteroidetes*, *Bifidobacterium* and *Prevotella*) ferment and depolymerize dietary fibre to produce SCFAs, the most abundant of which are acetate (C-2), propionate (C-3) and butyrate (C-4).[85] SCFAs are accessible to the host and are used as niche carbon sources and nutrients for enterocytes and other gut epithelial cells,[105] and promote the growth of other commensals through the complex interplay of 'cross-feeding'.[89]

If microbiota are starved of these nutrients through intermittent or chronic fibre deficiency, many adapt to obtain energy through digestion of the mucus barrier which increases attrition and exposes the underlying intestinal epithelium to luminal bacteria.[84,91] The loss of commensal bacteria which cannot digest mucus can negatively impact mucous barrier. A western style diet (high fat/sugar, low fibre) increased colonic mucus permeability in mice due to slower growth and poor organisation of the inner mucus layer associated with the production of immature, non-*O*-glycosylated Muc2 and a reduced abundance of fibre-fermenting *Bifidobacterium spp.*.[18] These effects could be alleviated with either the prebiotic inulin or probiotic *Bifidobacterium longum,*[18] consistent with similar evidence that non-mucin degrading *Bifidobacterium dentium* promotes goblet cell proliferation and mucus production, glycosylation and expulsion.[106]

In contrast, high fibre intake and increased SCFA production are beneficial for mucosal health. Acetate, propionate and butyrate improved tight junction formation and epithelial barrier function in colonic epithelial cells *in vitro.*[107] Increased microbiome-accessible fibre prevented mucus thinning and downregulation of tight junction proteins in mice fed a high-fat diet, leading to improved intestinal barrier function associated with

increased abundance of fibre-degrading bacteria such as *Faecalibacterium* and *Bifidobacterium spp.* and serum SCFA concentrations.[108] However, a causal role for the microbiota was not confirmed.[108] Propionate, produced by many *Clostridia spp.*, promotes production of the antimicrobial peptides regenerating islet-derived protein type-3β (Reg3B) and γ (Reg3G), which drive epithelial proliferation and intestinal barrier repair in mice.[109] This was mediated through activation of the G protein coupled receptor (Gpr)43, although downregulation of Reg3B and Reg3G in mice lacking the butyrate receptor Gpr109A indicated that other SCFAs likely have similar impacts.[109] Tolerance towards the commensal microbiome and food antigens is essential to limit GI inflammation and promote effective functioning of the mucosal barrier.[91] A breakdown in tolerance can lead to adverse immune responses targeting food antigens. Dietary fibre and probiotic SCFA-producing bacteria are proposed as therapeutic strategies for food allergy due to their ability to alter microbiome composition, promote immune tolerance, and improve mucosal health and barrier function as reviewed recently.[112-114]

In human studies, the impact of fibre on GI barrier function depends on numerous factors, including the study population, GIT location and the type of fibre administered. A recent systematic review did not identify any studies demonstrating that lower fibre intake was a risk factor for intestinal permeability.[115] Intestinal permeability was not altered by one month of treatment with barley β-glucan in healthy adults,[116] 4 weeks of pectin supplementation in healthy young adults or elderly subjects,[117] or 6 weeks of psyllium fibre in children with irritable bowel syndrome (IBS).[118] However, yeast-derived β-glucan did reduce paracellular and transcellular permeability in *ex vivo* cultures of terminal ileum.[119] Similar studies of colonic biopsies from elderly subjects showed that β-glucan significantly improved barrier function in those with GI symptoms, but had no impact in healthy controls.[120] Wheat-derived arabinoxylan was effective in both healthy controls and patients with GI symptoms.[120] In overweight, pregnant women, those with lower fibre intake and abundant fibre-fermenting *Faecalibacterium prausnitzii* had high levels of the intestinal permeability marker zonulin.[121] In adults with non-alcoholic fatty liver disease fibre intake correlated with lower zonulin levels.[122] Furthermore, a 48-week intervention with high fibre bean flour significantly reduced intestinal permeability in Malawian children.[123] Further research should investigate the impact of microbiome composition on the efficacy of such interventions, and whether this contributes to the variability between studies.

The role of dietary fibre and SCFAs in regulating the lung mucous barrier has primarily been elucidated through investigation in disease pathologies in animal models. For example, influenza A virus infection in mice reduced the abundance of *Lactobacillus* and SCFA production, and led to impaired macrophage killing and susceptibility to secondary *Streptococcus pneumoniae* infection.[53] Although acetate supplementation alleviated these effects and reduced bacterial invasion in a Gpr43-dependent manner, it is unclear whether this was associated with changes in the mucosal barrier.[53] Intraperitoneal injection of butyrate prevented mucus hypersecretion in an asthma-like mouse model of ovalbumin-induced allergic airways disease (AAD), suggesting a role in regulating mucus homeostasis after allergen exposure.[20] In humans with metabolic syndrome, fibre intake positively correlated with circulating interleukin (IL)-22 levels.[124] IL-22 reduces goblet cell hyperplasia in murine AAD models,[125,126] and improves epithelial barrier function in both influenza virus and secondary *S. pneumoniae* infection.[127,128] However, a direct relationship between fibre intake, the microbiome and maintenance of the mucous barrier through induction of IL-22 has yet to be demonstrated, and IL-22 and microbiome changes may have pathogenic roles in COPD.[1,2,17,129]

Lipids/fats

Dietary fats, such as triacylglycerols, are digested by host enzymes (lipases) into free fatty acids and monoglycerides, which mix with bile acids in the duodenum to form small aggregates (micelles) that are transported across the intestinal epithelium.[97] Notably, dietary fatty acids are mostly absorbed in the small intestine and thus are less accessible in the colon where microbial density is greatest.[97]

In a mucus gel *in vitro* with media containing lipids and bile acids designed to reflect GI contents after consumption of a normal meal, the generation of a lipid microemulsion formed a physical barrier to *E. coli* migration.[130] However, this study did not assess the impact of media containing a higher abundance of lipids to reflect digestion of a high fat diet (HFD), nor did it assess whether other microbiota may influence this relationship *in vivo*.

In mice, a 'Western-style' diet high in fat led to the degradation and permeabilization of the mucous barrier that was associated with reduced commensal bacteria such as *Bifidobacterium* spp. and *A. muciniphila* and increased *Proteobacteria*, a phylum containing pro-inflammatory pathogens and associated with IBD.[18,108,131,132] Mice fed a HFD also had reduced mucus volume in the colon,[133] and increased encroachment of bacteria into the

mucus layer through suppression of REG3G.[131] Saturated fat in particular induced oxidative and endoplasmic reticulum stress which impaired goblet cell differentiation, MUC2 and claudin-1 protein, and mucosal membrane barrier function which was associated with increased *Prevotella* and decreased *A. muciniphila* populations.[134]

It is difficult to discern whether other features of Western diet such as low fibre content contribute to these effects, particularly as a HFD reduces the total bacterial load in faeces indicating that insufficient microbiome-accessible nutrients are reaching the colon and compromising host-microbiome symbiosis.[131] Indeed, supplementation of HFDs with fibre can alleviate many of their negative effects on the mucous barrier by restoring bacterial load and microbiome composition.[18,108,131,135] Furthermore, mucus thickness, goblet cell numbers and tight junction proteins were reduced in mice fed a HFD containing soybean or pork, but not chicken protein suggesting that protein composition affects HFD-induced barrier dysfunction.[136]

In humans, fat intake is an independent risk factor for increased GI permeability,[115] although pregnant women with lower GI permeability often have greater consumption of omega-3 polyunsaturated fatty acids.[121] HFDs reduce bacterial load in human faecal samples, and negatively correlate with microbial diversity and richness and the abundance of commensals such as *F. prausnitzii* and *A. muciniphila* similar to changes associated with impaired barrier function in mouse models.[137-139]

There is less evidence of interactions between dietary lipids, the microbiome and lung mucus barrier in healthy states. Although mice fed HFDs have altered GI microbiome composition and develop respiratory inflammation, histopathology and impaired lung function, they do not have altered lung mucus production without another stimulus such as in disease models.[59,92,140] More detailed analysis of mucus composition and characterisation of the respiratory microbiome would provide further insights.

Protein

Dietary protein is the fundamental source of amino acids in mammals.[97] Though its composition and digestibility is influenced by the amount and source of dietary protein, most is digested and absorbed in the small intestine, which exhibits the highest concentration of amino acids along with short-chain carbohydrates. The microbiota in different locations of the gut is shaped by the availability of dietary proteins.[97] Fermentation of dietary proteins by primary fermenters like *Bacteroidetes* occurs in the distal colon, and moderating protein

intake can disrupt the microbiome and reduce the production of SCFAs and biogenic amines, which are amino acid deamination products.[141]

The biogenic amine histamine is produced by *E. coli*, *Lactobacillus vaginalis* and *Morganella morgani in vitro*,[142] and antagonism of the histamine receptor in colon epithelial cells impaired mucus production.[143] This suggests that microbial deamination of amino acids contributes to maintaining the mucous barrier. However, antagonism of the histamine receptor in mice increased goblet cell numbers in the jejunum,[144] indicating that the histamine effects may be location dependent, or regulated by other factors not present *in vitro*.

In a pig model, moderate protein intake (13% crude protein) improved bacterial diversity in the ileum compared to high (16%) or low (10%) protein diets.[141] Moderate protein intake also reduced the abundance of taxa associated with colorectal cancer such as *Peptostreptococcaceae*, *Streptococcaceae* and *Enterobacteriaceae* while increasing SCFA-producing commensals like *Clostridiaceae*, *Micrococcaceae*, *Lactobacillaceae* and *Actinomycetaceae*.[141] In the colon, the moderate protein diet increased proportions of *Lachnospiraceae*, *Prevotellaceae*, and *Veillonellaceae*, which positively correlate with the production of SCFAs and reduced proportions of *Ruminococcaceae*, *Christensenellaceae*, *Clostridiaceae*, *Spirochaetaceae*, and *Bacteroidetes* compared to the high protein diet.[145] Further reduction of protein (10% crude protein) increased the *Escherichia*:*Shigella* ratio of the microbiome and interfered with host nutrient absorption, which inhibited stem cell proliferation and damaged ileal morphology, though there was no evidence of increased intestinal permeability.[141,145]

Even if total protein intake is comparable, the type of protein may impact the GI mucus layer. Chicken protein promoted a thicker mucus layer and increased goblet cell numbers compared to soybean protein.[146] While this was associated with a greater abundance of *A muciniphila*, it was not clear if it was a causal relationship.[146] Another study showed that chicken protein increased mucus thickness compared to soybean protein in mice fed a HFD, but not a low fat diet whereas pork protein increased colon mucus thickness and goblet cell numbers irrespective of dietary fat.[136] Although microbiome composition was not assessed this study suggests that both protein source and interactions with other macronutrients impact the mucous barrier.

Human studies widely validate evidence from animal models and high protein intake, particularly animal protein, is associated with increased GI permeability and/or reduced barrier function.[115] However, supplementation with animal (casein) but not soy protein increased the expression of genes associated with epithelial barrier function and mucus

production in the rectal mucosa.[95] A dietary intervention study in humans demonstrated that different protein sources (red meat, white meat, non-meat) had effects on microbiome composition that differed between subjects with high or low intake of saturated fat.[147] This suggests that both microbiome composition and interactions with other nutrients may explain the differing impacts of protein intake on mucosal health. While this potential and the mechanisms underpinning it remain to be validated, it should be noted that several mucosa-associated taxa such as *Akkermansia, Faecalibacterium and Bacteroides* were reproducibly altered by changes in dietary protein, irrespective of the source of saturated fat content in humans.[147]

MICRONUTRIENTS: IMPACT ON THE MICROBIOME AND MUCOUS BARRIER

Along with macronutrients, micronutrients derived from both diet and microbial metabolism such as iron, B vitamins, vitamin A (retinol), and the antioxidant vitamins C and E, are essential for health and regulate microbiome composition, microbe-microbe and microbe-host interactions at the mucosal surface.[148,149]

Iron

Iron levels are lower in the colonic mucosa compared to the lumen, in part due to the secretion of host iron-binding proteins to limit bacterial growth, favouring colonisation of the outer mucus layer by non-pathogenic taxa.[88,150] In mono-colonised germ-free mice, mucosal-associated commensal *E. coli* (compared to luminal isolates) compensated for reduced iron availability by increasing the expression of genes in the ferric iron uptake pathway, and the production of the siderophore enterobactin.[88] Microbial metabolites such as diaminopropane or reuterin from *L. reuteri* inhibit hypoxia-inducible factor (HIF)2α-induced upregulation of iron transporters in the duodenum in mice on a low iron diet.[151] If intestinal barrier integrity is compromised, such as in *Muc2*$^{-/-}$ mice, host-microbiome interactions impair hepatic lipid biosynthesis and splenic erythrophagocytosis resulting in haemolysis that increases serum iron levels to promote bacterial growth during LPS-induced sepsis.[152] Thus, host and microbiota compete for the acquisition of iron with microbiota regulating host functions to increase iron availability. It is unsurprising, therefore, that dietary iron was a strong regulator of microbiome composition in mice.[150]

A high heme (iron porphyrin) diet in mice drastically altered microbiome composition, increasing the abundance of Gram-negative, mucin-degrading bacteria (*Bacteroides*, *Proteobacteria*, *Verrucomicrobia*), which disturbs host-microbiome symbiosis at the mucosal barrier and increases intestinal permeability.[153-155] Sulphide production from these taxa chemically reduces disulphide bonds within and between mucin monomers while heme-induced lipoperoxidation and formation of aldehydes, which may be regulated by microbiota, promotes mucosal inflammation and DNA damage and impairs tight junction formations, resulting in mucus denaturation and microbial penetration into underlying tissue.[153-156]

Iron overload with ferric citrate also increased intestinal permeability, which was associated with downregulation of *Muc2*, *Tff3*, and tight junction proteins in the jejunum.[157] However, other studies found that diets high in non-heme iron reduce the abundance of *Proteobacteria* and may improve mucosal health in murine colitis models.[158,159] Intriguingly, iron overload through diet, intravenous administration or transfusion of red blood cells increased the abundance of *Clostridia spp.* and reduced *Parabacteroides* and *Lactobacillus* genera.[158] Although the impacts of these changes in microbiota are unclear, both faecal and serum iron negatively correlated with faecal indoles, microbiome-derived tryptophan metabolites which promote mucosal health.[158]

Dietary iron intake may also impact the lung mucosa.[160-162] Opportunistic pathogens, such as *Neisseria meningitidis* which colonises the nasopharynx, require iron and upregulate iron transport mechanisms during infection.[74] Thus, iron availability in lung tissue may regulate the virulence of these bacteria. Naïve mice and those with AAD had increased iron in the lungs after consuming a high iron diet, while a low iron diet reduced lung iron levels only in mice with AAD.[160] Intriguingly, while a low iron diet induced a trend towards reduced mucus-secreting cells in the airways of naïve mice, both low and high iron diets significantly reduced mucus-secreting cell numbers in AAD.[160] This indicates that both iron deficiency and overload regulate mucus production in the lungs.

B vitamins

Many members of the microbiome are capable of *de novo* synthesis of B vitamins,[87,89,96,98,148,149,163] and many others possess partial synthesis pathways and are capable of scavenging precursors from other microorganisms to synthesise B vitamins such as cobamide (B_{12}).[164,165]

When micronutrient availability is reduced by dietary deficiency, microbes may migrate towards the epithelial surface where cross-feeding between mucolytic and non-mucolytic bacteria may help microbiota to obtain nutrients whilst maintaining the mucous barrier.[96] This relationship has been modelled *in vitro*, where the production of vitamin B_{12} analogues by *Eubacterium hallii* promotes *A. muciniphila* growth and propionate production.[89] *Anaerostipes caccae,* which contains a predicted complete vitamin B12 biosynthesis pathway, promoted the expression of mucin degradation components in *A. muciniphila* (which cannot synthesis vitamin B_{12}[163]) during co-culture.[90] Similarly, mucolytic *A. muciniphila* promoted growth and butyrate production in *E. hallii* and *A. caccae* that utilise mucus-derived sugars as an energy source.[89]

In mice, SCFAs, such as butyrate, promote mucus production and goblet cell differentiation,[87,98] whilst *A. muciniphila* promotes mucin turnover further demonstrating the importance of the symbiotic exchange of vitamin B12 in maintaining the mucous barrier.[89] Evidence suggests that similar cross-feeding occurs with other B vitamins, as dietary deficiency or excess of individual B vitamins has little impact on microbiome composition in mice even though in many cases ~20-30% of the microbiome was auxotrophic for the vitamin being tested.[165] Thus, symbiosis between mucus-associated microbes, particularly during micronutrient deficiency, may be essential for the maintenance of a healthy microbiome composition and the host mucous barrier.

Microbial synthesis of B vitamins promotes the integrity of the mucosal barrier. Like butyrate, niacin (B_3) activates GPR109A in mice to induce tolerogenic immune responses in epithelial cells, DCs, macrophages and regulatory T cells (Treg) which may limit inflammation and damage to the epithelial barrier.[110] Metabolites generated in the riboflavin synthesis pathway by microbiota in the gut and lungs stimulate the expansion and activation of mucosal-associated invariant T cells that promote tissue repair responses that help maintain epithelial barrier integrity.[166,167] Finally, prebiotic administration of galactooligosaccharides, polydextrose and sialyllactose increased the abundance of B vitamins in the colon contents of mice exposed to social stressors, in particular, *Bifidobacterium*-derived vitamin B6, which reduced systemic inflammation.[94]

Other vitamins

Microbiota-induced stimulation of host retinoic acid synthesis (active form of vitamin A) in small intestinal epithelial cells acts synergistically with SCFAs (particularly butyrate) to

promote immune homeostasis in mucosal DCs.[111] Stimulation of TLR2 by microbiota also increases immunoactive vitamin A synthesis in DCs, and enteric infection is associated with risk of vitamin A deficiency.[149] In the lungs, retinoic acid suppresses T-helper (T_h)9 cell differentiation and reduces mucus production and goblet cell hyperplasia in mice with AAD.[168]

Vitamin D deficiency in mice promotes GI mucus thinning and bacterial penetration associated with the expansion of mucus-degrading bacteria (*A. muciniphila, Solitalea canadensis*) and reduction of butyrate which could be alleviated by exogenous administration of active vitamin D (1, 25-dihydroxyvitamin D_3).[169] In part, the impairment of the mucous barrier in vitamin D deficiency is due to a reduction in IL-22 production from ILC3s in the colon, which is essential for the maintenance of the mucous barrier.[170] Finally, dietary antioxidants (e.g. vitamins C, E) are necessary for the survival of commensal anaerobes such as *Bacteroides*.[96,168] Overall, this demonstrates the important role of vitamin A, vitamin D and dietary antioxidants in promoting a healthy microbiome composition and tolerogenic mucosal immune responses.

DYSBIOSIS OF GUT MICROBIOME IN DIET-RELATED IMMUNE DISORDERS (Figure 5)

IBD

IBDs encompass ulcerative colitis and Crohn's disease.[171] They are characterised by impaired barrier function of the intestinal mucosa, leading to enhanced permeability and dysregulation of tight junctions that initiate defective activation of acquired mucosal immune responses.[29] Environmental factors, such as diet contribute to the pathophysiology of IBDs and animal models of disease are essential in understanding the relationship between microbiota and the mucous barrier in IBD.[29]

Animal models of colitis have been used to demonstrate the role of microbiota in pathogenesis, particularly during early disease where mice with *Firmicutes*-dominant communities were resistant to colitis development while *Bacteroides*- and *Proteobacteria*-dominant communities increased susceptibility through induction of innate or antigen-specific CD4+ T cell inflammatory responses.[132] HFDs increase *Proteobacteria* and reduce *A. muciniphila* and mucus thickness, impair tight junctions and cause low-grade inflammation in mice, which predisposes to colitis and this can be alleviated by supplementation with soluble fibre such as inulin or pectin.[131,134,175,176] Although these effects

were independent of SCFA production, other studies show that fibre deficiency predisposes mice to infection-induced colitis,[84] while acetate and propionate promote mucin and REG3 production, as well as GPR43-induced proliferation of intestinal ILC3s to maintain the mucous barrier and reduce disease severity.[109,131,177]

Diets high in animal fat and low in fibre are associated with the onset of ulcerative colitis and Crohn's disease in humans,[178] while high fibre intake is associated with reduced risk of Crohn's disease.[179] Experimentally β-glucan-based dietary fibre reduced paracellular and transcellular permeability in *ex vivo* terminal ileum cultures from Crohn's disease patients.[119] However, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) improved patient reporting in IBD, particularly in ulcerative colitis, which was associated with reduced fibre-digesting *B. longum, Bifidobacterium adolescentis* and *F. prausnitzii* and reduced faecal SCFAs.[180,181]

Perturbations in gut microbiomes may precede the development of IBD, as healthy individuals with high genetic risk of IBD due to functional genetic variants in genes involved in bacterial handling (e.g. nucleotide-binding oligomerization domain-containing protein (NOD)2, immunity-related GTPase family M protein (IRGM), autophagy related-16 like-1 (ATG16L1), caspase recruitment domain family member 9 (CARD9), FUT2) had reduced abundance of the acetate-to-butyrate converter *Roseburia spp.*[182] Moreover, the microbiome in biopsies from inflamed tissue of IBD patients is markedly different from non-inflamed tissue, suggesting that any associations are highly site-specific.[183] Significant reductions in butyrate-producing *Anaerostipes hadrus* were associated with inflamed tissue of Crohn's disease and ulcerative colitis patients and correspond to epigenetic changes in the host mucosa.[183] Further studies, in particular longitudinal population studies over the course of IBD development and progression, will be essential to elucidate the precise relationships between the microbiota, mucous barrier and IBD in humans.

Obesity and diabetes

Obesity and diabetes are metabolic diseases that have reached pandemic proportions, affecting >8% of the population.[190] Both are characterised by a state of chronic, low-grade inflammation with abnormal expression and production of inflammatory mediators, and the gut microbiome is implicated in their development.[191] Mice that consumed food with greater energy density had lower microbial diversity and levels of serum citrulline, a marker of intestinal health.[19] Excess supply of nutrients, in particular protein, reduced the need for

microbiota to rely on symbiosis with the host to obtain nutrients, facilitating the expansion of pro-inflammatory taxa such as *Clostridiaceae* and *Erysipelotrichaceae* and reducing the abundance of commensal taxa associated with the mucous barrier like *Lachnospiraceae*, *Ruminococcaceae* and *Akkermansia*.[19] Levels of the mucin degrading bacteria *A. muciniphila* inversely correlated with body weight in rodents and humans, and are reduced in obese mice.[192] However, *A. muciniphila* treatment in mice reversed HFD-induced metabolic disorders and increased the levels of intestinal endocannabinoids, which regulate inflammation, mucosal secretions and barrier integrity.[192]

In humans, high total energy or fat intake, serum glucose levels or insulin sensitivity are all associated with increased GI permeability that indicates dysfunction of the mucous barrier.[115] Obese children have reduced abundance of *Bacteroidetes* and *Bifidobacterium* and increased *Firmicutes* in the distal gut compared to lean participants.[193] The differences in gut microbiome composition may contribute to marked alteration in overall metabolic capacity potentially leading to variations in calorific values of diets and host weight gain, as microbiomes dominant in *Firmicutes* are more efficient at extracting energy than *Bacteroidetes*-dominant microbiota and are enriched with genes associated with nutrient transport.[22] In contrast, patients with diabetes had reduced *Firmicutes* and *Clostridia* abundance suggesting that different factors regulate microbiome composition in different metabolic diseases and that insulin sensitivity should be considered a separate variable in microbiome studies of obesity.[194,195] Thus, manipulation of gut microbiota by targeted dietary interventions may help regulate energy balance in individuals who are obese or diabetic.

Obesity is associated with exacerbating other inflammatory conditions, including respiratory disease.[135,196] Obese mice have more inflammation, epithelial damage and airway hyper-responsiveness (AHR) following challenge with ozone, a non-atopic asthma trigger, than lean mice.[197] This phenotype could be conferred to non-obese mice by transfer of faeces from obese mice and was alleviated by administration of antibiotics or the prebiotic fibre pectin, indicating a central role for the microbiome. Furthermore, obese asthmatics have elevated inflammation and increased airway remodelling pathways in the transcriptome of bronchial biopsies, which were associated with altered microbiomes of the oral and nasal cavities, lung and faeces.[198]

Rheumatoid arthritis (RA)

RA is a chronic and progressive autoimmune disease affecting ~0.5-1% of the global population and is caused by genetic and environmental factors.[199] Arthritis-prone (SKG) mice housed in germ-free conditions develop less severe and have delayed onset of autoimmune arthritis and ileitis than conventional mice after administration of curdlan (a purified β-glucan which triggers severe, chronic arthritis).[200] This was due to reductions in IL-17A production in neutrophils and intestinal endoplasmic reticulum stress and prevention of the loss of ileal goblet cells after curdlan administration. Co-housing conventional SKG with WT mice alleviated ileitis, but not arthritis indicating that only the former was microbiota-dependent.[200] High-fibre diet or direct SCFA supplementation can attenuate experimental arthritis and inhibit bone loss in mice.[201] Additionally, in a humanised mouse model, exposure to *Prevotella histicola* promoted tolerogenic dendritic cell (DC) and Treg responses, suppressed T_h17 responses and reduced intestinal permeability through increased expression of tight junction proteins, reducing arthritis severity.[202] However, the gut microbiome in humans with RA exhibited increased abundance of *Prevotella* (particularly *P. copri*) and reduced *Bacteroides*, and enrichment of *P. copri* in the gut microbiome in mice increased sensitivity to chemically-induced colitis.[203] This suggest that different *Prevotella* species exert different influences on disease pathogenesis. Nevertheless, enrichment of *P. copri* may provide evidence that RA patients have predominant Th1 and Th17 immune responses and increased risk of IBS.[204]

An ongoing clinical trial is examining whether an anti-inflammatory diet improves RA symptoms by modifying the individual's metabolic profile and increases antioxidant levels, but also by altering the intestinal microbiome.[205] This includes reduced intake of red meat, eggs, and dairy products, which contain choline and carnitine that are metabolised by microbiota, including *P. copri* to produce the pro-inflammatory metabolite trimethylamine-N-oxide.[205] Furthermore, in clinical trials a high fibre diet increased Tregs and T_h1/T_h17 ratio in whole blood, lowered serum IgA concentrations and anti-citrullinated vimentin peptide levels, and improved quality of life.[206] Further research is needed to demonstrate a causal role for the microbiome in these interventions. Finally, Zhang *et al*., conducted a case-control metagenomic study of the faecal, dental and salivary microbiomes in treatment-naïve and disease-modifying anti-rheumatic drug-treated RA patients, and found that the RA-associated microbiome was substantially different from healthy controls in all sampling sites, and that changes were partially reversed by treatment.[207] Moreover, metagenomic linkage groups ('species'/MLGs) enriched in healthy individuals correlated negatively with markers of acute inflammation (C-reactive protein) and RA-specific auto-antibodies (anti-cyclic citrullinated

peptide (anti-CCP) and/or rheumatoid factor).[207,208] In contrast, some MLGs enriched in RA individuals showed positive correlations with anti-CCP, rheumatoid factor, IgG and IgA.[207,208]

Atopic dermatitis (AD) and psoriasis

AD is a chronic, multifactorial inflammatory skin condition that severely impacts quality of life, especially in early childhood.[209] Gut microbiota have a higher proportion of *Clostridia*, *Clostridium difficile*, *E. coli* and *Staphylococcus aureus (*which contribute to inflammatory responses) and reduced *Bifidobacteria*, *Bacteroidetes* and *Bacteroides* in AD patients compared to healthy controls.[209] The proportions of butyrate-producing bacteria (e.g. *Coprococcus eutactus*) decrease as the severity of AD increases in infants.[210] Moreover, intestinal *Clostridia* and *E. coli* were associated with AD through eosinophilic inflammation.[211] More recently, a psoriatic core intestinal microbiome was proposed,[212] which categorises patients into three 'enterotypes', with 'enterotype 2' (predominance of *Prevotella*) associated with more frequent bacterial translocation and higher inflammatory status (71%) than enterotypes 1 (predominance of *Bacteroides*) and 3 (predominance of *Ruminococcus*). Depletion of *A. muciniphila* in the gut of children with AD has been reported.[213] Mucin degrading bacteria such as this provide an endogenous source of nutrients in early life before the introduction of dietary glycan. This is crucial in allowing gut colonization by diverse microbes and promote appropriate immune development including NOD-like receptor signalling, antigen processing and presentation and immune tolerance.[105,213,214]

AD gut microbiota are also characterised by low colonisation of bacteria involved in maintaining gut health, like *Actinomyces* and *Eggerthella*.[215] AD patients also have reduced propionate and butyrate availability that is associated with high levels of a strain of *F. prausnitzii* that is a poor butyrate-producer. The increase in this strain was proposed to be due to the inflamed epithelium with barrier dysfunction releasing nutrients that favour its growth.[215] A similar study showed increases in *Faecalibacterium*, along with a reduction in SCFA-producing species such as *Bifidobacterium, Blautia, Coprococcus, Eubacterium* and *Propionibacterium* which may further exacerbate aberrant inflammatory responses in AD.[216] Several studies have investigated the use of probiotics for AD prevention and treatment, but the efficacy of such interventions may depend on the strains used, study location, and/or ethnicity of the subjects.[216,217] *Lactobacillus plantarum* CCFM8610 increased the diversity

and richness of the microbiome and upregulated IL-10 indicative of an anti-inflammatory environment.[217]Similarly, *Bifidobacterium lactis* Bb-12, *Lactobacillus* strain GG (ATCC 53103),[218] and a mixture of *B. longum* CECT 7347, *B. lactis* CECT 8145, and *Lactobacillus. casei* CECT 9104 alleviated AD.[219] In contrast, *B. lactis* CNCM I-3446, *L. acidophilus* (LAVRI-A1),[220] and *L. rhamnosus.* failed to ameliorate symptoms.[221] The use of probiotics in preventing or managing AD requires further investigation.

Asthma

Animal models have been used to demonstrate a wide array of mechanisms by which diet and microbiota regulate asthma or AAD. Dietary fibre suppresses AAD in mice through reducing *Firmicutes* and increasing *Bacteroidetes*, and promoting SCFA production that in turn suppresses DC maturation,[224] T_h2 responses[54] and eosinophil migration, while increasing eosinophil apoptosis[54] and Treg activity.[223,225] Administration of a synbiotic containing pectin, dextrin and *B. longum* in pregnant female mice alleviated ovalbumin-induced AAD, including mucus hypersecretion, in their offspring.[226] However, these effects were only observed in C57BL/6, but not A/J mice suggesting host genetics may impact the relationship between microbiota and lung mucus.[226] HFD-induced obesity in male mice promoted transforming growth factor (TGF)β-induced goblet cell hyperplasia and TGF-β-independent AHR in murine AAD.[59] A similar experiment in female mice showed that HFD reduced inflammation and AHR due to an impaired ability of pulmonary DCs to induce T_h1 and T_h17 responses.[92] Although lung mucus production was comparable to levels in control diet-fed mice, there was no investigation of GI tissues and it is unclear whether an HFD-induced increase in faecal *Proteobacteria* and decrease in *Firmicutes* may have impacted the GI mucous barrier.[92] Sex-specific differences in HFD-induced obesity and AAD are well documented,[227] and further research may elucidate the effect of microbiota on these differences. The composition of dietary fats in mice fed HFDs must also be considered. This is because pro-inflammatory omega-6 polyunsaturated fatty acids (PUFA) exacerbated neutrophilia but attenuated goblet cell hyperplasia whereas anti-inflammatory omega-3 PUFAs attenuated goblet cell hyperplasia and altered mucin gene expression, reducing *Muc4* and increasing *Muc5b,*[58,228] the latter of which is essential for mucociliary clearance and control of bacterial infection.[4]

Changes in the lung mucous barrier may also contribute to differences in lung microbiota in asthma. Increased Fut2 in murine AAD led to heavy α(1,2)fucosylation of lung

epithelial cells and goblet cell hyperplasia,[229] which may increase adherence and colonisation by pathogens leading to exacerbations, as noted in humans with the FUT2 secretor genotype.[230]

Allergy, atopy and wheeze are common physiological indicators for children at risk of developing asthma.[222] Fujimura *et al*., showed that gut microbiota from infants could be divided into three composition states with different relative risks for asthma. The highest risk group had reduced *Bifidobacteria*, *Akkermansia* and *Faecalibacteria* and increased fungi and pro-inflammatory metabolites, including primary and secondary bile acids and the omega-6 PUFA product 12,13-DiHOME.[231] Faecal water from this group promoted T_h2 and reduced Treg responses in naïve CD4+ T cells co-cultured with DCs. Interestingly, other PUFA metabolites, especially omega-3 PUFAs such as docosapentaenoate, and the lipid signalling molecules endocannabinoids, were associated with reduced risk of asthma in children and inversely associated with the abundance of *Christensenellaceae*.[232]

In adults, non-obese asthmatics had elevated histamine-producing *M. morgani* that may contribute to Type-2 immune responses,[142] and both obese and non-obese patients with severe asthma had reduced abundance of *A. muciniphila*.[198] A recent crossover study using inulin or a synbiotic containing inulin, *L. acidophilus, L. rhamnosus* and *Bifidobacterium animalis* improved asthma control, with changes in lung function correlated with faecal SCFAs.[93]

The lung is not sterile and the pulmonary microbiome could play a role in asthma,[2,5] particularly with increased abundances of *Haemophilus* and *Staphylococcus* in asthmatic patients, while *Prevotella* were associated with healthy controls.[233,234] A clinical study of the effect of azithromycin in a cohort of adults with persistent uncontrolled asthma (AMAZES) showed fewer exacerbations and reduced *Haemophilus,* although long term treatment increased antibiotic resistance.[235,236] Highly controlled complementary studies in well-defined patient cohorts and representative mouse models will enable the elucidation of the roles of microbiomes in different phenotypes, particularly severe steroid-resistant asthma, which is the greatest clinical need in asthma management.[235,237,238]

COPD

COPD is a heterogeneous condition caused primarily by cigarette smoking but also air pollution.[29,61] Whilst predominantly affecting the lungs, patients often present with GI co-morbidities such as IBDs, nutritional absorption deficiencies and increased intestinal

permeability.[29,56] Though few studies have investigated the gut microbiome in COPD, there is increasing evidence for roles of the gut-lung axis.[1] A study in mice have demonstrated that cigarette smoke exposure increased the abundance of *Lachnospiraceae* and expression of the mucin *Muc4* in the colon, while *Muc2* and *Muc3* expression were increased in the ileum.[239] Whether this impacts on the interactions of microbiota with the mucous barrier is unclear, but specific bacteria may target *Muc2* for adhesion.[76] Cigarette smoke exposure reduced anti-inflammatory SCFA levels in caecum contents of rats,[240] and induced mild colitis-like changes in the gut which predisposes to chemically-induced colitis in mice.[56] Conversely, chemically-induced colitis induced IL-6-driven neutrophilic lung inflammation associated with presumably gut-derived bacterial endotoxin,[55] and increased platelet-activating factor receptor that also drives inflammation and potentially predisposes to infection.[241,242] Cigarette smoke also increased colonic hypoxia and oxidative stress in mice.[242] Mucosal-associated, oxidative stress-sensitive bacteria are generally beneficial and promote immune tolerance while oxygen-resistant bacteria promote inflammation.[148] Thus, the balance of oxidative stress and hypoxia in colonic tissue may contribute to GI disturbance in COPD by regulating microbiota at the gut mucosal surface.[243] Dietary antioxidants such as vitamin C and E may be potential preventative or therapeutic strategies.[244]

Oral feeding of probiotic *L. rhamnosus* increased the secretion of the anti-inflammatory cytokines, IL-10 and TGF-β, as well as suppressor of cytokine signalling 3 (SOCS3) and tissue inhibitor of metalloproteinases (TIMP)1/2 in bronchial tissue, indicating the induction of an anti-inflammatory environment. Even though this study focused only on the lung, it suggests a role for the gut-lung axis.[245] Moreover, polymeric immunoglobulin receptor $(pIgR)^{-/-}$ mice develop spontaneous COPD-like remodelling under normal housing conditions but are protected if they are maintained in a germ-free environment.[246] Though germ-free conditions in the lung are likely the primary reason for this protection, further research should investigate the involvement of the GI microbiota.

In human studies, duodenal biopsies from cigarette smokers have increased *Firmicutes* (*Streptococcus, Veillonella*) and *Rothia,* and decreased *Prevotella and Neisseria* compared to never smokers, which may result from changes in bacterial adhesion to mucus components.[247] However, in faecal samples, smokers had increased *Bacteroidetes* and reduced *Firmicutes* and *Proteobacteria.*[213] Fibre intake is associated with reduced risk of COPD, [243,248] and the common co-morbidity Crohn's disease.[179] However, it is unclear if this impacts the mucous barrier.

Iron deficiency in COPD patients was associated with reduced exercise tolerance and increased exacerbation frequency, though it is unclear whether the effects were associated with dietary intake or microbiome composition.[249] Finally, remodelling of the airway epithelium in COPD patients contributes to the dysregulation of PUFA metabolism in the lung.[250] Indeed, increased abundance of omega-6 PUFA metabolites correlates with impaired lung function in female COPD patients.[251] Although microbiota are known to metabolise PUFAs,[231,232] it is unclear whether microbiome composition contributes to these changes and evidence that dietary PUFAs influence COPD pathogenesis in humans is limited.[252,253]

CONCLUSIONS

The burden of immuno-metabolic disorders, in particular, inflammatory respiratory and bowel diseases, are rising globally. Recent evidence produced by high-throughput sequencing of previously non-culturable microbes significantly implicate gut microbiota in the progression and/or severity of these chronic life-threatening disorders. In addition, the transition of research to increased focus on the site of host-microbiome interactions, namely the mucous barrier, has significantly improved our understanding of how the microbiome regulates host health. Crucially, the rheological and nutritional properties of the mucous barrier, in part, determine the overall composition of gut microbiota, and whether these microbes can interact with host intestinal epithelial cells. Physiological or chemical changes in mucus properties lead to alterations in the gut microbiome, and translocation of microbes through intestinal tissues. This results in the dysregulation of host immunity, both locally (gut) and systemically (e.g. blood, lungs). Novel therapeutic strategies that manipulate the gut microbiome with antibiotics, pre and probiotics, diets or natural products have been tested in various diseases in clinical and experimental studies and in many cases repair microbial dysbiosis and improve immunity. In particular, diet represents a safe, readily modifiable and cheap method of early intervention in chronic inflammatory diseases, which may have significant benefits to health through regulating the gut microbiome.

However, there remain several limitations in current research and understanding of diet-microbiome-mucus interactions. There is an urgent need for further clinical trials to implement findings in practice. While short-term dietary interventions have advantages in cost and subject compliance, long-term interventional studies in humans are necessary to more fully understand the role of diet in protecting against chronic inflammatory diseases. Improved characterisation of dietary patterns is necessary, as different components may all

alter the microbiome and mucous barrier through inter-related processes and regulating the intake of single factors in the diet without altering others is practically impossible in clinical settings. Finally, many studies remain observational and do not directly demonstrate whether functional outcomes of dietary interventions are caused by changes in the microbiome. Cause and effect and interventional studies are needed to elucidate these relationships. In addition to characterisation of the microbiome composition, a detailed understanding of microbial functions through improved transcriptomic, proteomic and metabolomic technologies and analyses will be essential to demonstrate causality, as will the use of robust animal models of disease. The diet-microbiome-mucous barrier axis is an exciting area of exploration to unravel the mechanisms that underpin immuno-metabolic disorders that are amenable to therapeutic modulation. An improved understanding of these complex systems could be exploited to develop novel preventative and/or therapeutic strategies.

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Table 1: Known mucolytic microbes of the gut and lung

	Mucolytic microbes	**Mucin Glycoprotein**	**Ref**
Gastrointestinal tract			
	Bifidobacterium bifidum *B. longum*	Unknown	252,253
	Ruminococcus gnavus *Ruminococcus torques*	MUC2	254
	Escherichia coli spp	MUC 2 MUC5A MUC1	255-257
	Bacteroides thetaiotaomicron	Purified *O*-glycans	258
	Akkermansia muciniphila	MUC3	259
	Helicobacter Pylori	MUC7 MUC5B	260
Lung			
	Pseudomonas aeruginosa	MUC1 MUC5AC	78,79
	Staphylococcus	Mucin-7 Mucin-16	261,262
	Veillonella parvula	Unknown	263
	Fusobacterium nucleatum	Unknown	
	Prevotella	Unknown	

	melaninogenica		
	Streptococcus parasanguinis	Unknown	

FIGURE LEGENDS

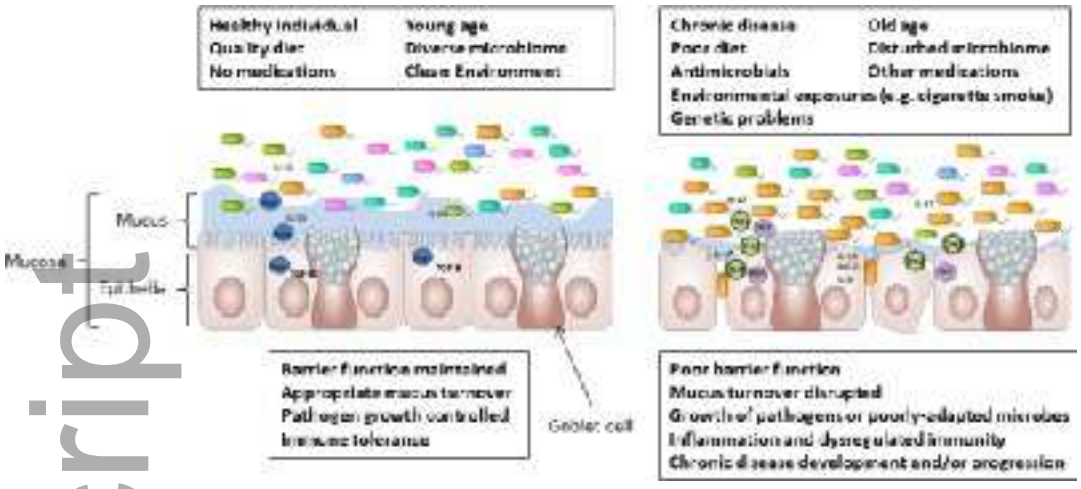
Figure 1: Mucus and the microbiome in health and disease. The mucosa, comprised of mucus and the underlying epithelia, forms a protective barrier that separates the host from the microbiome. In healthy individuals (left), diet, a diverse microbiome and other modifiable and non-modifiable factors that lead to tolerogenic dendritic cell and Treg responses, suppressed T_h17 responses and reduced intestinal permeability maintain barrier function, mucus turnover, pathogen growth and immune tolerance. However, in chronic disease (right), factors such as old age, poor diet, disturbances in the microbiome and exogenous exposures result in poor barrier function and mucus turnover, growth of pathogens or poorly-adapted microbes that reduce diversity in the microbiome, increase T_h2 ,T_h17 and pro-inflammatory cytokine responses. These changes contribute to chronic inflammation and the development and progression of disease.

Figure 2: (2a): Physiology of the gastrointestinal tract mucosa: The basal layer constitutes stem cells that can differentiate into goblet cells, enterocytes and/or Paneth cells. All the cells, except Paneth cells, differentiate and move towards the lumen of the gut. Enterocytes are covered with a glycocalyx and undertake nutrient digestion and absorption. Goblet cells contain mucus producing vesicles that produce two layers of the mucus barrier. A dense inner layer and an outer loosely hanging layer. Mucus is made up of inorganic salts, antimicrobial enzymes (such as lysozymes), immunoglobulins, glycoproteins and mucins. The lumen contains commensal and mutualistic bacteria, as well as dietary macro- and micro-nutrients.
(2b): Physiology of the respiratory mucosa. The airways are lined with ciliated columnar epithelial cells, interspersed with mucus-secreting goblet cells. The highly hydrated mucus is largely comprised of mucin glycoproteins, and include both secreted (gel-forming and non-gel forming) and membrane-associated mucins which closely adhere to the epithelial surface. The beating of cilia is responsible for the movement of mucus and expulsion of microorganisms and particulates.

Figure 3: Early life shaping of the gut microbiome: The placental environment is devoid of a microbiome. The gut microbiome is influenced by many factors from neonatal to adult life such as Mode of delivery, initial diet, timing of transition to solid foods and day care attendance.

Figure 4: Diet affects both the microbiome and the mucus membrane.Maconutrients such as Low dietary fibre primes gut microbiota to utilise glycoprotein from the glycocalyx as a nutrient source, leading to mucus degradation, which is also linked with increased susceptibility to the pathogen Citrobacter rodentium. High dietary lipid increases Mollicutes compared to Bacteroides and reduces goblet differentiation, which results in increase in endoplasmic reticulum oxidative stress and decreases MUC2 production. Increases in dietary heme iron causes increases in sulphur promoting sulphur-utilising bacteria to grow that degrade mucus. Reduction of dietary protein decreases stem cell proliferation.
Along with macronutrients, micronutrients derived from both diet and microbial metabolism (e.g. iron, B vitamins, vitamin A/retinol, antioxidant vitamins C and E), are essential for health and regulate microbiome composition, microbe-microbe and microbe-host interactions at the mucosal surface.

Figure 5: Summary of dysbiosis and diet-related immune disorders. Numerous immune disorders, including inflammatory bowel diseases, obesity/diabetes, , rheumatoid arthritis, atopic dermatitis and psoriasis, chronic obstructive pulmonary disease (COPD), and asthma are associated with changes in the microbiome and diet. These changes may be either deleterious or protective, depending upon the nature of the disease and the change and may be targeted therapeutically. CS = cigarette smoke; DiHOME = dihydroxy-9Z-octadecenoic acid; DMARDs = disease-modifying anti-rhematic drugs; IL = interleukin; SCFAs = short chain fatty acids.



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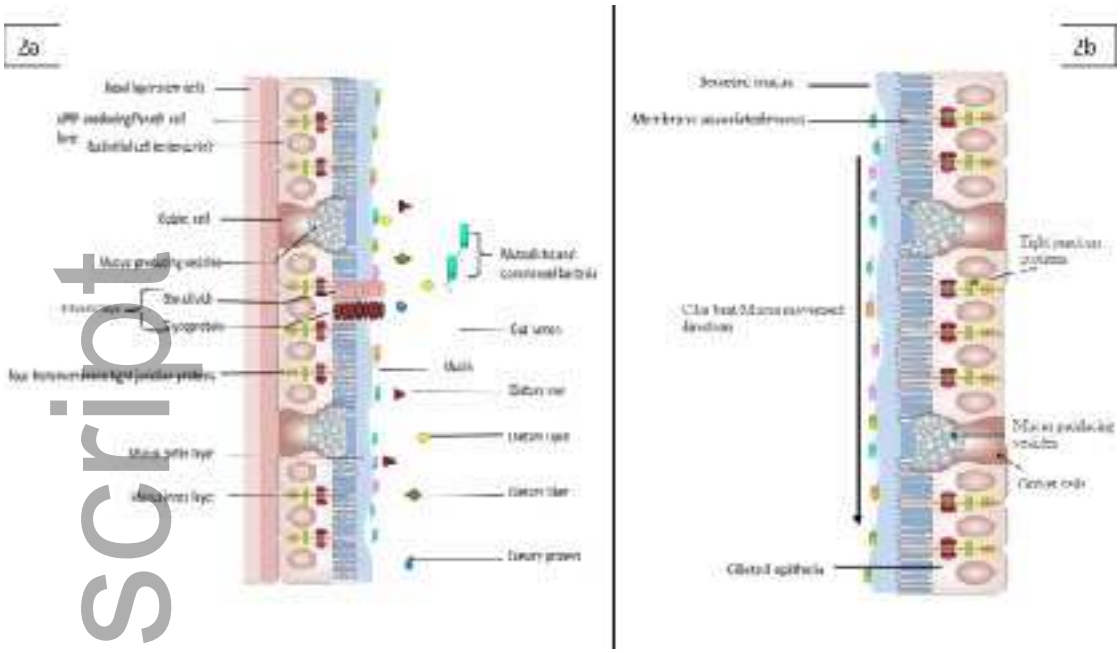

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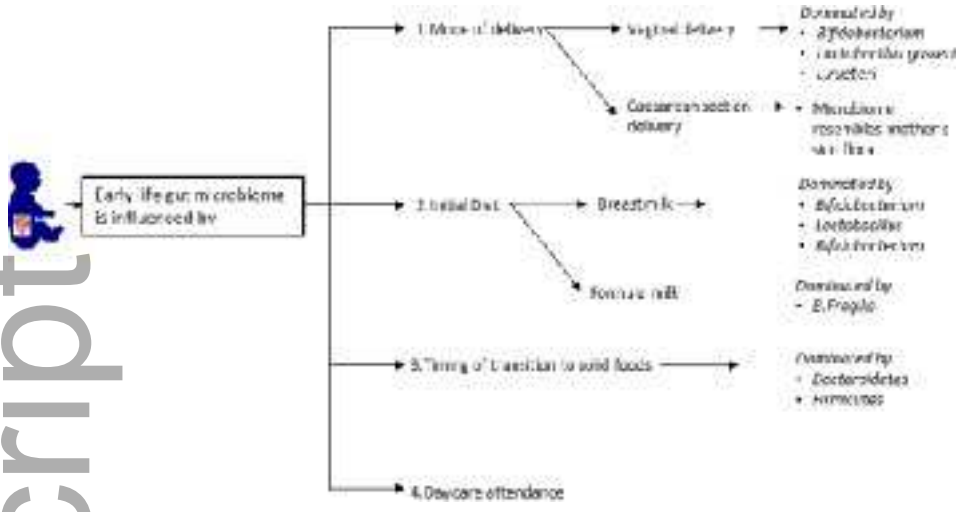

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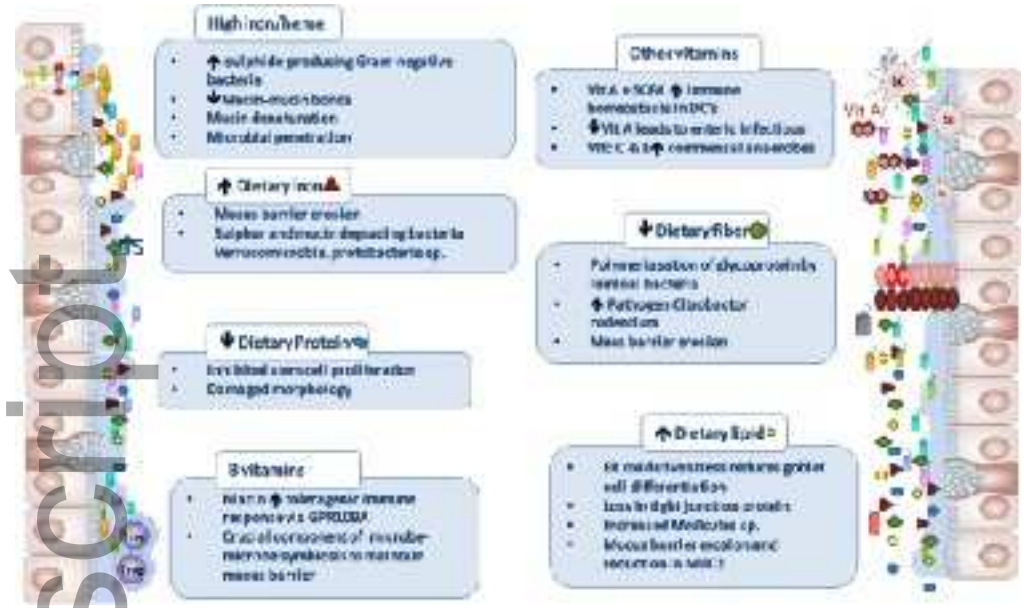

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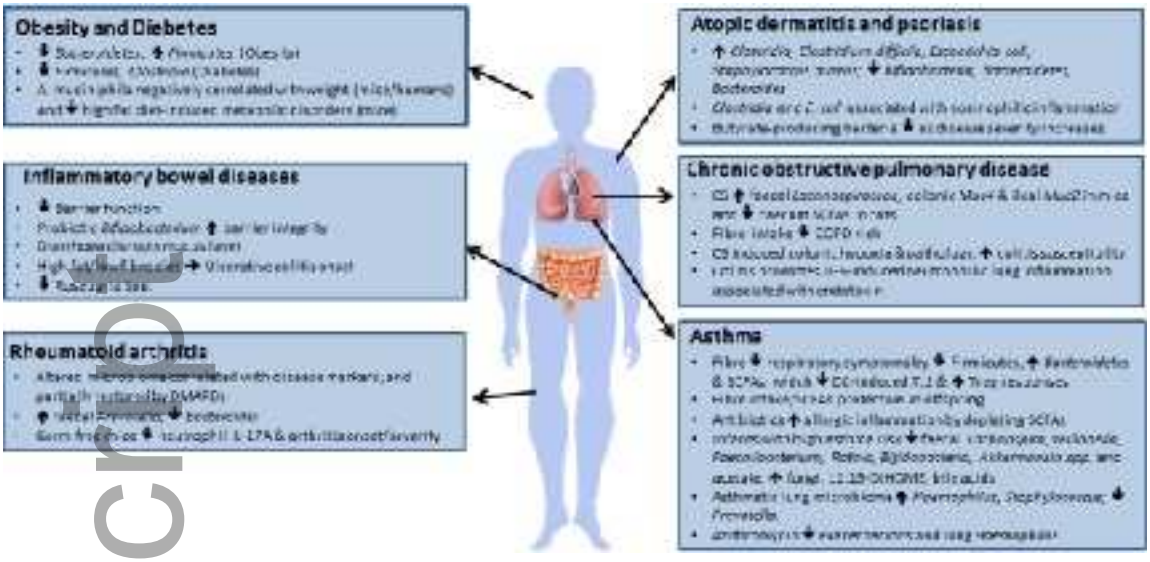

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