University of Groningen

Bachelor Thesis

Dysbiosis in the Microbiome Associated with Inflammatory Bowel Disease and the Potential of Dietary Fibers

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Abstract
The microbiome is an important regulator in the development of the immune system. The complexity and composition of the microbiota are crucial for maintaining health and intestinal homeostasis. The Western, high-fat/low-fiber, diet causes vital changes in the composition of the microbiota and is correlated with the development of multiple Western diseases, such as inflammatory bowel disease (IBD). A good balanced diet, contains the right dietary fibers and is proven to be effective against the alteration of the gut microbiota. Whereat each dietary fiber is characterized with its own specific health benefits. The indirect effects mainly cause an increased level of short-chain fatty acids (SCFAs), but the dietary fibers can also affect receptors directly. Research discovered the TLR2 and 4 as the most commonly affected receptors. In this thesis, the increasing dysbiosis of the microbiota is discussed, in which the dietary fibers inulin, β-glucan, and pectin are discussed in association with their direct and indirect effects on the microbiota, immune system and intestinal health.

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1. Introduction

The human gut is colonized by 100 trillion bacteria, divided in more than 35,000 bacterial species (1, 2). The two dominant bacterial phyla, the Bacteroidetes and Firmicutes, compose about 90% of the gut microbiome. The other 10% is devoted to phyla like Proteobacteria and Actinobacteria (3). Firmicutes, for example, can be sub-grouped into Clostridium coccoides (Clostridium cluster XIVa) and Clostridium leptum (Clostridium cluster IV). The bacteria, *Ruminococcus* and *Faecalibacterium*, are bacterial species of the Firmicutes phylum, in which *Ruminococcus* is placed into the Clostridium class (4). The three major genera of the Bacteroidetes phylum are *Bacteroides*, *Prevotella*, and *Porphyromonas* (3). Previously, research has analyzed all the human metagenomics and classified them in three clusters called enterotypes depending on the bacteria genus which is prevalently present in the gut of the individual (5). Enterotype 1 has the *Bacteroides* as the representative bacteria. Enterotype 2 and 3 respectively have *Prevotella* and *Ruminococcus* as most prevalent and abundant bacteria (4). However, this approach was followed by many controversial discussions since not all researchers agreed with this classification. Bacterial species within the same genus can vary from beneficial commensal to deadly pathogen. This variation is neglected when classification is simply grouped into the aforementioned enterotypes (6). Despite this, the enterotypes highlight the distinction and the relationship between the bacteria in the human gut (3). Based on environment, the type of diet, age, and possible diseases, the gut microbiome differs from individual to individual. The microbiome influences a variety of processes in the human body, such as metabolisms and immune responses, providing a well controlled nutrient metabolism and protection against infections pathogens (1, 7-9). Maintaining the symbiosis of the microbiome and its host is extremely important, as well as maintaining the microbiome in the desired composition.

2. The Health Properties of the Right Microbiome

2.1 Immunological Development

The composition of the microbiome determines the quality of the immune responses (10). It has been shown, for example, that the microbiome induces production of secretory IgA (SIgA) in the host. This is illustrated by a significantly lower SIgA concentration in germ-free mice (11, 12). IgAs are the most abundant antibodies found in the intestinal lumen and, after binding to the polymeric Ig receptor (pIgR), intestinal B cells translocate to the surface of the epithelial cells where they generate SIgAs (13). SIgAs protect the intestinal epithelium, they inhibit the entrance of pathogens by blocking the epithelial receptors for these pathogens. Also, they capture them in mucus and facilitate their removal out of the body (14). Altogether, the SIgA production is important for maintaining the intestinal structure and function and does not develop without the microbiome. Moreover, the microbiome is responsible for proliferation of intraepithelial lymphocytes (IELs) (15). IELs are specialized cells that are important in supporting the epithelial barrier homeostasis (16). In addition, the presence of the microbiome is associated with an increase in cytokine production, such as IL-12, interferon gamma (IFN-y), and IL-10 (17). The microbiome induced cytokines are also acknowledged for supporting expansion of B and T cells in Peyer's patches and the mesenteric lymph nodes of which CD4+ T cells and FOXp3-expressing regulatory T cells (Tregs) are increased the most (17). Depending on the microbiome and its host's condition,

it can modify immune responses by either promoting inflammation (by expanding CD4+ T cells) or suppressing it (by inducing more Tregs).

2.2. Bacterial Characteristics in the Immune Response

Specific bacteria are the driving force behind gut immune development. It has been shown that a higher concentration of *Bifidobacteria* causes maturation of the SIgA system, necessary for protecting the mucosal intestinal barrier (18). Colonization with *Bacteroides fragilis* is associated with a down-regulation of the response against a characteristic molecule for gram-negative bacteria, lipopolysaccharide (LPS) (18). LPS binds to Toll-like receptor 4 (TLR4) and consequently activates NF-κB, secreting pro-inflammatory cytokines and inducing intestinal inflammation (19). Down-regulating this response will lead to reduced inflammation and can prevent colitis. However, the bacterial surface protein polysaccharide A (PSA) of the *Bacteroides fragilis* can stimulate intestinal dendritic cells (DCs) to activate CD4+ T cells resulting in an inflammatory response with IL-12 and IFN-y secretion, as well as Th1 differentiation; a necessary response to pathogen infiltration (20). This confirms the immune modulating role of the microbiota. On the one hand, the microbiota can function as an immunosuppressant whereas, on the other hand, it can induce an inflammatory response. The result is dependent on the need of the host. For example, a downregulation in a body with an autoimmune disease or the induction of extra stimuli to fight an infection in an immunocompromised host, respectively. More bacteria with this modulating function are characterized in the human gut.

Recent research has demonstrated that segmented filamentous bacteria (SFB), a *Clostridium* related species from the Firmicutes phylum, also significantly contributes to development of the gut immune system. SFBs are tightly attached to the ileum and are known for inducing pro-inflammatory T helper 1 (Th1) and 17 (Th17) cells, as well as for Treg development (21-23). Th17 cells mainly produce IL-17 and IL-22 in the lamina propria and participate in the extracellular immunity against bacteria, thereby increasing the responsiveness against pathogens (22). While Tregs suppress unnecessary inflammatory responses and counteract reactions of self-reactive T cells (24). With an increase of Tregs, due to induction by microbiota, the T cell response can be properly maintained (25). The microbiome composition is crucial for maintaining homeostasis in T cell population. How the bacteria sense the host's need is unknown and more research needs to focus on the specific bacterial actions. The bacterial composition is vital for a healthy life as alterations may create a dysbiosis leading to a higher risk of diseases (26).

2.3. Compositional Changes Due to Diet

Emerging insight of the last decade has demonstrated that the microbiome is rather versatile and that the composition of the microbiome can be affected by lifestyle changes such as diet (9, 27). The most extreme changes in the microbiome were associated with two of the greatest dietary shifts in human evolution. The shift from the hunter-gatherer (the Paleolithic) to the farmer (Neolithic) society where a high carbohydrate diet was introduced. Moreover, a transition into the industrialized era influenced the diet with processed flours and sugars (28, 29). Living in the Western world of today is associated with high fat and low fiber intake, better known as the Western diet (30). Comparative studies have assessed the different microbiomes between Europeans living in accordance with the Western diet, and a rural African population from Burkina Faso whose diet consists of high amounts of fibers. Results showed a completely different bacterial composition between the two populations (27). Whereas Europeans are known for a dominant enterotype 1 (*Bacteroides*), the African

population showed a clear prevalence of enterotype 2 (*Prevotella*). Although many other factors are different between Europe and Africa, more studies have proven the effect that diet has on the alteration of the gut microbiome (31, 32). Significantly increased *Prevotella* bacteria were seen after introducing a high fiber diet, as well as an increased level of Firmicutes (4). On the other hand, a high-fat diet worked in the opposite direction and increased the level of *Bacteroides*, whilst decreasing the presence of *Prevotella* and Firmicutes (33). These bacterial shifts have been connected with serious health issues.

2.4. Consequences

Diet changes and the associated microbiome alterations have significant and sparsely discussed consequences. Studies have demonstrated that changes in microbiota, obtained after living according to the Western diet, are still reversible after only one generation (34). However, after several generations merged into the Western diet, progressive and non-recoverable diversity loss of the microbiota was observed (35). These alterations are the underlying cause of many Western diseases, such as diabetes, obesity, and cardiovascular diseases (36-39). Alteration of the microbiome even plays a role in the development of neurological diseases such as Alzheimer and autism as well as the development of certain cancers (40-42). The occurrence of these Western diseases is increasing significantly (43, 44). Therefore, awareness for the consequences of the Western diet, its impact on the microbiome composition, and the risks to develop Western diseases must increase. Moreover, one worldwide increasing Western disease is a chronical inflammation in the human intestine, known as inflammatory bowel disease (IBD) (45).

3. IBD as a Low-Fiber Related Disease

3.1. Alteration of Gut Microbiota

Inflammatory bowel disease (IBD) is the umbrella term which includes both ulcerative colitis (UC) and Crohn's disease (CD), a disease which has increased worldwide over the last decades (45). It is classified as one of the many Western diseases that is correlated with lower dietary fiber intake. Although the underlying cause of the development of IBD is still not understood, it is associated with an altered microbiota in patients. The gut bacteria triggers excessive immune responses by activating specific receptors called pathogen-recognition receptors (PRRs). Pathogens are recognized by PRRs, because of their characteristic molecules, known as pathogen-associated molecular patterns (PAMPS). Toll-like receptors (TLRs) are the best known PRRs in the human gut, expressed at the cell surfaces of almost every immune cell, as well as the intestinal epithelial cells (46). More receptors like NOD-like receptors (NLRs), which are intracellular, are present in these cells as well (46). These receptors will stimulate a suitable immune response after recognizing the PAMPs, inducing autophagy of the microorganism, and present pathogenic proteins to other immune cells. However, PAMPs are not only associated with pathogens. Since commensal bacteria are characterized by the same molecules, they will activate the PRRs too (47). It is acknowledged that TLR activation by commensals contributes in maintaining the intestinal epithelial homeostasis and protects against direct damage in healthy conditions (48). However, in the case of IBD, the ratio between commensals and pathogens is changed, therefore homeostasis cannot be remained (49).

The concentration of the Proteobacteria *Escheria coli* is proven to be significantly increased in IBD (49, 50). It is their presence that is linked to bacterial invasion into epithelial cells that, therefore, makes them pathogenic (45). Furthermore, a reduced microbiota

diversity is observed in IBD patients of which mainly bacteria from the Firmicutes phylum, such as *Faecalibacterium prausnitzii,* are decreased. Previous studies declared that *F. prausnitzii* increases the anti-inflammatory cytokines IL-10 and IL-8, together with metabolites that could possibly block NF-κB activation. On the other hand, the production of the inflammatory cytokines IL-12 and IFN-y is significantly lowered (51). Moreover, *F. prausnitzii* is a butyrate-producing bacteria, that increases the mucin production, as well as the production of antimicrobial peptides (AMPs) (52). In IBD patients, butyrate is observed to be decreased, which possibly contributes to gut inflammation (52). Studies also have shown that CD patients frequently have bacteria that resides in the inner mucus layer, tightly adhered to the epithelium, which is normally sterile in healthy controls (53). Bacteria, such as *Ruminococcus gnavus* and *Ruminococcus torques,* are known for degrading mucins, and not only use it as an energy source, but also offer it as nutrients to other bacteria in this mucus layer. Where healthy controls are able to keep fecal bacteria outside the mucus layer, an impaired barrier function in IBD patients is observed (54). The PRRs aforementioned will get activated by these bacteria, subsequently triggering an inflammatory response (46). Furthermore, the opposite effect that the commensal bacteria execute on the PRRs cannot be guaranteed in IBD. A poorer bacterial recognition is associated with a subset of PRR gene mutations discovered in IBD that will oppose intestinal homeostasis (48, 52).

3.2. NOD2 Mutation

Some CD patients have been recorded with mutations in the NOD2 gene that causes a dysregulated interaction between bacteria and the NOD2 receptor. The NOD2 protein is a receptor in the cytosol, present in intestinal epithelial cells, dendritic cells, and macrophages (52). It recognizes bacterial cell wall components, like peptidoglycans, that stimulate the NOD2 receptor and induce autophagy in the infected cells (55). Consequences of the NOD2 mutations are controversial. Whereas some suggest that mutations result in impaired activation of NF-κB (56), others suggest that an enhanced NOD2 activation leads to NF-κB upregulation, resulting in an excessive Th1 response (57). It is unclear whether NOD2 mutations cause deficient pathogen recognition, followed by failing in autophagy induction and the lack of sensing it to the innate immune system or causing commensal bacteria to be recognized as pathogens, resulting in an unnecessary inflammation induction (55). Nevertheless, increased pro-inflammatory cytokine production, such as TNF-α, IL-1β, and IL-6 have long been associated with IBD. Where these innate immune defects can be linked to NOD2 mutations, more susceptibility genes were found with mutations in IBD patients, enhancing the alteration of the microbiome.

3.3. ATG16L1 & TLR8 Genes

The ATG16L1 gene is correlated with a specific T300A mutation in CD patients leading to impaired bacterial uptake via autophagy (58). ATG16L is a vital protein to fulfil autophagy, an important mechanism against intracellular pathogens and thereby maintaining homeostasis (59). In addition, mutations in TLR8 genes were also reported to be an increased risk for inflammation in IBD patients (60). Both mutations can lead to a deficient bacterial recognition thereby inducing an inappropriate immune response. Overproduction of pro-inflammatory cytokines causing inflammation of the mucosal intestinal barrier, and increase permeability (61). Subsequently, more pathogens will be able to infiltrate the mucosal layer of the gut and thereby creating a positive feedback loop where more and more pro-inflammatory cytokines will be released. Moreover, the beneficial bacteria in the

gut will be dominated by the pathogenic bacteria, shifting the microbiome in the wrong direction (62).

3.4. Paneth Cell Dysfunction

Often associated with the susceptibility gene mutations and another cause for the dysbiosis is an impaired Paneth cell function (63, 64). Paneth cells are specialized intestinal epithelial cells, located at the bottom of the intestinal crypts. They are crucial in the regulation of the microbiome, achieved by secreting granules with antimicrobial peptides (AMPs), such as α-defensins (65). AMPs are important in the innate immunity and can directly kill or inhibit the growth of pathogens (64). However, they will do no harm to commensal bacteria, therefore, regulating the microbial composition (65). Impaired Paneth cell function may be a key contributor to the development of inflammation in IBD patients with the altered microbiota as an underlying cause (66). Mutations in the NOD2, as well as the ATG16L gene, are associated with impaired Paneth cell function, resulting in a lower production of AMPs (56, 58, 64). IBD patients are frequently recorded with defective expression of AMPs (52), correlated with an expansion in *Escherichia shigella (67)* and *E. coli (68)*. The gene mutations give a higher risk in developing deficient Paneth cells, therefore, fewer AMPs will get secreted and the intestinal microbiota cannot be regulated fully, resulting in a more pathogenic appearance that will induce inflammatory reactions, leading to IBD. Due to less functional Tregs in IBD (69), suppressing inflammatory responses might be harder to obtain. Simultaneously, an unregulated and exaggerated T cell response (Th1/Th17) has been noticed, leading to even more induction of the inflammation (55,82).

3.5. What Now?

Existed therapies for IBD are currently only focussing on reducing inflammation. Since the cause of IBD is still unknown and little is known about the disease itself, developing a cure is not possible yet (69). Most medication is synthetic and associated with unwanted side effects. Therefore, more research should be executed, focussing on naturally occurring supplements (70). Evidence has already been presented and nutrition therapy has gained a lot of interest in recent years (71). Especially when nutrition gets less immune modulating and a lack of fiber and high fat intake are associated with the increase in Western diseases (72). Consciousness about a healthy diet is critical. Studies have shown that a greater knowledge of nutrition among students results in consuming less unhealthy fats (73). Research has already acknowledged a correlation between the lack of dietary fibers in diet and the altered microbiota. To grow and function, the microbiota needs dietary fibers. For this reason, more research into dietary fiber intake has become increasingly relevant upon illustrating the effects on the microbiota.

4. Dietary Fibers

4.1. Classification

Dietary fibers can be classified in different groups but all can improve bowel habits. They are plant-based carbohydrate polymers that cannot be digested in the small intestines, and therefore reach the large intestines (74). Here, they serve as a food source for gut bacteria that can then produce health-promoting substances (75). They contain at least three monomeric units (MUs) and in previous literature, dietary fibers are often distinguished into

soluble or insoluble fibers (76). However, these physiological terms are not always reliable when not all characteristics are mentioned such as viscosity, fermentation, and bulking effects (74). Dietary fibers can also be subdivided by using their main source: 1) Non-starch polysaccharides (NSP), such as cellulose, β-glucan, pectin, and gear gum. Abundantly present in cereals, and the cell walls of fruits, and vegetables. 2) Resistant (non-digestible) oligosaccharides (ROs), like inulin, fructo-oligosaccharides, and galacto-oligosaccharides. Mainly found in plants, beans, and human milk. And 3) Resistant starches (RSs), including physically trapped, resistant granules (74). Dietary fibers are mostly known for their indirect effects on gut immunity. The microbiota-accessible carbohydrates (MACs) in the dietary fibers stimulate the growth of beneficial gut bacteria that will consequently produce substances such as short-chain fatty acids (SCFAs) (35, 77). These substances themselves, affect the host immunity in a positive way.

4.2. Fermentation Products

4.2.1. Beneficial Effects of Short-Chain Fatty Acids

SCFAs are fermentation products, just like methane, carbon dioxide, hydrogen, and lactate. These products contribute to the energy metabolism and will, therefore, increase the bacterial mass in the gut (78). SCFAs consist of one to six carbon molecules of which acetate, propionate, and butyrate are the most common SCFAs. They are water-soluble and are passively absorbed into the bloodstream where they contribute for 7-8% to the energy metabolism (78). It is suggest that SCFAs activate AMP-activated protein kinase (AMPK), a major regulator for metabolic homeostasis. A high concentration of SCFA is obtained via the effect of dietary fibers, and causing AMPK activation in the liver (79). Leading to the activation of ATP-producing catabolic pathways, like the oxidation of glucose or fatty acids. Whereas it simultaneously leads to inhibition of energy-consuming biosynthesis of these energetic molecules (80, 81). Suggesting that this AMPK activation may be a promising therapeutic pathway to tackle metabolic diseases, whereby the increase of dietary fiber intake can result in achieving this activation.

SCFAs are the primary energy source for epithelial colonic cells. Butyrate (C4) is deemed to be a key factor for the energy supply in colonocytes and may be critical for preventing colonic disorders (78). Moreover, SFCAs also stimulate the enlargement of Tregs in the colon (82-84). SCFAs bind to the G-protein coupled receptors (GPR) 41 and 43 present in almost all immune cells, such as intestinal epithelial cells (IECs), and also Tregs (82, 85). The intake of dietary fibers has already shown increased expression in the GPR 43 (86). Furthermore, SCFAs are able to activate mitogen-activated protein kinase (MAPK) which mediate cell differentiation, cell proliferation, cell death, and protective immunity (85, 87, 88). In addition, SCFAs hold the ability to inhibit histone deacetylase (HDAC) activity, which can then regulate transcription factors and on their turn, gene expression (89). It can also activate the peroxisome proliferator-activated receptor (PPAR), which is known for its transcription factor function. Forming a heterodimer with the retinoid X receptor, it regulates the expression of genes intricated in immunity and metabolism (89). Moreover, SFCAs lower the pH in the intestines, not only leading to inhibition of growth of pathogenic organisms but also reducing enzyme activities produced by the gut bacteria (90, 91). Unfortunately, SCFA levels can be reduced when the microbiome is altered. Changes in diet can cause these alterations and so, consequently affect the SFCA concentration.

4.2.2. Western Diet Alters SCFA Production

Conversely, a lower SFCA concentration leads to dysfunctional intestinal epithelial cells and causing a thinning of the intestinal barrier. This barrier separates the inner and outer environment and is necessary for maintaining healthy conditions. Reducing the protective layer causing encroachment of pathogens which has clear correlations with the development of diseases like IBD (50, 83). Clinical studies have already proven the positive influence after administering dietary fibers and therefore increasing the SCFA levels (90, 92-94). Although all studied dietary fibers show SCFA production, different fibers result in slightly different end-effects. Whereas β-glucans increase the production of propionate, oligosaccharides enhances the growth of *Bifidobacterium,* while inulin promotes the concentration of *Collinsella* (95). Without the induction of dietary fibers, the diversity of the microbiome will decrease. Not only will this have an effect on the SCFA production, also on the conversion of bile acids, regulated by the microbiome as well.

4.2.3. Another Fermentation Product Affected by Western Diet

Furthermore, the concentration of secondary bile acids is linked to the consequences of the Western diet. Normally, the primary bile acids (BAs): cholic acid (CA) and chenodeoxycholic acid (CDCA), are being converted into the secondary BAs: deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. Among others, the 7 a-dehydroxylase enzyme catalyzes this conversion in the gut, due to the presence of microbiota (91). The lower pH, obtained by SCFAs, regulates this conversion by inhibiting the enzyme's activity. However, a lower SCFA concentration dysregulates the conversion of the BAs in the gut. Research has shown that a high-fat, low-fiber intake also directly leads to an elevated production of secondary BAs (96, 97). Also exposed were enhanced bile salt hydrolase gene expression, increased levels of the portal fibroblast growth factor 19 (FGF19) and the farnesoid X receptor (FXR) (96, 97). Associated with the inhibited growth of some members of the dominating phyla Bacteroidetes and Firmicutes, the high secondary BA levels might, therefore, result in the emergence of inflammation in the intestines (33). When changing the diet into a more healthy one containing less fat and more fibers, the SCFA production will increase while the secondary BAs will decrease. Simultaneously, other fermentation products will become present, enhancing the regulation of the immune response even more.

4.2.4. Dietary Induced AhR Ligands

Currently, a lot of research is focussed on SCFAs as main immune active bacterial substrates but more immune active fermentation products are made by bacteria, such as indole derivatives. Whereas SCFAs are produced in reaction to dietary fiber intake, indole derivatives are molecules converted from another vital nutrition source, namely proteins. Some bacterial species in the gut, such as *Lactobacilli*, are able to generate indole derivatives from the essential amino acid tryptophan (98). The indole derivatives, such as indole-3-carbinol (I3C), indole-3-acetic acid (IAA), and indole-3-aldehyde (IAld), have the ability to serve as a ligand for the aryl hydrocarbon receptor (AhR) (99). The AhR is a ligand-dependent transcription factor, expressed by a variety of immune cells (100-102). Once activated, it triggers immune responses, providing protection against pathogens and metabolizes toxic chemicals, like dioxin, a typical AhR ligand (100). Although the most potential ligand for AhR is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), it is recently shown that dietary compounds (such as indole) provide a molecular link between the intestinal immune system and the microbiota (103, 104). Studies demonstrated a reduced intestinal

pathology as a result of a diet rich in the indole derivative I3C (103). I3C can be converted into 3,3-diindolylmethane (DIM) and indolo[3,2-b]carbazole (ICZ), two high-affinity AhR ligands (105). They activate AhR, which enables the maintenance of intraepithelial lymphocytes (IELs), and therefore, the homeostasis of the epithelial barrier (16).

4.2.5. Health Effects of AhR Ligands

The diet-induced AhR ligands have immunomodulatory effects and a lower intake entails higher risks for the development of diseases. Whereas a lack of AhR ligands corresponds with increased disease activity and more epithelial damage after a dextran sulfate sodium (DSS)-induced colitis, only mild symptoms were observed by inducing AhR ligands into the diet (103). Protection against pathogens, like *Candida albicans*, was also observed after the intake of AhR ligands (106). Research stated that this was due to rising IL-22 levels, produced by type 3 innate lymphoid cells (ILC3s). ILCs mimic the helper T cell response by producing similar cytokines (107). As a consequence of a healthy diet with a sufficient amount of tryptophan, AhR ligands activate the AhR and promote ILC3-producing IL-22 to protect the intestine (98). Another important aspect of AhR activation is the upregulation of cytochrome P450 1A1 (CYP1A1), that is known as a detoxification enzyme (108, 109). It possesses the ability to metabolize toxic compounds, whereat polycyclic aromatic hydrocarbons (PAHs) are typical CYP1A1 substrates. Although, non-specific substrates, such as indole derivatives, can be metabolized by CYP1A1 as well (109). Over-expression of CYP1A1 is recently associated with a loss of ILC3 and Th17 cells (110). Consequently, a decrease in IL-22 and IL-17 cytokines have been observed. Therefore it becomes more likely to assume that AhR ligands, like indole derivatives, not only can promote but also maintain ILC3 in order to mediate the inflammatory response. Stimulating inflammation when necessary but counteracting over-inflammation or autoimmune diseases is the balance AhR ligands can achieve. While these ligands are crucial for maintaining homeostasis in the intestinal epithelial barrier, the Western diet provides food with less immune modulating components and minor AhR ligand become present in the gut. Researches imply therefore, that an unbalanced diet and a lower intake of tryptophan, corresponds with a loss and dysregulation in the microbiome and an increased vulnerability to IBD (111). IBD patients, but also people with a higher risk for IBD, will benefit from a healthy and balanced diet (112). Whereas individualized diets are favorable, it definitely should contain specific dietary fibers that all have their own characteristic feature. Until now, most health advisory agencies focus on the quantitative intake of dietary fibers which is of limited use because it negates the potential for fiber-specific treatment. Therefore, it should focus more on individual fibers posing unique immunological effects (75).

4.3. Inulin

Inulin is a common prebiotic dietary fiber that is associated with several health benefits, like balancing the microbiome composition as well as directly affecting the immune system by activating PRRs. Inulin is a fructose-based dietary fiber that includes all □(2→1) linear fructans, like chicory inulin and long-chain inulin (inulin HP). Oligofructose is a partial enzymatic hydrolysis product of chicory inulin. Oligofructose combined with inulin HP, known as oligofructose-enriched inulin, is the most active product (113). Inulins naturally occur in sources such as chicory, onion, banana, artichoke, and asparagus (114). Unique to inulin is the selectivity of colonic fermentation by the *Bifidobacteria* specific (115). Causing the significant growth of beneficial and health-promoting bacteria, whereas pathogenic bacteria

become reduced, resulting in a vital change in microbiota composition (113). The increased SCFAs due to fermentation of inulin is only part of the beneficial systemic effects. It is shown that inulin promotes colon mass and increases enterocyte proliferation (116). Enhanced by a thicker mucus layer and a decline in mucosal lesions, regeneration of the epithelium reduces the risk of microbiota encroachment (117). Studies also have acknowledged an increase in the cytokines transforming growth factor-□ (TGF-□) and IL-10, which both induce the production of Tregs, known to suppress detrimental immune responses in the gut (118). Inulin appears to have direct effects on the gut immunity as well. It can activate PRRs to modulate different immune responses.

Controversial effects of inulin are demonstrated, as it can down-regulate as well as promote inflammatory immune responses. Inulins are detected in the intestine through PRRs present on immune cells. Among others, dendritic cells (DCs) express TLR2 on their surfaces. TLR2 recognizes inulin, which induces the activation of the receptor and causing production of the regulatory cytokine IL-10, previously described as an inducer for Tregs (119-121). Studies have proven that TLR2 activation is chain length-dependent and that it is only obtained via short-chain □2→1-fructans, not by long-chain □2→1-fructans (122). Activation of other PRRs is tested as well. Whereas some studies only indicated the activity of TLR2, other studies also acknowledged the stimulation of TLR4 activation by inulin (123, 124). Studies associated the TLR4 activation with the induction of a pro-inflammatory reaction. In response to pathogenic infiltration and tumor growth and development, cytokines like TNF-α and IL-6 are secreted to stimulate the innate immune system (123). Interestingly, the release of the cytokines IFN-γ and IL-17 was inhibited, suggesting a reduced activation of Th17 cells (123). While it was noticed that IL-10 production was increased as well. Subsequently inducing the differentiation of Tregs, inulin balances the immune response by regulating the T cell differentiation. Moreover, inulin treatment has also shown to enhance phagocytosis in macrophages by directly activating the TLR4 pathway, resulting in a better pathogenic clearance. The treatment had a maximal effect with a dose of 1 mg/mL for every 6 hours (124). In summary, the prebiotic dietary fiber inulin is known for its health-promoting effects but does not work in one single way. It can affect multiple TLRs and also induce different immune responses. Promoting regulation of the immune system in a homeostatic condition but stimulating inflammation when necessary.

4.4. β-glucan

One of the major components of Non-Starch Polysaccharides (NSPs) is the dietary fiber □-glucan, associated with its immunomodulatory role it can be used in treatment for diseases like IBD as well as certain cancers (125, 126). β-glucans consist of □-glucose polymers connected with a glycosidic bond, differing in position (127, 128). Cellulose, for example, is an (1,4)□-D-glucan, whereas □-1,3-glucans are commonly present too. Although the structures are heterogeneous, the common name "□-glucan" is used. β-glucan is present in the cell walls of yeast, fungi, and seaweed, and is known for its physiological effects (127). Research showed the controversial effects of □-glucan. Whereas □-glucan can stimulate the immune system and thereby offers protection against pathogens, it can also reduce inflammatory cytokines and decreases disease activity (128-132). β-glucan is already used in some therapies for many years. For example, the □-1,3-glucan, lentinan, present in mushrooms has already been used in combination with chemotherapy for 30 years to stimulate the immune systems of cancer patients (128, 132).

β-glucans in fungi, like mushrooms, can be effective in the treatment against pathogens, whereby β-glucan plays an immunostimulating role. Since many fungi are

poisonous, our body will recognize fungal components with for example TLR2s present on immune cells. □-glucans, which are the main component of the cell wall of the fungus, are known to trigger the TLR2 signaling pathway (126). Via the MyD88 adaptor, TLR2 activates NF-κB and controls fungal infection (133). In this way, harmless compounds can stimulate the immune response against dangerous microbes. However, □-glucans do not only interact with TLR2. The most important receptor for □-glucan is found to be the C-type lectin-like receptor (CTLR) Dectin-1, expressed by immune cells such as macrophages, DCs, and neutrophils (134). Fungal □-glucan triggers Dectin-1 and results in activating the spleen tyrosine kinase (Syk) pathway, a different pathway than TLRs, but also leading to NF-κB activation (133). Even though Dectin-1 is not a TLR, it can collaborate with TLR2, as well as with TLR4, 5, 7, and 9. Subsequently, phagocytosis is induced, together with an inflammatory cytokine response in order to control the fungal infection (135, 136). Mushrooms consist of a high concentration of fungal □-glucans that will be recognized by the immune system and act immunostimulating, therefore, induce more resistance against infections. However, much research acknowledged the immunosuppressive role of mushrooms derived □-glucan (137). Controversial results of □-glucans are abundantly present. So is □-glucan also associated with suppressing the NF-κB pathway by interacting with TLR2, 4, as well as Dectin-1 (138).

Several studies have proven the immunomodulating role of □-glucan, at which □-glucan mainly lead to less inflammation by tackling different pathways. Studies determined the reduction of Th17 signaling molecules in the colon. They found a decreased expression of Th17-related cytokines (IL-17A, IL-17F, IL-22) (131). Since the unbalanced Th17 response has been associated with the inflammation occurrence in IBD, □-glucan can contribute to the therapy for IBD. DSS-induced IBD mice treated with □-glucan showed reduced expression of IL-17A and IL-17F as well as other pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α. This all was associated with less intestinal damage, decreased clinical symptoms, and reduced disease activity (126, 139). Moreover, administration of □-glucan led to an increase of Tregs, together with a recovered NK cell population (126). Additionally, a significant increase of IgA concentration was noticed after administration with doses up to 400 mg/day (140). Furthermore, studies have acknowledged the inhibitory effect of □-glucan on mast cell activation that induces hyperpermeability in the gut of IBD patients (141, 142). More studies demonstrated the positive effects of □-glucan administration on DSS-induced colitis resulting in less inflammation in the colon (128). The reduced pro-inflammatory cytokines can be assigned to a suppressed MAPK pathway due to □-glucan. Activation of the MAPK pathway is associated with the production of pro-inflammatory cytokines (137). □-glucans can seize on different steps by inhibiting phosphorylation of several proteins (JNK/ERK1/2, p38, Elk-1, PPARγ) that normally further activate the MAPK pathway (128, 137). To conclude, □-glucans are able to stimulate the immune response in order to protect infections, but at the same time they can suppress inflammation and reduce cytokine release.

4.5. Pectin

One of the most in-depth investigated dietary fiber, known to modulate the immune response in its own characteristic way is the dietary fiber pectin. Commonly present as a plant cell wall component in vegetables and fruits. Pectin is a water-soluble fiber and its backbone consists of a long linear chain of α(1-4)-glycoside-linked-galacturonic acids, which can differ in degree of methyl esterification (DM) (143, 144). Depending on the number of methanol moles per 100 mol galacturonic acid (145). Like other dietary fibers, pectin reaches

the large intestine where it gets fermented by the bacteria in the gut (145). During the fermentation, unsaturated oligogalacturonic acids are formed as intermediate products (143). It was noticed that single bacteria cultures, such as *Bacteroides thetaiotaomicron,* are able to degrade pectin, whereas only *E.coli* not possess this ability (143). In addition to *Bacteroides,* bacteria like *Bifidobacteria, Eubacteria, and Clostridia*, are also known to degrade pectin. Therefore, a pectin-containing diet will increase the quantitative as well as the qualitative composition of gut microbiota (145). Moreover, some bacterial strains are even classified into pectinolytic and can only grow on pectin or pectin-related compounds (146). As a result, due to the induced pectin consumption, the SCFA concentration raises together with all its positive health effects, like mucosal proliferation (147). Whereat a higher pectin concentration appears to be more effective (148), the DM of pectin has an adverse effect on the SCFA production. An increase in DM decreases the SCFA production, suggesting that a lower DM ensures more positive health effects (145). Low DM pectin revealed to be effective against inflammation already (144). The study has demonstrated the inhibition of the TLR2 due to the administer of pectin, and low-DM pectin that causes the most efficient inhibition. Activation of the TLR normally results in activating NF-κB and the production of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, leading to intestinal tissue damage (149). The NF-κB pathway is known to be hyperactive in IBD patients, whereby an elevated level of pro-inflammatory cytokines is detected (150). Low-DM pectin has shown to specifically block the formation of the TLR2-TLR1 dimer, whereas the formation of the regulatory TLR2-TLR6 dimer was not disturbed (144). NF-κB can be reduced through a higher pectin intake (151).

Furthermore, pectin has shown to downregulate the inflammatory response in the colon in IL-10 deficient mice and in mice with DSS-induced colitis (152, 153). Other studies have acknowledged the anti-inflammatory effects of pectin by showing an attenuated level of IL-6 after inducing pectin into the diet (19, 154). The bacterial molecule, LPS, stimulates the upregulation of TLR4 on the cell membrane of immune cells. Activation of TLR4 causes, among other pro-inflammatory cytokines, IL-6 to produce. Citrus pectin, as well as apple pectin, have shown to have an anti-inflammatory effect on the TLR4 activation and reduce the IL-6 concentration (19, 154). Derived from apple pectin is the molecule apple oligogalactan (AOG). AOG reduces the TLR4 expression in intestinal tissue by redistributing the TLR4 from the cell membrane back to the cytoplasm, thereby changing the LPS responsiveness and impair inflammation (19, 155). Suggesting that AOG binds, just like LPS, to the TLR4 but competitively antagonize the binding of LPS (19). Once again, the dietary fiber can also send the immune response in an inflammatory direction. The pectin rhamnogalacturonan has shown to activate TLR4 in a cancerous situation. The TLR4 activation causes CD8+ T cells to proliferate and induces pro-inflammatory cytokines, all in order to inhibit the growth of tumors (156). In conclusion, pectin has already proven to be protective against endotoxin shocks, diabetes, colitis, and colitis-associated colon cancer (19, 148, 154, 157). Altogether, the administration of pectin results, mostly, in an anti-inflammatory effect and could even prevent or cure intestinal inflammation (144).

5. Conclusion and Future Perspectives

The composition of the microbiome determines the quality of the immune responses. However, the Western diet is known to be responsible for a shift in the microbial composition. The low amount of fibers has many side effects that influences the intestinal

homeostasis. The gut bacteria will reduce diversity as detrimental bacteria will dominate health-promoting bacteria. As a consequence, the SCFA concentration will decrease, leading to the thinning of the protective intestinal mucus layer. Therefore, the encroachment of pathogens becomes more likely. Additionally, a higher secondary BA concentration will be obtained, linked with a higher vulnerability to develop intestinal inflammations. All those side effects are also observed in patients suffering from IBD and are as well linked to other Western diseases. Whereas some IBD patients are recorded with specific gene mutations, the altered composition of the microbiota, due to the Western diet, is a key player in the development of the disease. The Western diet is besides a high fat and low fiber concentration also associated with a lower intake of proteins. This leads to a reduction in AhR ligands that normally can maintain the homeostasis in a healthy condition. Nevertheless, a special focus in this thesis is on the mentioned dietary fibers; inulin, β-glucan, and pectin, that have their own characteristic health effects. In most cases, the fibers cause an anti-inflammatory effect which can prevent or cure intestinal inflammation. However, in some conditions the immune system needs to be extra stimulated, in an immunocompromised situation for example. Here, the dietary fibers modulate a pro-inflammatory response and can contribute to the prevention of infections. Whether these functional changes are due to the dietary fiber itself or due to the microbiota is unclear. What we do know is that the microbiota plays a crucial role in modulating the immune response. The microbiota can conduct the immune response in the direction beneficial for its host. Therefore, it is likely to assume that the microbiota also can convert the dietary fibers into the molecules needed for the right condition. More research into dietary fibers is needed, whereat a special focus needs to be on inducing clinical trials. Evidence is presented and specific dietary fibers are proven to be health promoting. The knowledge needs to be introduced to a wider audience at which clear attention needs to be on the intake of only specific dietary fibers.

6. References

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