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Dietary SCFAs Immunotherapy: Reshaping the Gut Microbiota in Diabetes

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Abstract

Diet-microbiota related inflammatory conditions such as obesity, autoimmune type 1 diabetes (T1D), type 2 diabetes (T2D), cardiovascular disease (CVD) and gut infections have become a stigma in Western societies and developing nations. This book chapter examines the most relevant pre-clinical and clinical studies about diet-gut microbiota approaches as an alternative therapy for diabetes. We also discuss what we and others have extensively investigated- the power of dietary short-chain fatty acids (SCFAs) technology that naturally targets the gut microbiota as an alternative method to prevent and treat diabetes and its related complications.

Keywords

Clinical trials · Diet · Microbiota · SCFAs · T1D · T2D

Diabetes is a chronic immune-metabolic disease in which different mechanisms cause insulin deficiency and impaired insulin action, essential for regulating blood glucose levels. A persistent elevation of glucose concentration in the blood, also known as hyperglycemia, can cause damage to various organs in the body. If left untreated, individuals with hyperglycemia are at a significantly higher risk of developing life-threatening health complications, including CVD, infections, and kidney failure (International Diabetes Federation 2017). Although the exact cause of diabetes remains undetermined, the interactions between genetic and environmental factors cause inflammation, β-cell damage or dysfunction, and hyperglycemia, leading to the diagnosis of diabetes and with it, an increased risk of morbidity and mortality. Many epidemiological studies point to diet as one of the most influential lifestyle factors contributing to the rise of diabetes (Thorburn et al. 2014; Marino 2016). Diet alters the balance of the commensal gut microbiota and the availability and production of microbial metabolites such as SCFAs that can affect many physiological processes. As such, the interplay between the microbiota, metabolism, the immune system, and the nervous system is fundamental in determining the fate of diabetes.

1 Factors Influencing the Gut Microbiota and Type 1 Diabetes

Insulin-dependent diabetes, commonly known as type 1 diabetes (T1D), is an organ-specific autoimmune disease that arises from the immune-mediated destruction of pancreatic β-cells that

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produce insulin (Atkinson et al. 2014). High concentrations of blood glucose induce classic symptoms of T1D such as increased urination (polyuria) and thirst (polydipsia), and uncharacteristic weight loss. Some individuals may also experience fatigue, increased hunger, diminished visual acuity, and numbness in the hands and feet (Harrison 2019). Patients with T1D typically require a lifelong need for exogenous insulin replacement to sufficiently manage the disease (Flier et al. 1986; Atkinson and Eisenbarth 2001; Bluestone et al. 2010). Most commonly diagnosed in young people between the age of 10 and 14 years, it has been estimated that around 85% of T1D patients are 20 years and under (Maahs et al. 2010).

In the past decade, the global incidence of T1D in children <14 years old has increased by 30%, at an average rate of 2.8% per year (Maahs et al. 2010). The development of beta-cell autoimmunity occurs very early in life before the onset of clinical T1D (Krischer et al. 2015). During this early period, the widespread use of antibiotics has been proposed as a cause for the growing rate of T1D (Boursi et al. 2015; Abela and Fava 2013; Livanos et al. 2016). Antibiotics cause profound changes to the gut microbiota (Koren et al. 2012; Tamburini et al. 2016), which play a central role in the development of the infant immune system (Belkaid and Hand 2014). Likewise, mother's nutrition is key to establishing the microbiota in infants (Marino 2016; Koren et al. 2012). During the perinatal stage (pregnancy and breastfeeding), T1D has not yet manifested, but subtle biological changes that contribute to the development of the disease might be already occurring (Tamburini et al. 2016). However, very little is known about the early immune and microbial events that happen during the perinatal stage and how these may impact disease progression.

It has been shown that a drop in the diversity of the gut microbiota occurs in infants well before the onset of TID (Kostic et al. 2015). Similarly, infants present a distinct autoreactive gene signature well before the appearance of beta-cell antigen-specific memory T cells or autoantibodies (Heninger et al. 2017; Mehdi et al. 2018). Thus, strategies to reprogram the immune system to tackle T1D represent an entirely novel approach. Diet shapes the composition of the gut microbiota (Kau et al. 2011) and therefore modulates the production of microbial SCFAs. It has been shown that non-obese diabetic (NOD) mice treated with antibiotics during the perinatal stage cause profound changes in the gut microbiota and accelerate the development of T1D in the offspring (Boursi et al. 2015; Livanos et al. 2016). A single antibiotic treatment not only significantly altered taxonomic and metagenomic composition but also reduced the production of host-signaling microbial SCFAs early in life (Zhang et al. 2018).

Antibiotics are commonly used during pregnancy and delivery (Martinez de Tejada 2014) for treatment of urinary and gastrointestinal (GI) infections, and bacterial vaginosis, as well as for preventative measures during the intrapartum/peripartum stages to decrease the risk of infection in mother and/or infant after delivery (Tormo-Badia et al. 2014). At least 11 types of broad-spectrum antibiotics can cross the placenta and reach the fetus (Nahum et al. 2006). Antibiotics during fetal development and breastfeeding can induce metabolic changes (Cho et al. 2012) via the gut microbiota (Cox et al. 2014) and increase gut permeability (Kerr et al. 2015), thus accelerating T1D development (Livanos et al. 2016; Rautava et al. 2012). In contrast, findings from a Danish population-based case-control study found no association between overall antibiotic exposure in childhood and the risk of developing T1D (Mikkelsen et al. 2017; Kemppainen et al. 2017). Despite conflicting findings on the impact of antibiotics on T1D risk, there is mounting evidence that perturbations to the gut microbiota may significantly affect disease pathogenesis (Jamshidi et al. 2019).

It is also well understood that diet can shape the gut microbiota (Kau et al. 2011; Makki et al. 2018). The Environmental Determinants of Diabetes in the Young (TEDDY) study found that compared to formula fed babies, breastfeeding was associated with higher levels of Bifidobacterium species (Stewart et al. 2018), a

lack of which has been observed in the stool of children with β-cell autoimmunity (de Goffau et al. 2013). Certain dietary components such as protein have been proposed to increase the risk of developing T1D (Serena et al. 2015; Lefebvre et al. 2006). Disease incidence in NOD mice on gluten-free diets were found to be significantly reduced (Marietta et al. 2013; Funda et al. 1999). Furthermore, this protective effect was observed in pups from pregnant NOD mice on a gluten-free diet, even after they had been weaned to a standard diet (Hansen et al. 2014). In humans a gluten-free diet reduced GI symptoms and severe hypoglycemia while significantly increasing the need for exogeneous insulin (Abid et al. 2011; Hansen et al. 2006).

2 Dietary Short-Chain Fatty Acids and Type 1 Diabetes

Yet another component in our diet, dietary fiber, has shown promise in alleviating many inflammatory diseases in recent years (Thorburn et al. 2014; Richards et al. 2016). The gut microbiota ferment undigestible carbohydrates to produce metabolites such as the SCFAs acetate, propionate and butyrate, which are absorbed by the colon epithelium and have downstream effects on metabolic and immune responses (Richards et al. 2016). Research from our lab has demonstrated that the deterioration of immune tolerance in T1D is strongly associated with an altered microbiota and deficiency of acetate and butyrate in mice (Marino et al. 2017). Likewise, T1D individuals have shown reduced bacterial pathways involved in the bio-synthesis of these SCFAs (Vatanen et al. 2018). In a cross-sectional study, similar albeit modest differences have been found in fecal butyrate concentrations in subjects with established T1D, who also exhibited lower intestinal alkaline phosphatase (IAP) activity, immunoglobulin A (IgA) antibody concentrations and elevated fecal calprotectin concentrations (Lassenius et al. 2017). These findings are also supported by reduced SCFA-producing bacteria observed in T1D and T2D individuals (de Goffau et al. 2013, 2014 Zhao et al. 2018). Thus, one promising therapy appears to be reducing inflammatory responses and inducing immune tolerance through the use of gut microbiota-derived SCFAs.

We have demonstrated that a breakthrough diet intervention protected 90% of NOD mice against T1D, yielding exceptionally high levels of fecal and systemic concentrations of the respective SCFAs acetate and butyrate without any detrimental effects. SCFAs-induced T1D protection happened via changes in gut/immune regulation by expanding regulatory T cells (Tregs) and reducing pathogenic B cells, $CD4^+$, and $CD8^+$ T cells. Diets rich in acetate and butyrate not only reduced the levels of serum LPS and pro-inflammatory interleukin 21 (IL-21) but also increased the concentrations of serum IL-22, an important cytokine that maintains a healthy commensal microbiota, gut epithelial integrity, mucosal immunity and ameliorates metabolic disease (Hasnain et al. 2014; Wang et al. 2014; Dudakov et al. 2015; Sabat et al. 2014).

In T1D, the effects of SCFAs are beyond the gut and the immune system. SCFAs also increase the production of antimicrobial peptides (AMPs) in β-cells (Sun et al. 2015). As previously shown, C-type lectin regenerating islet-derived protein 3 gamma (REGIIIγ) and defensins disrupt surface membranes of bacteria enabling a broad regulation of commensal and pathogenic bacteria in the gut (Gallo and Hooper 2012; Bevins and Salzman 2011; Mukherjee and Hooper 2015). NOD mice present defective production of cathelicidin-related antimicrobial peptide (CRAMP) in insulin-secreting β-cells and administration of soluble butyrate stimulated CRAMP production via G protein-coupled receptors (GPCRs) correlating with the conversion of inflammatory immune cells to a regulatory phenotype (Sun et al. 2015). Likewise, we demonstrated that microbial SCFAs contribute to increased concentrations of serum IL-22 (Marino et al. 2017), which has been shown to be required for β-cell regeneration by up-regulating the expression of regenerating Reg1 and Reg2 genes in the islets (Hill et al. 2013). Altogether, these findings establish an important role of dietary SCFAs in T1D.

There is evidence that mice and humans with T1D display compromised gut integrity and dysbiosis associated with GI inflammation (Alam et al. 2010; Bolla et al. 2017; Bosi et al. 2006; Lee et al. 2010; Leeds et al. 2011; Halling et al. 2017), similar to other inflammatory or autoimmune gut diseases such as infections, celiac disease and inflammatory bowel disease (IBD). Diabetes sufferers present symptoms such as nausea, heartburn, vomiting, diarrhea, abdominal pain, and constipation (Du et al. 2018; Maleki et al. 2000). The gut microbiota and the enteric nervous system (ENS) play a critical role in diabetic gastrointestinal motility disorders. As such, slow GI motility leads to alterations of the gut microbiota that favors pathogenic bacterial overgrowth and subsequently diarrhea (Nguyen et al. 2014; Sellin and Hart 1992). On the other hand, animal studies have suggested that accelerated colonic transit time relative to constipation, could be cause by autonomic neuropathy and diabetes-induced denervation of sympathetic nerve terminals (Du et al. 2018; Rosa-e-Silva et al. 1996). Deficiency of dietary SCFAs can also modulate intestinal motility and survival of enteric neurons by miRNAs, which are involved in energy homeostasis, lipid metabolism and proliferation and development of GI smooth muscles. miRNAs have been vastly studied in organ damage caused by diabetes, and one study in mice have shown that high-fat diets (HFD) delay the GI transit, partly by inducing apoptosis in enteric neuronal cells, an effect mediated by Mir375 associated with reduced levels of 3-phosphoinositide-dependent protein kinase-1 (Pdk1) (Nezami et al. 2014). There is still too much to understand about the intrinsic mechanisms underlying the connection between the gut microbiota and the ENS, and how this impacts the course of T1D. As an example of many beneficial properties ascribed to dietary SCFAs, high-amylose maize starch (HAMS) by itself used as oral rehydration solution decreased diarrhea duration in both adults and children hospitalized for acute infectious diarrhea (Binder et al. 2014).

3 Diet/Gut Microbiota-Interventions in Type 1 Diabetes: Clinical Trials

Treatment of T1D is typically focused on optimizing blood glucose control through different modes of exogenous insulin delivery. Although scientific and technical advances over the past 30 years have resulted in the control of hyperglycemia in those with T1D, methods of prevention and curing the disease remains as elusive as ever. Therefore, recent efforts have been made to identify other targets such diet and the gut microbiota to treat and prevent T1D. Based on 16S rRNA sequencing, these 4 bacterial phyla – Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, are usually dominant in the GI tract (Consortium 2012). Several human studies have shown that T1D could be attributable to an altered microbiota compared to healthy subjects. However, it is particularly challenging to establish a causal relationship between microbiota alterations and T1D in humans due to the complex nature of dietary habits and microbial differences across cultural backgrounds. Taxonomic changes in gut microbiota associated with T1D pathogenesis in humans include a lower Shannon diversity and higher Bacteroides/Firmicutes ratio (Giongo et al. 2011), and a reduction in butyrate producers (i.e., *Faecalibacterium*), lactic acid bacteria (i.e., *Lactobacillus, Bifidobacterium*) and mucin degraders (*Prevotella, Akkermansia*) (Vatanen et al. 2018; de Goffau et al. 2014; Brown et al. 2011; Mejia-Leon and Barca 2015). Alterations in the composition of the gut microbiota in T1D also include changes to the abundance of *Streptococcus spp., Clostridium spp., Staphylococcus spp., Blautia spp.,* and *Roseburia spp.* (de Goffau et al. 2013, 2014; Vatanen et al. 2018; Kostic et al. 2015; Gavin et al. 2018). Moreover, studies have reported correlations between gut microbiota ecology changes and diabetic markers such as HbA1c and inflammatory markers such as TNFα, IL-6, IL-10, IL-13 and IL-1β (Table 1).

Table 1 The gut microbiota: correlations with clinical markers in type 1 diabetes

Study design	Study aims	Outcome/measures	References
Case-control	To evaluate the alteration of gut microbiota between children with newly diagnosed T1D and healthy controls	Gut microbiota was associated with the development of T1DM by affecting autoimmunity. Results suggested modulating the gut microbiota as a potential therapy	Qi et al. (2016)
Case-control	To evaluate the difference in the composition of gut microbiota and glycemic level between children with T1D and healthy controls	The abundance of *Bifidobacterium* and *Lactobacillus*, and the Firmicutes to Bacteroidetes ratio correlated negatively and significantly with plasma glucose levels, while the abundance of *Clostridium* correlated positively and significantly with plasma glucose levels in the diabetic group	Murri et al. (2013)
Case-control	To evaluate the gut inflammatory profile and microbiota in subjects with T1D and healthy controls, and patients with celiac disease as gut inflammatory disease controls	Duodenal mucosa in T1D presents disease-specific abnormalities in the inflammatory profile and microbiota	Pellegrini et al. (2017)
Case-control	To compare the gut microbiota profiles of T1D, MODY2, a monogenic cause of diabetes, and healthy control subjects	Compared with healthy controls, T1D was associated with significantly lower microbiota diversity. Proinflammatory cytokines and LPS, and gut permeability were significantly increased in T1D and MODY2. T1D was also associated with an increment of genes related to lipid and amino acid metabolism, LPS biosynthesis, arachidonic acid metabolism, antigen processing and presentation, and chemokine signaling pathways	Leiva-Gea et al. (2018)
Case-control	To investigate whether intestinal dysbiosis in T1D patients correlate with clinical inflammatory cytokines	IL-6 was significantly increased ($P = 0.017$) in T1D. There was a correlation among patients with poor glycemic control, represented by high levels of HbA1C and Bacteroidetes, Lactobacillales, and *Bacteroides dorei* relative abundances	Higuchi et al. (2018)

T1D type 1 diabetes, *MODY2* type 2 maturity-onset diabetes of the young, *LPS* lipopolysaccharide

Studying the substantial changes in the number of specific species within the makeup of the microbiota may prove an invaluable tool allowing for earlier detection. Beyond the analysis of the gut microbiota composition, detection of microbial SCFAs could be more precise and accurate as biomarkers in autoimmunity. We have already demonstrated through a dietary intervention that the deterioration of immune tolerance in T1D is strongly associated with a deficiency in microbial SCFAs acetate and butyrate. When this deficiency is rectified in the gut by increasing the production of microbial SCFAs, the β-cell damage that leads to T1D ceases (Marino et al. 2017). One of the major barriers to the growth of the T1D market is the high failure rate of trials for disease-modifying (immunomodulatory) therapies. Although the use of diets for the treatment or prevention of T1D is still new, Table 2 provides a summary of selected, currently active clinical trials exploring the role of the microbiota in T1D prevention in high risk or newly diagnosed children and adults.

4 Type 2 Diabetes: A "Gut Origin" Disease

As the most common type of diabetes, T2D accounts for nearly 90% of all cases (Yan et al. 2017). Contrary to T1D, hyperglycemia in T2D is

Table 2 Trials in type 1 diabetes studying the role of diet and gut microbiota

Study design	Intervention	Outcome/measures	References
Single group assignment	To investigate whether a soluble fiber supplement (Benefiber) can improve glycemic control and/or reduce the risk of hypoglycemic events in children with T1D	Decrease in excursion of glucose or hypoglycemia incidence was not observed. However, a strong negative correlation was found between the amount of added fiber and the mean maximum post-prandial blood sugar after the main meals (lunch and breakfast). Researchers suggested that different types of fiber may act differently on regulating the blood glucose level as wheat dextrin showed a higher dampening effect	Nader et al. (2014) NCT01399892
Parallel assignment	A 12-week pilot randomized, double blind, placebo controlled clinical trial testing the effect of prebiotic fiber (1:1 oligofructose: inulin 8 g orally/day) on gut microbiota, intestinal permeability and glycemic control in children (8–17 years of age) with T1D	Serum HbA1c; Gut microbiota composition; Changes in gut permeability	Ho et al. (2016) NCT02442544
Parallel assignment	A randomized placebo controlled clinical trial testing the effect of a gluten-free diet on endogenous insulin production and gut microbiota to reverse or arrest islet destruction in 60 children and adolescents (1–17 years of age) with new onset T1D	AUC of C-peptide on mixed meal tolerance test at baseline, 6 months and one-year post enrolment. Stool sampling to characterize gut microbiota at each time point	NCT02605564
Single group assignment	The ToGeTher trial: specialized fiber supplement in T1D. A single arm, safety, tolerability and feasibility trial of a fiber supplement in 25 adults 18–45 years old with T1D	HbA1c, circulating immune cells numbers, microbiota analysis, C-peptide, fecal and blood SCFAs measurements, proteomics and RNA-seq.	ACTRN12618001391268
Crossover assignment	Experimental: Intervention group. Participants will be instructed to consume HAMS-AB in two divided doses at breakfast and dinner No intervention: Control group	To assess the effect of administering a prebiotic, such as HAMS- AB, on the gut microbiome profile, glycemia and β-cell function in new onset children with T1D in the last 4–24 months	NCT04114357
Sequential assignment	A phase 1b/2a, multi-center study in participants with clinical recent-onset T1D in 2 age groups (18–40 years of age and 12–17 years of age)	A prospective study to assess the safety and tolerability of different doses of AG019 administered alone or in association with Teplizumab in patients with clinical recent-onset T1D. AG019: *Lactococcus lactis*, a naturally occurring gut bacteria genetically modified (GM) to secrete human pro-insulin and IL-10.	NCT03751007

(continued)

Table 2 (continued)

Study design	Intervention	Outcome/measures	References
Single group assignment	Modulation of T1D susceptibility through the use of probiotics (VSL#3). 30 participants (5–17 years old) Child. After 6 weeks of taking VSL#3, they will return for their final visit for stool and blood samples	VSL#3 contains eight probiotic strains: bifidobacteria (*B. longum*, *B. infantis,* and *B. breve*), *lactobacilli* (*L. acidophilus, L. casei, L. bulgaricus, and L. plantarum*) and *Strepococcus thermophile*	NCT03423589

T1D type 1 diabetes, *AUC* area under curve, *SCFA* short-chain fatty acids, *HAMS* high amylose maize starch, *A* acetate, *B* butyrate

a result of insufficient insulin production and the inability of the body to respond to insulin, also known as insulin resistance (IR). A feedback loop between insulin-secreting β-cells in the pancreas and insulin-sensitive tissues such as liver, muscle and adipose tissue ensures the homeostatic regulation of glucose metabolism (Kahn et al. 2014). A breakdown in this crosstalk between insulin action in tissues and insulin secretion by the pancreas results in abnormal blood glucose levels. The rise in obesity, sedentary lifestyles, energy-dense diets and an ageing population are the main causes of the global T2D epidemic (Chatterjee et al. 2017). Overall, diabetes prevalence has risen steadily in every country since 1980, however the incidence and prevalence of T2D vary across geographical regions and ethnicity. Recent studies suggest that more than 80% of individuals living with T2D reside in low-to-middle-income countries ((NCD-RisC) NRFC 2016). Typically diagnosed in adults over the age of 45, T2D is increasingly seen in younger age groups due to the rising prevalence of childhood obesity (Chen et al. 2011). Indeed, T2D patients have a 15% increased risk of all-cause mortality compared to people without diabetes, especially in young people and those with worse glycemic control (Tancredi et al. 2015).

The variability in T2D prevalence based on ethnicity may also be partially explained by inherent differences in genetic background and phenotype. For example, individuals of Asian descent are generally predisposed to have a higher percentage of total body fat, and visceral and abdominal adiposity (Chan et al. 2009; Kong et al. 2013) compared to their Caucasian counterparts at a given body mass index (BMI). Furthermore, Asians generally have poorer β-cell function and higher IR compared to Caucasians for a given BMI and waist circumference (Kong et al. 2013). While genetic variants may reveal mechanisms behind T2D development, we have so far been unable to predict disease beyond what is already achieved using current clinical measurements. Therefore, the missing piece of the T2D heritability puzzle may be explained by interactions between genetics, diet and their effects on the gut microbiota.

Although many cases of T2D could be prevented by adopting a healthy lifestyle and maintaining a healthy body weight, some individuals are more susceptible to T2D than others. Genome-wide association studies (GWAS) have implicated up to 250 genomic loci that are significantly associated with T2D (Feero et al. 2010; Anubha et al. 2014; Fuchsberger et al. 2016; Mahajan et al. 2018), primarily affecting insulin secretion and to a lesser degree, insulin action. One such example is the transcription factor 7 like 2 (TCF7L2) gene, which has important biological roles in the pancreas, liver and adipose tissue (Liu and Jin 2008). TCF7L2 polymorphisms can increase T2D susceptibility by decreasing production of glucagon-like peptide 1 (GLP-1), an insulinotropic hormone secreted by intestinal enteroendocrine cells, that works in tandem with insulin to maintain blood glucose homeostasis (Grant et al. 2006). More recently, plasma lipid profiling is an emerging discovery approach that identifies biomarkers in human studies and have been used to predict the development of obesity

(Pietiläinen et al. 2007), T1D (Orešič et al. 2008; La Torre et al. 2013), T2D (Rhee et al. 2011), and CVD (Fernandez et al. 2013). We have identified microbial products and pro-inflammatory molecules that predict the development and progression of diabetes. Thus, if we can effectively and safely target this chronic inflammatory state, it has the potential to reduce body weight gain, halt the progression of diabetes and reduce the risk of other diabetic complications. Microbial SCFAs can act as histone deacetylase (HDAC) inhibitors in immune cells and adipocytes. For example, the protein histone deacetylase 3 (HDAC3) regulates the progression of diet-induced obesity by modulating lipid metabolism of intestinal enterocyte cells in mice (Davalos-Salas et al. 2019). Additionally, we have demonstrated that dietary SCFAs markedly diminished the expression of *Hdac3* transcripts in B cells in T1D (Marino et al. 2017). This would lead to a phenotype similar to that of HDAC3 deficiency in select cells (Davalos-Salas et al. 2019) or of enzymatic inhibition of HDACs with chemical inhibitors such as butyrate, which has anti-inflammatory properties. It will be a novel technology to identify SCFAs-microbiota-inflammation dependent biomarkers involved in disease progression and most importantly to detect early biological clues to stop it.

However, there are currently few if any, real solutions to address the deleterious health consequences from T2D. All efforts to tackle T2D in adults and childhood are worthy of consideration. Diet and lifestyle factors can impact on the gut microbiota, the production of SCFAs and the development of obesity and T2D (Cani et al. 2008a; b; Durack and Lynch 2019; Sanna et al. 2019). As such, the Nutrition Forum from the National Academies of Sciences, Engineering, and Medicine have discussed the potential of utilizing dietary SCFAs during lifespan with an emphasis on healthy aging, beginning in pregnancy and early childhood (National Academies of Sciences, Engineering, and Medicine 2017).

5 Dietary Short-Chain Fatty Acids: Modulators of Meta-Inflammation in Type 2 Diabetes

Our diet is composed of a variety of dietary macronutrients – carbohydrates, proteins, fats, and fibers. Changes in these nutritional components can act as priming triggers for autoimmunity (Funda et al. 2008; Lerner and Matthias 2015), while overconsumption can lead to cell damage and inflammation (Chassaing et al. 2015). The amount of fiber and fat in the diet shapes large bowel microbial ecology (Kau et al. 2011; Makki et al. 2018). The stool samples of African children whose diet consists of cereals, legumes and vegetables are more abundant in bacteria from the phylum Bacteroidetes and less abundant in Firmicutes compared to European children consuming a typical Western diet (De Filippo et al. 2010). Consistent with this result, early studies demonstrated a higher Firmicutes-to-Bacteroidetes ratio in both obese individuals and mouse models of obesity compared to their lean counterparts (Turnbaugh et al. 2008a; Ley et al. 2005). Indeed, diet-associated complications such as CVD are less prevalent in Mediterranean countries where high intakes of fiber from vegetables, fruits and nuts are consumed in preference over highly processed meats and industrialized goods (Estruch et al. 2013). In line with these observations, the global decline in dietary fiber consumption below recommended daily intakes, particularly in Westernized societies, is linked to the rising incidence of inflammatory diseases (Hartley et al. 2016) thus establishing the importance of fiber in affecting the state of health or disease. Foods high in fiber provide many health benefits as it is the source of energy for both our own gut cells and the symbiotic microbial communities that reside within (Bird et al. 2000).

Resistant starches are the preferred energy source for the symbiotic microbiota in our gut. These complex carbohydrates that can be

obtained from vegetable, fruits, wheat, corn and nuts, are one such form of dietary fiber (Zaman and Sarbini 2016). They are aptly named due to their strong ability to resist degradation by the body's digestive processes, continue through to the caecum and large intestine where they are fermented by the gut microbiota (Topping and Clifton 2001). This unique property of resistant starches is often utilized in commercial foods to reduce energy density due to the inability of the human body to digest it. In the mammalian gut, primarily the colon, resistant starches are degraded and fermented by the gut microbiota to produce the SCFAs, acetate, propionate and butyrate (Topping and Clifton 2001). These metabolites are produced at varying ratios with acetate being the most abundant in the colon (~60%), followed by propionate (~20%) and butyrate (~20%) (Canfora et al. 2015). In addition, acetate may itself fuel the production of other SCFAs such as butyrate via alternate biochemical pathways. More than 95% of SCFAs are absorbed by the colon, with butyrate being the preferential energy source for colonocytes, as well as having a profound effect on maintaining gut epithelial homeostasis and function (Topping and Clifton 2001). Meanwhile, propionate is metabolized in the liver and thus is only present in small concentrations in the periphery. Acetate, on the other hand, is the most abundant SCFA found in circulation and have been shown to cross the blood-brain barrier (Perry et al. 2016).

Patients with obesity and T2D (and other inflammatory diseases) have reduced levels of beneficial gut bacteria (Zhao et al. 2018). Several studies from our laboratory have demonstrated a remarkable and beneficial role for a SCFAs dietary intervention in the pathogenesis of several inflammatory diseases, such as allergies, asthma, arthritis, IBD, colon cancer, kidney disease, wound healing, hypertension and T1D (Thorburn et al. 2014; Marino et al. 2017; Maslowski and Mackay 2011; Felizardo et al. 2019; Marques et al. 2017). SCFAs are able to lower blood pressure, decrease cardiorenal hypertrophy and fibrosis, and improve cardiorenal function (Marques et al. 2017). These metabolites also have positive effects on appetite regulation and balance of energy intake/expenditure via the nervous system and the brain-gut axis with additional effects inducing lipid oxidation in brown adipose tissue, adipose tissue, liver and intestine (Knauf et al. 2008; den Besten et al. 2015; Kondo et al. 2009; Lu et al. 2016; Canfora et al. 2017; van der Beek et al. 2016). In line with previous findings, SCFAs have beneficial influence on hepatic metabolism preventing progression of non-alcoholic fatty liver disease (NAFLD), T2D and IR in mice and rats (Zhao et al. 2019a; Endo et al. 2013), and in humans (Zhao et al. 2019b; Ding et al. 2019). Similarly, several studies demonstrated that SCFAs are key to reducing and preventing body weight gain and obesity (Cani et al. 2008b; den Besten et al. 2015; Henao-Mejia et al. 2012; Bonfili et al. 2019). In skeletal muscle, SCFAs function in two ways. First, there is a low supply of lipids due to the positive effect of SCFAs in adipose tissue lipid storing capacity and consequent reduction of inflammatory cytokines which in turn prevent IR (Canfora et al. 2015; Chriett et al. 2017; Gao et al. 2009). Secondly, SCFAs directly increases fatty acid oxidation in muscle by stimulating AMPK signaling (Chriett et al. 2017) and inducing expression of metabolic genes like peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PCG1α) and peroxisome proliferator-activated receptor (PPAR) (Gao et al. 2009; Clark and Mach 2017).

SCFAs stimulate the release of the gut hormones GLP-1 and GLP-2 (Tolhurst et al. 2012), which are responsible for modulating gut barrier function and reducing uptake of inflammatory compounds that may trigger chronic low-grade inflammation often linked with obesity and CVD. In addition, the progression of diabetic kidney disease (DKD) is associated with an altered gut microbial ecology and deficiency of SCFAs, which contributes to activation of the Renin-Angiotensin-Aldosterone System (RAAS) (Fernandes et al. 2019; Lu et al. 2018). Two studies using microbiome and metabolomic

approaches in DKD patients suggest that dysbiosis in DKD is associated with increased urease-containing bacteria and reduced SCFAs-producing bacteria, resulting in accumulation of toxic metabolites (uremic toxins) (Sharma et al. 2013; Wong et al. 2014). We recently demonstrated that pre-treatment with a high butyrate-yielding diet protected against nephropathy in a mouse model of glomerular disease (Felizardo et al. 2019). Butyrate protected glomerular podocytes from damage thereby reducing proteinuria and glomerulosclerosis, and an overall kidney inflammation. This protective phenotype was associated with maintaining podocyte expression of key functional proteins and a normalized pattern of acetylation and methylation at promoter sites of genes essential for podocyte function (Felizardo et al. 2019). Similarly, oral delivery of sodium butyrate to mice protected against the onset of albuminuria, inflammation, and glomerulosclerosis in a model of type 1 DKD (Dong et al. 2017).

Obesity has been associated with dramatic changes in gut microbial community in both mice and humans (Turnbaugh et al. 2008a, b; Ley et al. 2005; Turnbaugh et al. 2006). Both obesity and T2D in humans have been associated with decreased microbial diversity and reduced abundance of butyrate-producing bacteria (i.e., *Roseburia, Eubacterium halii, Faecalibacterium prausnitzii*) (Qin et al. 2012; Karlsson et al. 2013). However, different to the microbiota profile of T1D patients, the Bacteroides/Firmicutes ratio in T2D subjects appear to be lower (Qin et al. 2012; Karlsson et al. 2013). Having said that, the association between Bacteroides/Firmicutes ratio and diabetes pathogenesis remains controversial and unconfirmed, and therefore may not be a useful biomarker to determine disease causality. A study showed germ free (GF) mice were protected from diet-induced obesity (DIO) and IR (Backhed et al. 2007), elegantly demonstrating the association of the gut microbiota in the development of obesity, inflammation and metabolic dysfunction. Furthermore, treatment of obese mice with antibiotics reduced inflammation and improved glucose tolerance and insulin sensitivity (Cani et al. 2008a). Moreover, only GF mice transplanted with fecal preparations from obese twins developed increased weight gain and IR (Ridaura et al. 2013), indicating that gut microbiota can transfer and directly induce a metabolic status. Likewise, in humans, the infusion of microbiota from lean donors improved insulin sensitivity in recipients with metabolic syndrome (Vrieze et al. 2012).

6 Harnessing the Potential of the Microbiota for Diabetes Therapy

Obesity-associated deficiency in circulating microbial SCFAs can be due to intestinal permeability and altered microbiota composition. Reduced thickness of the mucosal layer and increased epithelial-cell uptake and translocation all contribute to increased intestinal permeability. Consequently, this allows more bacteria and inflammatory microbial products to enter the circulation. The host innate immune system recognizes the pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) in microbial products (Kumar et al. 2011). LPS subsequently activates toll-like receptor 4 (TLR4) to induce inflammatory responses in immune cells as well as insulin target cells (Shi et al. 2006). Furthermore, LPS have been shown to alter the expression of tight junction proteins thereby increasing intestinal permeability (Guo et al. 2013). Genetically obese mice have increased intestinal permeability and LPS levels in the portal blood, which promote inflammatory liver damage. This is correlated by increased levels of TNF-α and reduced zona occludens 1 mRNA in the proximal colon of obese mice, which correlated with increased macrophage infiltration and levels of inflammatory cytokines TNF-α and IL-6 in the mesenteric fat (Cani et al. 2008a; Cani et al. 2007). Additionally, high-fat feeding in mice have been shown to induce translocation of gram-negative bacteria across the

intestinal barrier in a TLR4-dependent manner, to possibly contribute to IR (Amar et al. 2011). Short-term changes in diet such as a single meal high in fat, resulted in an acute elevation of circulating LPS in humans (Erridge et al. 2007). In contrast, the gut anti-inflammatory agent 5-aminosalicyclic acid (5-ASA) was shown to improve metabolic parameters in DIO mice, with associated regulation of gut adaptive immunity and reduced gut permeability (Luck et al. 2015), thus implicating the role of gut leakiness and inflammation in obesity.

Several studies have tried to target the gut microbiota through the use of probiotics and prebiotics to ameliorate or treat T2D. Zhao et al. (2018) showed in a randomized clinical study that diabetic subjects who consumed a high-fiber diet (large amounts of diverse fibers composed of whole grains and traditional Chinese medicinal foods) had better improvement in hemoglobin A1c (HbA1c) levels, partly via increased GLP-1 production. Control and treated group received acarbose (an amylase inhibitor) as the standardized medication. Acarbose transforms part of the starch in the diet into a "fiber" by reducing its digestion and making it more available as fermentable carbohydrate in the colon. Patients exposed to the high fiber diet also showed increased fecal SCFAs and presented diminished bacteria producers of metabolically detrimental compounds such as indole and hydrogen sulfide (Zhao et al. 2018, 2019b). Overall, these findings establish proof-of-principle that a strategy to increase SCFAs may be effective to treat inflammatory and metabolic diseases such as T2D.

7 Diet/Gut Microbiota-Interventions in Type 2 Diabetes

A diet containing high-quality fats (low in trans-fatty acids and high in polyunsaturated fatty acids) (Ley et al. 2014), and carbohydrates (Bhupathiraju et al. 2014) is significantly more effective in preventing T2D, rather than reducing the relative quantities of these nutrients (Schulze and Hu 2005). Most dietary recommendations for T2D prevention usually promote higher intakes of whole grains, fruits, vegetables, nuts and legumes, and reduced intakes of refined grains, processed meat and sweetened beverages (Ley et al. 2014). The Look AHEAD (Action for Health in Diabetes) trial in the USA (Wadden et al. 2006) is a large multicenter randomized clinical trial spanning 8 years. This clinical trial is one example of how intensive lifestyle intervention through caloric restriction and increased physical activity can impact weight loss and CVD outcomes. However, the study was discontinued as it was determined that the intervention did not reduce the rate of cardiovascular events compared to the control group. Another multicenter study conducted in Spain, the PREDIMED trial, reported that a Mediterranean diet significantly reduced CVD risk by 30% in patients with T2D (Estruch et al. 2013, 2018). Additionally, post hoc analysis of the same trial postulated that a Mediterranean diet supplemented with extra-virgin olive oil or nuts may provide a degree of protection against diabetic retinopathy, but not nephropathy (Diaz-Lopez et al. 2015).

Increased intake of non-digestible fermentable dietary fiber has also been associated with alleviation of T2D phenotypes in various clinical trials (Zhao et al. 2018; Chandalia et al. 2000; Soare et al. 2014; Silva et al. 2015). A 6-week randomized, crossover study found that a high fiber diet composed of 25 g soluble fiber improved glycemic control, decreased hyperinsulinemia and lowered plasma lipid concentrations in patients with T2D (Chandalia et al. 2000). In further support of these findings, participants with T2D who consumed a low-glycemic index and/or high fiber breakfast presented with lower plasma glucose, insulin and ghrelin concentrations (Silva et al. 2015). The MADIAB trial (Soare et al. 2014) investigated the macrobiotic Ma-Pi 2 diet which consisted of whole grains, vegetables and legumes as a potential dietary intervention for the management of

T2D. Short-term intervention with the Ma-Pi 2 diet resulted in significantly better metabolic control compared to the recommended standard diets. As previously discussed, dietary fibers can alter the composition of gut microbiota which may affect glycemic control.

The earliest anti-obesity drugs belong to amphetamine derivatives have undesired effects on the central nervous system, often causing agitation, hallucinations and increased heart rate, and are therefore not optimal for obese patients (Colman 2005). A common drug often used in intervention strategies is metformin, which mainly works to decrease hepatic glucose production through gluconeogenesis inhibition (Aroda et al. 2017). Metformin has been reported to activate 5' AMP-activated protein kinase (AMPK) in hepatocytes, resulting in reduced fatty acid oxidation and suppressed expression of lipogenic enzymes (Zhou et al. 2001). Additionally, metformin has recently been shown to alter macrophage polarization by decreasing proportion of M1, and increasing M2 macrophages in palmitate-stimulated bone marrow-derived macrophages (BMDMs) (Jing et al. 2018). Metformin, prescribed along with lifestyle intervention, has been shown to be effective in preventing diabetes in subjects with impaired fasting glucose (Knowler et al. 2002). Orlistat, which is another commonly used drug for obesity, inhibits pancreatic lipases, leading to reduced fat uptake by the gut (Sternby et al. 2002). Conversely, glucagon-like peptide 1 receptor (GLP-1R) agonists work by suppressing glucagon production, stimulating insulin secretion from the pancreas and promoting satiety (Turton et al. 1996). As such, anti-obesity drugs combined with lifestyle modifications can improve weight loss. However, long-term therapy is required and patients may develop tolerance to the drugs or continue to gain weight during the drug regimen (Martin et al. 2015).

Indeed, therapies combining dietary treatment with immunotherapy are now starting to be tested in various disease models. For example, a very recent study testing the combination of a ketogenic diet and PI3K inhibitors, such as metformin and SGLT2, demonstrated significantly enhanced efficacy/toxicity ratios in various murine models of cancer (Hopkins et al. 2018). If these findings were successful, translation into human clinical trials may revolutionize our current therapeutic strategies to eventually pair dietary or medicinal food supplementation with targeted immunotherapy for the treatment of many autoimmune and inflammatory diseases. Table 3 provides a summary of selected clinical trials exploring the role of the microbiota in human T2D.

8 Conclusions and Future Perspectives

Research into the role of the microbiota and diabetes has grown exponentially in recent years. There is some evidence to suggest the strong influence of diet and gut microbiota in the development of inflammatory diseases such as autoimmune T1D, obesity, and T2D. Although studies in experimental animals have provided us with hints on future strategies and therapies targeting the gut microbiota by dietary intervention to prevent or reverse dysbiosis and reduce the diabetes incidence, current literature in humans is still in early stages. This is the new era of the gut microbiota, and several efforts have been directed to design microbiota-based diets as personalized nutrition extensively discussed in Elinav's review (Kolodziejczyk et al. 2019). Advancing on the power of "superfoods" such as dietary SCFAs, they can act as personalized diets as they target in the same beneficial way the different microbiota of each individual. The mechanism behind this process relies on reprogramming and restoring the microbiota-metabolite signature that has multifactorial effects on many physiological processes. In synergy with each individual's genetics and lifestyle, the gut microbiota is sophisticatedly designed to fight against disease (Fig. 1). Simple alterations in the intestinal microbiota, such as robustly increasing the abundance of SCFA producers and thereby boosting SCFA concentrations by specialized medicinal diets, may represent a novel and attractive therapeutic approach for prevention and treatment of diabetes.

Table 3 The gut microbiota and type 2 diabetes in humans

Study design	Intervention	Outcomes/measures	References
Cohort	Patients diagnosed with clinical T2D: 27 in the W group (acarbose and high fiber diet) and 16 in the U group (acarbose and usual care)	Dietary fiber promoted a select group of acetate- and butyrate-producing bacterial strains and diminished indole and hydrogen sulfide producers	Zhao et al. (2018)
		Participants in W group presented with lower plasma HbA1c partly through increased GLP-1 production	
Case control	In total 100 participants: 65 T2D patients divided into 2 subgroups: 49 with and 16 without chronic complications, and 35 healthy controls	T2D patients had a higher abundance of Proteobacteria and Firmicutes/ Bacteroidetes ratio	Zhao et al. (2019b)
		Fecal SCFA concentrations were significantly reduced in T2D patients	
Case control	In total 61 participants with T2D: 31 in the probiotics group and 30 in the placebo group	6-month supplementation with multi-strain probiotics significantly reduced inflammation and HOMA-IR, and improved cardiometabolic profile	Sabico et al. (2019)
Crossover assignment	A randomized trial on 37 with T2D treated for 6 weeks supplementation with a prebiotic fiber mix of inulin and oligofructose compared to maltodextrin as placebo	Additional outcome measures: blood glucose, insulin, GLP-2, ghrelin, PYY, and leptin after a standardized mixed meal test. Also measured changes in microbiota composition and SCFA in feces before and after intervention/placebo periods, and subjective measures of appetite	NCT02569684
Parallel assignment	Role of gastrointestinal microbes on digestion of resistant starch and tryptophan availability to humans. A non-randomized trial on 20 patients	(48 g total/day) suspended in water. 24 g will be consumed 2 times per day. Plasma amino acid levels	NCT02974699
Crossover assignment	Rectal short chain fatty acids combinations and substrate and energy metabolism. A randomized trial on 12 patients obese and T2D	Measure fat oxidation and energy expenditure, hormones that influence energy metabolism and circulating metabolites [Time frame: 4 h total (2 h fasting and 2 h postprandial)	NCT01983046
Parallel assignment	A 12-week pilot randomized controlled trial testing the efficacy of the LoBAG diet (30% carbohydrate low in starch, 30% protein, 40% fat) in 38 participants with T2D	Changes in serum HbA1c, weight, fasting plasma glucose, fasting serum insulin, postprandial plasma and serum insulin, serum fructosamine, fasting serum lipids; Gut microbiota composition at baseline, week 6 and week 12; Urine nitrogen to creatinine ratio	NCT02717078
Single group assignment	A single site, prospective, open label, observational, single arm trial in 30 patients (≥18 years of age) with T2D with GI complaints testing the efficacy of Pendulum Glucose Control formulation (contains 5 human commensal microbial strains including butyrate-producing and mucin-producing strains) to be taken twice daily for 8 weeks with an option of continuing up to 6 months	Decreased GI symptoms in 6 weeks; increased time in glucose range; decreased time in hypoglycemic range; improvement in serum HbA1c at 6, 12 and 24 weeks; improvement in serum fructosamine at 6 weeks	NCT04228003

T2D type 2 diabetes, *HbA1c* hemoglobin A1c, *GLP-1* glucagon-like peptide 1, *SCFA* short-chain fatty acids, *HOMA-IR* homeostatic model assessment of insulin resistance, *PYY* peptide YY, *GI* gastrointestinal

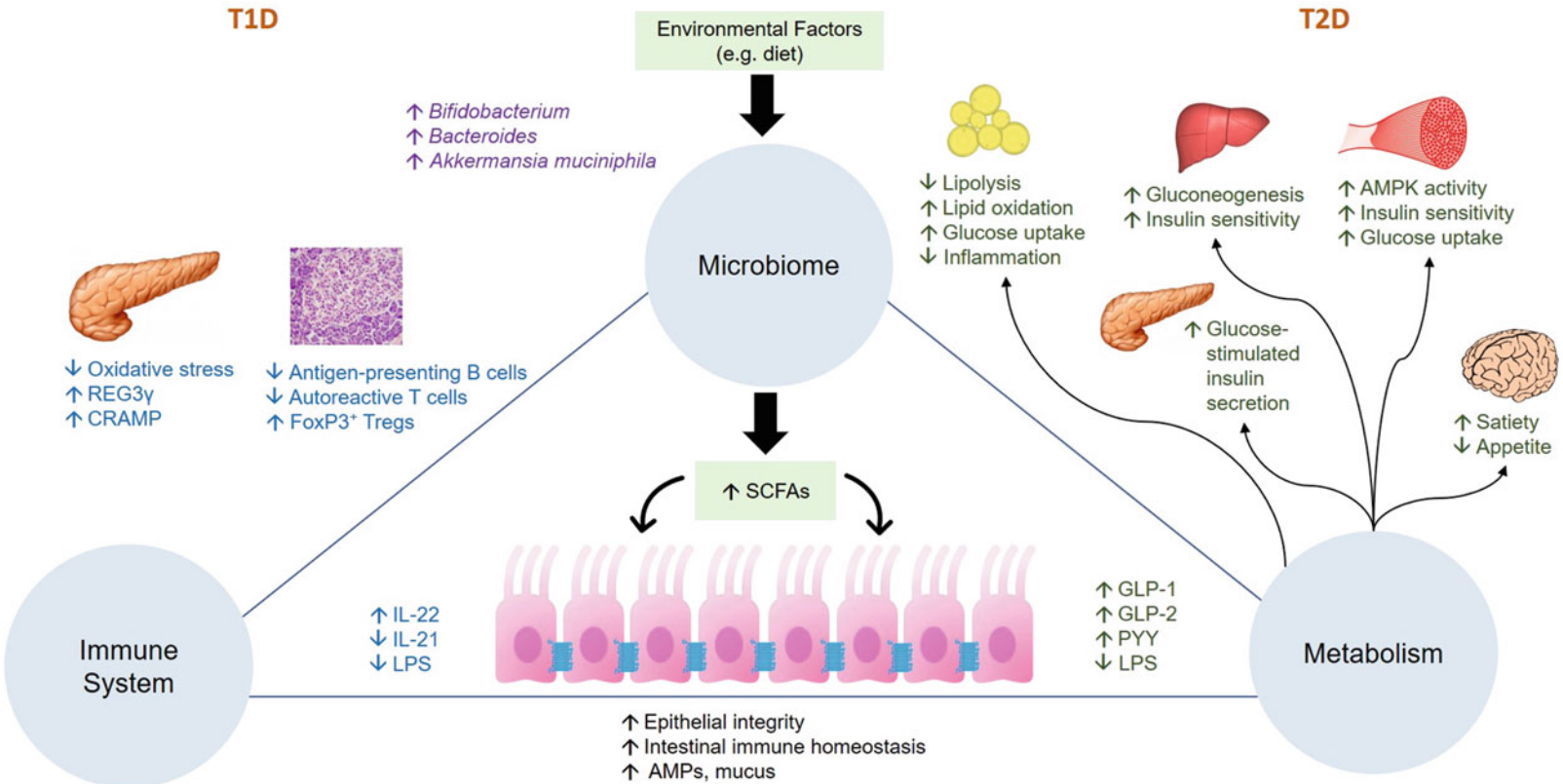

Fig. 1 Schematic representation showing the interactions between dietary SCFAs, the gut microbiota, the immune system, and metabolism in diabetes. The SCFAs acetate, propionate, and butyrate produced from bacterial fermentation of non-digestible carbohydrates are released from the gut lumen into the hepatic portal system and rapidly transported to the liver. In the gut, SCFAs prevent dybiosis by altering the composition of the gut microbiota, improving epithelial integrity, and regulating immune homeostasis. In T1D, dietary SCFAs reduce serum LPS and modulate the cytokine profile to subvert immune responses in the periphery and prevent the autoimmune destruction of pancreatic β-cells. In T2D, SCFAs prevent insulin resistance and low-grade inflammation by reducing serum LPS and increasing plasma gut hormones that improve insulin secretion, gut motility, and satiety to modulate host metabolism and immune homeostasis in peripheral tissues. *T1D* type 1 diabetes, *T2D* type 2 diabetes, *REG3γ* regenerating islet-derived protein 3 gamma, *CRAMP* cathelicidin-related anti-microbial peptide, *FoxP3* forkhead box P3, *SCFAs* short-chain fatty acids, *LPS* lipopolysaccharide, *GLP* glucagon-like peptide, *PYY* peptide YY, *AMP* antimicrobial peptide

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